PARTIAL ALKYLATION AND AMIDOSULFATION OF MONOSACCHARIDE DERIVATIVES IN DIMETHYL SULFOXIDE—METHANOL IN PRESENCE OF SODIUM METHYLATE

V. V. Deryabin and A. I. Usov

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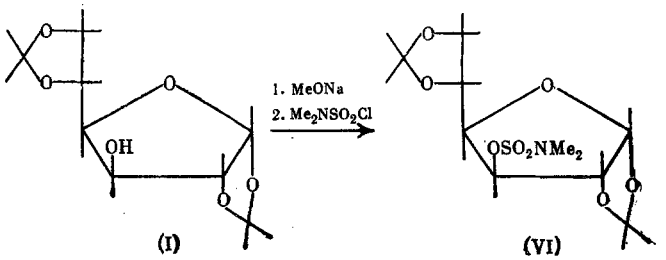
A simple method for the preparation of sugar amidosulfates is treating the alcoholate of a partially protected manosaccharide with the acid chloride of an N,N-dialkylsulfamic acid [1]. Sugar alcoholates are also used to alkylate hydroxyl groups, in which connection the most efficient procedure for obtaining the alcoholates is treatment with NaH in DMSO. Used initially for the methylation of carbohydrates [2] (Hakomori method), this procedure was also used recently to synthesize monosaccharide amidosulfates [3]. However, due to the high efficiency of the indicated method it is not suitable for running selective partial substitution [4].

In the present paper, in order to obtain the alcoholates before treating the monosaccharide derivatives with either alkylating or acylating agents, we used the exchange reaction with methanolic MeONa solution, which was added to the solution of the compound in DMSO. As the monosaccharide derivatives with protective groupings, stable toward bases, we selected 1,2,5,6-di-O-isopropylidene-α-D-glucofuranose (I), methyl 3,4-O-isopropylidene-α-D-galactopyranoside (II), 1,2-O-isopropylidene-α-D-glucofuranose (III), methyl α-D-glucopyranoside (IV), and methyl α-D-galactopyranoside (V).

That monosaccharides could be amidosulfated in the presence of MeONa was demonstrated on the example of synthesizing the 3-dimethylamidosulfate of 1,2,5,6-di-O-isopropylidene-α-D-glucofuranose (VI). It proved that the treatment of a solution of (I) in DMSO with excess MeONa (10% solution in abs. methanol), followed by the addition of Me_2NSO_2Cl in an amount equivalent to the MeONa, gives (VI), whose structure was proved by mass spectrometry and by comparing with an authentic specimen, which was obtained by us previously [1]. In the absence of the MeONa the reaction of (I) with Me_2NSO_2Cl did not go in DMSO. As a result, in the system MeONa—(I) under the employed conditions the equilibrium is apparently shifted strongly toward the alcoholate (I).



The analogous treatment of (II) gives only the 2-dimethylamidosulfate of methyl 3,4-O-isopropylidene-α-D-galactopyranoside (VII). The structure of (VII) was proved by mass spectrometry, by comparing with an authentic specimen, which was obtained by the detritylation of the 2-dimethylamidosulfate of methyl 3,4-O-isopropylidene-6-O-trityl-α-D-galactopyranoside (VIII) [5], by conversion to the 2-dimethylamidosulfate of methyl 3,4,6-tri-O-acetyl-α-galactopyranoside (IX), which has a characteristic mass spectrum [5], and also by the electrophoresis data on paper of the 2-dimethylamidosulfate of D-galactose (X), which was obtained from (VII) by acetolysis and subsequent deacetylation [5]. As a result, despite the presence of two free OH groups in the starting (II), under the employed conditions of hydroxyl at C^2 undergoes selective amidosulfation, evidently due to its greater tendency to ionize when compared with the hydroxyl at C^6; cf. [6].

