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Note

The C-substitution of methylsulfonyloxy groups on alkylation

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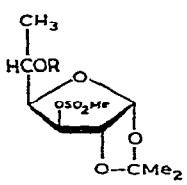
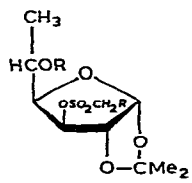
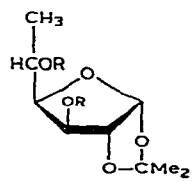
As mentioned in a previous paper[1], treatment of 1,2-*O*-isopropylidene-3-*O*-(methylsulfonyl)-β-L-idofuranose (**1**) in *N*,*N*-dimethylformamide with benzyl chloride in the presence of powdered potassium hydroxide gave, besides unreacted starting-material (23%), the expected 5-*O*-benzyl derivative (**2**; 53%) and a third component (3.5%), the structure of which (according to ^{1}H-n.m.r. data) corresponded to the 5-*O*-benzyl-3-*O*-(phenethylsulfonyl) derivative **4**. Theoretically, a further compound,



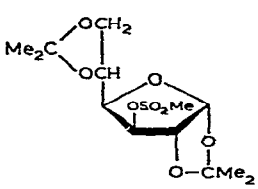
1 R = H
2 R = Bn
3 R = Me
Bn = $PhCH_2$



4 R = Bn
5 R = Me



6 R = H
7 R = Bn



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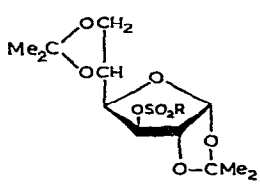
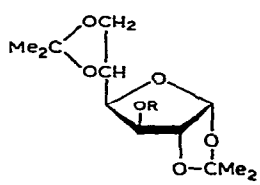


9 R = $BnCH_2$
10 R = Bn_2CH
11 R = Et
12 R = Me_2CH
13 R = Bn(Me)CH
14 R = $Bn_2(Me)C$



15 R = H
16 R = Bn

the 3,5-di-*O*-benzyl derivative **7**, could also be formed in the reaction, as *O*-mesyl groups can be hydrolyzed by strong base[2], and the resulting diol (**6**) should yield **7**. The absence of the latter in the crude reaction-mixture was proved by t.l.c., as well as by ^{1}H-n.m.r. spectroscopy and by comparing it with an authentic sample of **7**.

The formation of the *C*-benzylated derivative **4** is a consequence of the electron-withdrawing effect of the sulfonyloxy group (which makes it a good leaving-group), but the same effect also loosens the protons of the α-situated* carbon atom. Similar behavior of the sulfoxide[3,4] and sulfone groups[5,6] is well-documented in the literature. Accordingly, *C*-substituted byproducts should always be formed when mesyloxy derivatives are treated with alkylating agents in the presence of a strong base.

In order to test this hypothesis, the aforementioned reaction of **1** was repeated with methyl iodide, whereupon the 5-*O*-methyl-3-*O*-(methylsulfonyl) (**3**) and 3-*O*-(ethylsulfonyl)-5-*O*-methyl derivative (**5**) were formed in the ratio of 3 : 1. The increase in the yield of the *C*-methylated product **5**, compared to the *C*-benzylated compound (**4**), was probably due to the different reaction-conditions applied (35° for the methylation, and 25° for the benzylation).

As the electron-withdrawing effect of the sulfonyloxy group should loosen all protons attached to the α-carbon atom, the *C*-alkylation process should lead to mono-, di-, and even tri-, *C*-substituted mesyloxy derivatives, depending on the reaction conditions applied. For investigating this behavior, 1,2 : 5,6-di-*O*-isopropylidene-3-*O*-(methylsulfonyl)-α-D-glucose (**8**) was used as the model compound (see Table I).

When a solution of **8** in *N*,*N*-dimethylformamide was treated with one equivalent of benzyl chloride, the phenethylsulfonyl derivative **9** was obtained in a yield of 32%, and an almost equal amount of unreacted **8** (30%) was recovered. When the reaction was repeated with six equivalents of benzyl chloride, the mono-*C*-benzylated compound **9** was further benzylated to the di-*C*-benzylated derivative **10** (77%), and only one byproduct could be isolated (5%); this proved to be the 3-*O*-benzyl derivative **16**. This indicates that, in the presence of a large excess of potassium hydroxide, the expected, partial hydrolysis of the mesyloxy group takes place, and the resulting hydroxy compound **15** is immediately *O*-benzylated. The absence of any tri-*C*-benzylated derivative is probably due to steric factors, as the di-*C*-benzylated mesyl group is already too crowded to undergo further *C*-benzylation.

Investigation of the analogous methylation-reaction yielded, in the presence of 1 mol of methyl iodide, the ethylsulfonyloxy derivative **11** and unreacted starting-material **8** in the ratio of 11 : 10, comparable to the 32 : 30 ratio found for the benzylation reaction. However, when the amount of methyl iodide was increased to five equivalents, an inseparable mixture of two derivatives was obtained, which, according to ^{1}H-n.m.r. data, contained only 20% of the isopropylidene-sulfonyloxy derivative **12** (di-*C*-methylation) besides 80% of **11** (mono-*C*-methylation). This is in sharp contrast to the analogous, benzylation reaction, wherein no mono-*C*-benzylated, but 72% of di-*C*-benzylated product (**10**) was obtained. The lower conversion of **11** → **12**

*The carbon atom attached to the sulfur atom.

compared with **9** → **10** can be explained by the different electronic features of the mono-*C*-substituted intermediates **11** and **9**, as, in the former, the introduced *C*(α)-methyl group diminishes the influence of the electron-withdrawing effect of the sulfonyloxy group, and, consequently, the removal of a further α-proton will be less favored than in the case of the *C*(α)-benzyl group.

This assumption was proved indirectly by using the ethylsulfonyl derivative **11** as the starting material; on benzylation with an excess of benzyl chloride, it gave a mixture of the mono- (**13**) and di-benzylated (**14**) products, the latter constituting a tri-*C*-substituted mesyloxy derivative.

In carbohydrate chemistry, the mesyloxy substituents are mostly used as chemically active groups that can be readily replaced, with inversion of configuration. From this point of view, the observed, *C*-alkylation reaction of the mesyloxy groups merely makes the purification of the intermediates difficult, but it does not influence further reactions, as the reactivity of the mesyloxy groups is not essentially altered by their *C*-substitution, and consequently, both types undergo the same reactions.

EXPERIMENTAL

General methods. — After organic solutions had been dried with sodium sulfate, all evaporations were conducted in a rotary evaporator under diminished pressure. Melting points are uncorrected. Light petroleum had b.p. 60–80°. Optical rotations were determined in chloroform (*c* 1). T.l.c. was effected on Kieselgel G with ethyl acetate–carbon tetrachloride, 1 : 3 (*A*) and 1 : 5 (*B*). For detection, 1 : 1 0.1M potassium permanganate–M sulfuric acid was used at 105°. Column chromatography was performed on Kieselgel 40 (62–200 μm). ^{1}H-N.m.r. spectra (90 MHz) were recorded at room temperature with a Varian EM-390 spectrometer for solutions in chloroform-*d*, with tetramethylsilane as the internal standard.