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow.
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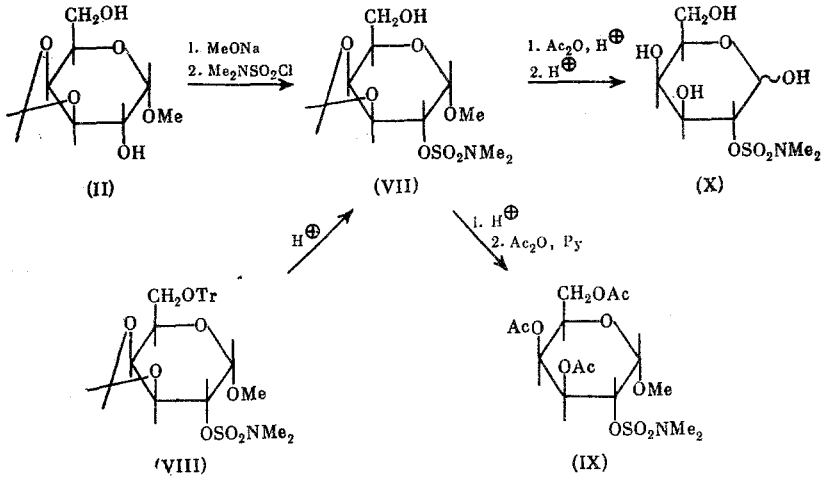
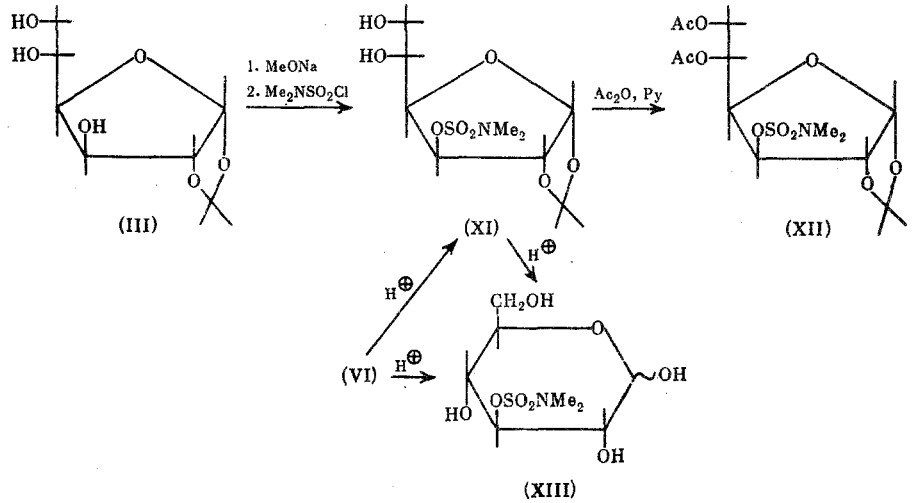
TABLE 1. Peaks of Principal Ions and Their Intensity Relative to the Peak of the Ion with m/e 233 in Mass Spectra of Compounds (XIX)-(XXI)

m/e	(XIX)	(XX)	(XXI)	m/e	(XIX)	(XX)	(XXI)
233 (M–15)	1,0	1,0	1,0	173 (M–75)	5,1	–	5,3
217 (M–31)	–	–	1,1	159 (M–89)	–	2,0	–
203 (M–45)	0,8	0,5	–	89 (CH_2OCH_3–$CHOCH_3$)	–	2,7	–

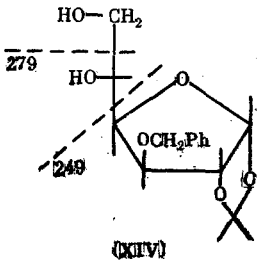
The reaction of (III) with Me_2NSO_2Cl in the presence of MeONa also gives only the 3-dimethylamidosulfate of 1,2-O-isopropylidene-α-D-glucofuranose (XI). The structure of (XI) follows from the mass spectrum of its acetate (XII), which is identical with that of the authentic specimen, which was obtained from (VI) after partial hydrolysis and acetylation.



The samples of D-glucose 3-methylamidosulfate (XIII), obtained by the hydrolysis of (XI) and (VI), have the same electrophoretic mobility. As a result, of the three free OH groups in compound (III) the most inclined to enter into the amidosulfation reaction is the hydroxyl at C^3.

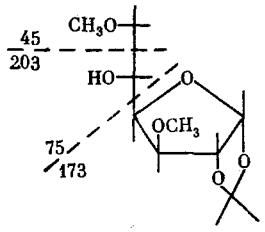


The predominant formation of the 3-O-substituted derivatives is also observed when (III) is treated with alkylating agents in the presence of MeONa. Reaction with benzyl chloride leads to 1,2-O-isopropylidene-3-O-benzyl-α-D-glucofuranose (XIV), although a chromatographic study of the reaction mixture permits detecting small amounts of the isomeric monobenzyl ethers. The main reaction product (XIV) was isolated by preparative chromatography in ~80% yield. Its structure was confirmed by the mass spectrum, in which the peaks of the ions with m/e 279 (M – 31) and 249 are present, but the peak of the ion with m/e 159, which is characteristic for the (III) derivatives with an unsubstituted OH group at C^3, is absent.

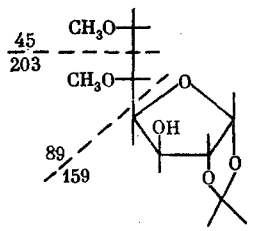


(XXIV)

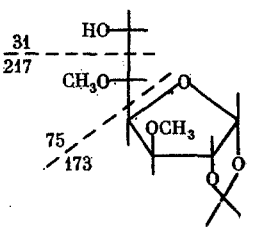
A similar treatment of (III) with MeI gives predominantly 1,2-O-isopropylidene-3-O-methyl-α-D-glucofuranose (XV). The structure of (XV) follows from the fact that the chromatographic properties and mass spectrum of its 5,6-di-O-acetate (XVI) coincide with those of the authentic specimen, which was obtained from 1,2,5,6-di-O-isopropylidene-3-O-methyl-α-D-glucofuranose via partial hydrolysis and acetylation. However, together with (XV), the methylation products of (III) also contained 1,2-O-isopropylidene-5-O-methyl-α-D-glucofuranose (XVII), which was identified via chromato-mass spectrometry as the 3,6-di-O-acetate (XVIII). Based on the GLC data, the (XVI):(XVIII) ratio is ∿8:1. A substantial increase in the amount of MeONa in the alkylation step (10-20-fold excess) makes it possible to obtain the di-O-methyl derivatives (XIX)-(XXI) in an ∿0.4:0.7:1 ratio, the overall yield of which can reach 50%. The structure of these compounds follows from their mass spectra (Table 1).



(XIX)



(XX)

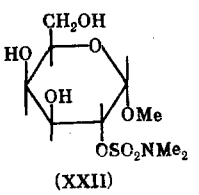


(XXI)

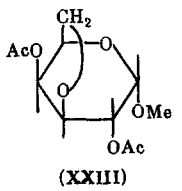
When the results, obtained in treating (III) with Me_2NSO_2Cl, $PhCH_2Cl$, and MeI are compared, we see that in all cases the first to react is the OH group at C^3, but the selectivity of substitution decreases in the enumerated order of the reactants.

The unsubstituted methyl α-D-glucopyranoside (IV) when treated with MeONa and MeI under the above-described conditions gives a mixture of practically only the monomethyl ethers; the reactivity of the OH groups, like in methylation by the Hakomori method [4], decreases in the order: 2-OH > 6-OH > 4-OH ≥ 3-OH. The structure of the monomethyl ethers of (IV) follows from the mass spectra of their acetates, which resemble the known [7] spectra of the acetylated mono-O-methyl derivatives of methyl α-D-mannopyranoside [7].

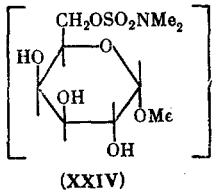
As was to be expected, the treatment of (V) with MeONa and Me_2NSO_2Cl leads mainly to the 2-dimethylamidosulfate of methyl α-D-galactopyranoside (XXII), which was identified as the acetate (IX). Analysis of the acetylation products of the reaction mixture by the CMS method disclosed that it was accompanied by methyl 2,4-di-O-acetyl-3,6-anhydro-α-D-galactopyranoside (XXIII) [8], which is probably formed by the intramolecular cleavage of N,N-dimethylsulfamic acid in the presence of a base from the intermediate 6-dimethylamidosulfate of methyl α-D-galactopyranoside (XXIV).



(XXII)



(XXIII)



(XXIV)

EXPERIMENTAL

The TLC was run on plates covered with a loose layer of silica gel L 5/40 μ in the solvent mixtures: $CHCl_3$—acetone, 95:5 (A), 8:2 (B), 65:35 (C); the zones were detected with conc. H_2SO_4. The electrophoresis on Filtrak FN 11 paper was run in pH 9 borate buffer at 10 V/cm; the zones were detected with aniline phthalate; the mobilities of the substances

are given relative to D-glucose and D-galactose. The CMS was run on a Varian MAT-111 instrument using columns packed with 3% ECNSS deposited on Chromosorb Q (D), at 110-200°C, or with 5% Se-30 deposited on Chromaton N (E), at 150-300°. The retention times (T) are given relative to methyl 2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside (XXV) and methyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside (XXVI). The mass spectra of (VII) and (XIV) were obtained on a Varian MAT CH-6 mass spectrometer, with direct insertion into the ion source at 80-120°.