*6-Deoxy-1,2-*O*-isopropylidene-5-*O*-methyl-3-*O*-(methylsulfonyl)-β-*L*-idofuranose* (**3**) *and 6-deoxy-3-*O*-(ethylsulfonyl)-1,2-*O*-isopropylidene-5-*O*-methyl-β-*L*-idofuranose* (**5**). — To a stirred solution of compound **1** (5.64 g) in *N*,*N*-dimethylformamide (80 mL) were added methyl iodide (6 mL) and powdered potassium hydroxide (20 g) simultaneously, in small portions, during 30 min, the temperature of the mixture being kept at 32–35° by gentle cooling. Thereafter, stirring was continued for 1 h at this temperature. The resulting slurry was filtered, and the filtrate was evaporated. The residue was dissolved in chloroform, and the solution was washed with water, dried, and evaporated. The crude product so obtained was separated by column chromatography, using solvent *A* for elution. The fractions having R_F 0.4 gave, on evaporation, and crystallization of the residue from ether–light petroleum, pure **5** (0.9 g, 14.5%), m.p. 94–96°, $[\alpha]_D^{20}$ −30.6°; ^{1}H-n.m.r. data: δ 5.98 (d, $J_{1,2}$ 4 Hz, H-1), 5.00 (d, $J_{3,2}$ 0, $J_{3,4}$ 3 Hz, H-3), 4.80 (d, $J_{2,1}$ 4 Hz, H-2), 4.15 (dd, $J_{4,3}$ 3, $J_{4,5}$ 7 Hz, H-4), 3.40 (dd, $J_{4,5} = J_{5,6} = 7$ Hz, H-5), 3.48 (s, OMe), 3.20 (q, *J* 7 Hz, CH_2-CH_3), 1.45 (t, *J* 7 Hz, CH_2-CH_3), 1.53 and 1.37 (s, CMe_2), and 1.23 (d, *J* 7 Hz, H-6).

TABLE I

REACTION OF 1,2:5,6-DI-*O*-ISOPROPYLIDENE-3-*O*-(METHYLSULFONYL)-α-D-GLUCOSE (**8**) WITH ALKYLATING AGENTS

R	*Ratio of R-Hal*:CH_3SO_3	CH_3SO_3 (%)	RCH_2SO_3 (%)	R_2CHSO_3 (%)
$PhCH_2$	1:1	30	32	—
$PhCH_2$	6:1	—	—	72[a]
CH_3	1:1	40	44	—
CH_3	5:1	—	80[b]	20[b]

[a]3-*O*-Benzyl derivative **16** (5%) was isolated as the sole byproduct. [b]Composition of the reaction mixture was analyzed by ^{1}H-n.m r. spectroscopy.

Anal. Calc. for $C_{12}H_{22}O_7S$: C, 46.44; H, 7.15; S, 10.33. Found: C, 46.33; H, 7.08; S, 10.43.

On evaporation, and crystallization of the residue from ether–light petroleum, the fractions having R_F 0.35 gave pure compound **3** (2.7 g, 46%), m.p. 112–114°, $[\alpha]_D^{20}$ −35.7°; ^{1}H-n.m.r. data: δ 5.95 (d, $J_{1,2}$ 4 Hz, H-1), 4.97 (d, $J_{3,2}$ 0, $J_{3,4}$ 3 Hz, H-3), 4.80 (d, $J_{2,1}$ 4 Hz, H-2), 4.15 (dd, $J_{4,3}$ 3, $J_{4,5}$ 27 Hz, H-4), 3.5 (qd, $J_{5,4}$ 7, $J_{5,6}$ 6 Hz, H-5), 3.40 (s, OMe), 3.05 (s, SO_2Me), 1.50 and 1.30 (s, CMe_2), and 1.10 (d, $J_{4,5}$ 6 Hz, H-6).

Anal. Calc. for $C_{11}H_{20}O_7S$: C, 44.58; H, 6.80; S, 10.82. Found: C, 44.65; H, 6.89; S, 10.76.