General Method. To a solution of 0.1 g of the monosaccharide derivative in 5 ml of dry DMSO was added an excess of 10% MeONa solution in abs. MeOH. The mixture was kept for 20-30 min at 20°, and then either the alkylating or the acylating agent was added in an amount equivalent to the MeONa. The end of reaction was checked by the disappearance of alkaline solution (5-30 min). The reaction mixture was poured into water, extracted thrice with $CHCl_3$, and the extract was washed with water, dried, and evaporated. In the case of forming water-soluble compounds [monomethyl ethers of (III) and (IV), amidosulfates of (V)] the reaction mixture was first concentrated in vacuo, then treated with a 1:1 Ac_2O—pyridine mixture for 24 h, and the obtained acetates were isolated as described above.

3-Dimethylamidosulfate of 1,2,5,6-Di-O-isopropylidene-α-D-glucofuranose (VI). From (I) and a 1.5-2-fold excess of MeONa and Me_2NSO_2Cl we obtained (VI) in 75-80% yield after recrystallization from MeOH, R_f 0.7 (A), mp 95-96°, $[\alpha]_D$ −74° (C 0.8, $CHCl_3$). Mass spectrum, m/e: 352 (M − 15), 294 (M − 15 − 58), 266, 234 (M − 15 − 58 − 60), 185, 127, 113, 108 (Me_2NSO_2), 101, 85, 81, 59, 43; cf. [1].

2-Dimethylamidosulfate of Methyl 3,4-O-Isopropylidene-α-D-galactopyranoside (VII). From (II) and a 1.5-3-fold excess of MeONa and Me_2NSO_2Cl we obtained (VII) as a syrup with R_f 0.35 (A). Based on the TLC data, the yield was ∿100%. Mass spectrum, m/e: 326 (M − 15), 310 (M − 31), 233 (M − 108), 208, 201, 185, 173 (M − 108 − 60), 115 (M − 108 − 60 − 58), 108 (Me_2NSO_2), 85, 83.

Compound (VII) was also obtained by heating the 2-dimethylamidosulfate of methyl 3,4-O-isopropylidene-6-O-trityl-α-D-galactopyranoside (VIII) [5] in 80% AcOH solution until solution was complete and then isolating the substance with R_f 0.35 (A) by chromatography on a silica gel column. The mass spectra of the two (VII) specimens coincide.

2-Dimethylamidosulfate of Methyl 3,4,6-Tri-O-acetyl-α-D-galactopyranoside (IX). The hydrolysis of (VII) with 60% AcOH solution (100°, 4 h) and subsequent acetylation gave (IX), T = 3.1 [230°, (E), relative to (XXV)]. Mass spectrum, m/e: 396 (M − 31), 332, 319, 303, 284, 259, 256, 243, 234, 183, 169, 167, 149, 141, 139, 129, 127, 115, 109, 108, 103, 97, 87, 69, 43; cf. [5].

The acetolysis of (VII) with 1.25 ml of Ac_2O, 0.9 ml of AcOH, and 0.125 ml of conc. H_2SO_4 (20°, 15 h) and subsequent treatment with 2 N H_2SO_4 solution (100°, 3 h) gave the 2-dimethylamidosulfate of D-galactose (X), M_{Gal} 0.28 [5].

3-Dimethylamidosulfate of 1,2-O-Isopropylidene-α-D-glucofuranose (XI). From (III) and a 1.5-3.5-fold excess of MeONa and Me_2NSO_2Cl we obtained (XI) with R_f 0.3 (C). Based on the TLC data, the yield was ∿100%.

The acetylation of (XI) gave the 3-dimethylamidosulfate of 1,2-O-isopropylidene-5,6-di-O-acetyl-α-D-glucofuranose (XII), R_f 0.7 (A), mp 104-104.5° (from MeOH), $[\alpha]_D$ −53.1° (C 1.0, $CHCl_3$). Mass spectrum, m/e: 396 (M − 15), 280, 266 (M − 145), 244, 229, 208, 197, 187, 180, 169, 155, 145, 141, 139, 129, 127, 115, 108, (Me_2NSO_2), 100, 85, 81, 43.

Compound (XII) was also obtained by treating (VI) with 50% AcOH solution (50°, 3 h) and subsequent acetylation. The mixed melting point of the two (XII) samples was not depressed. The treatment of (VI) and (XII) with 50% AcOH solution (100°, 4 h) gave the 3-dimethylamidosulfate of D-glucose (XIII), M_{Glc} 0.79.

1,2-O-Isopropylidene-3-O-benzyl-α-D-glucofuranose (XIV). From (III) and a 1.5-3.5-fold excess of MeONa and $C_6H_5CH_2Cl$ we obtained a syrup with R_f 0.33 and 0.30 (C). Chromatography on silica gel (eluant = $CHCl_3$) gave (XIV) in 75-80 yield as a syrup with R_f 0.3 (C) and $[\alpha]_D$ −28.6° (C 1.6, $CHCl_3$). Mass spectrum, m/e: 310 (M), 295 (M − 15), 279 (M − 31), 249 (M − 61), 235, 234, 216, 203, 191, 175, 163, 149, 145, 133, 129, 120, 113, 107, 100, 91, 85, 71.

1,2-O-Isopropylidene-3-O-methyl- (XV) and 1,2-O-Isopropylidene-5-O-methyl-α-D-glucofuranose (XVII). From (I) and a 1.5-2-fold excess of MeONa and MeI we obtained 1,2,5,6-di-O-

isopropylidene-3-O-methyl-α-D-glucofuranose, which was treated with 50% AcOH solution (50°, 3 h) and acetylated. We obtained 1,2-O-isopropylidene-3-O-methyl-5,6-di-O-acetyl-α-D-glucofuranose (XVI), R_f 0.65 (A), mp 72-73°, $[\alpha]_D$ −84.2° (C 0.6, $CHCl_3$). Mass spectrum, m/e: 303 (M − 15), 226, 197, 187, 184, 183, 175, 173, 169, 158, 142, 141, 129, 127, 115, 100, 87, 85, 73. From (III) and a 1.5—2-fold excess of MeONa and MeI, followed by acetylation (see above), we obtained a syrup, R_f 0.65 (A), which was deacetylated with 0.01 N MeONa solution in MeOH (20°, 10 min). By chromatography (eluant = $CHCl_3$) we isolated a fraction that contained a substance with R_f 0.35 (C), which was reacetylated. Based on the CMS data (D), the mixture contains (XVI) and 1,2-O-isopropylidene-5-O-methyl-3,6-di-O-acetyl-α-D-glucofuranose (XVIII). Mass spectrum, m/e: 303 (M − 15), 245 (M − 73), 201 (M − 73 − 44), 187, 169, 143, 117, 87, 43, in an ∿8:1 ratio.

1,2-O-Isopropylidene-3,6- (XIX), 1,2-O-Isopropylidene-5,6- (XX), and 1,2-O-Isopropylidene-3,5-di-O-methyl-α-D-glucofuranose (XXI). From (III) and a 10-20-fold excess of MeONa and MeI we obtained a syrup (45-50% yield), which, based on the CMS data (D), consisted of three main components: (XIX), m/e: 233, 203, 187, 173, 145, 142, 127, 115, 113, 87, 85; (XX), m/e: 233, 203, 189, 183, 159, 145, 129, 113, 101, 100, 89, 87, 85, 59, and (XXI), m/e: 233, 217, 189, 173, 145, 115, 101, 87, 85, in an ∿0.4:0.7:1.0 ratio. Compounds (XIX) and (XX) had R_f 0.45 (B), and (XXI) had R_f 0.40 (B). By chromatography (eluant = $CHCl_3$) we isolated (XXI) as a syrup with $[\alpha]_D$ −24.5° (C 0.7, $CHCl_3$).

Methyl O-Methyl-α-D-glucopyranosides. From (IV) and a 5-7-fold excess of MeONa and MeI we obtained the glucopyranosides, which, as the corresponding acetates, were identified by CMS (165°, D). The overall yield was ∿40-45%. The relative amount and T [relative to (XXVI)] were: 2-OMe (1.0, 0.77), 3-OMe (0.18, 0.60), 4-OMe (0.19, 0.70), 6-OMe (0.46, 0.37). The mass spectra of the acetates of the methyl mono-O-methyl-α-D-glucopyranosides and the corresponding acetates of the methyl mono-O-methyl-α-D-mannopyranosides [7] were identical.

2-Dimethylamidosulfate of Methyl α-D-Galactopyranoside (XXII). From (V) and a 5-fold excess of MeONa and Me_3NSO_2Cl we obtained after acetylation a mixture, which, based on the CMS data, contains acetates (XXII) and (IX). See above for mass spectra. Signal T = 0.33 [230°, E, relative to (XXV)], m/e: 229 (M − 31), 200 (M − 60), 157, 144, 140, 127, 103, 99, 98, 85, 83, 69, 43, which corresponds to methyl 2,4-di-O-acetyl-3,6-anhydro-α-D-galactopyranoside (XXIII) [8]. The ratio of (IX) and (XXIII) is ∿1.0:0.1.

CONCLUSIONS

The partial amidosulfation and alkylation of monosaccharide derivatives was run in DMSO—methanol in the presence of MeONa. Under these conditions the polyhydroxyl compounds give predominantly the monosubstituted derivatives, in which connection the reaction proceeds selectively in a number of cases.

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