*3,5-Di-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-β-*L*-idofuranose* (**7**). — A solution of compound **6** (20.4 g) in *N,N*-dimethylformamide (400 mL) was treated with benzyl chloride (68 mL) and powdered potassium hydroxide (100 g) at 23–27°, as described for compound **1**. The crude product obtained was separated by column chromatography, using solvent *A* for elution. The fractions having R_F 0.8 gave, on evaporation, and crystallization of the residue from light petroleum, pure compound **7** (28.4 g, 74%), m.p. 66–68°, $[\alpha]_D^{20}$ −9.5°; ^{1}H-n.m.r. data: δ 6.00 (d, $J_{1,2}$ 4 Hz, H-1), 1.60 and 1.42 (s, CMe_2), and 1.12 (d, J 7 Hz, H-6).

Anal. Calc. for $C_{23}H_{28}O_5$: C, 71.75; H, 7.34. Found: C, 71.78; H, 7.39.

*Reaction of 1,2:5,6-di-*O*-isopropylidene-3-*O*-(methylsulfonyl)-α-D-glucofuranose* (**8**) *with an equivalent of benzyl chloride.* — A solution of compound **8** (20.4 g) in *N,N*-dimethylformamide (120 mL) was treated with benzyl chloride (6.8 mL) and powdered potassium hydroxide (20 g) at 30–35°, as described for compound **1**. The crude product was separated by column chromatography, using solvent *B* for elution. The fractions having R_F 0.6 gave, on evaporation, and crystallization of the residue from ether–light petroleum, pure **9** (8.2 g, 32%), m.p. 86–88°, $[\alpha]_D^{20}$ −39.2°; ^{1}H-n.m.r. data: δ 5.90 (d, $J_{1,2}$ 4 Hz, H-1), 5.00 (d, $J_{3,4}$ 2, $J_{2,3}$ 0 Hz, H-3), 4.80 (d, $J_{2,1}$ 4 Hz, H-2), 3.15 and 3.45 (m, $PhCH_2$), and 1.20, 1.32, 1.37, and 1.50 (s, 2 CMe_2).

Anal. Calc. for $C_{20}H_{28}O_8S$: C, 56.10; H, 6.59; S, 7.48. Found: C, 55.98; H, 6.50; S, 7.59.

After elution of compound **9** from the column, the elution was continued with ethyl acetate, affording unreacted starting-material (6.1 g, 30%).

Reaction of compound **8** *with an excess of benzyl chloride.* — A solution of compound **8** (3.4 g) in *N,N*-dimethylformamide (80 mL) was treated with benzyl chloride (6.8 mL) and powdered potassium hydroxide (20 g) at 30–35°, as described for compound **1**. The crude product was separated by column chromatography, using solvent *B* for elution. On evaporation, the fractions having R_F 0.7 gave pure **10** as a colorless syrup (3.65 g, 72%); ^{1}H-n.m.r. data: δ 5.75 (d, $J_{1,2}$ 4 Hz, H-1), 5.05 (d, $J_{3,4}$ 2, $J_{3,2}$ 0 Hz, H-3), 4.60 (d, $J_{2,1}$ 4 Hz, H-2), 3.3 and 2.85 (m, 2 Ph-CH_2), and 1.42, 1.35, 1.23, and 1.20 (s, 2 CMe_2).

The second fraction, having R_F 0.6, gave on evaporation, pure compound **16** as a colorless syrup (0.23 g, 6.7%); ^{1}H-n.m.r. data: δ 5.83 (d, $J_{1,2}$ 4 Hz, H-1), 4.50 (d, $J_{2,1}$ 4, $J_{2,3}$ 0 Hz, H-2), 4.10 (d, $J_{3,4}$ 2 Hz, H-3), and 1.25, 1.32, 1.39, and 1.45 (s, 2 CMe_2).

Reaction of compound **8** *with an equivalent of methyl iodide.* — A solution of compound **8** (17 g) in *N,N*-dimethylformamide (100 mL) was treated with methyl iodide (3 mL) and powdered potassium hydroxide (20 g) at 35–38°, as described for compound **1**. The crude product was separated by column chromatography, using solvent *B* for elution. The fractions having R_F 0.4 gave, on evaporation and crystallization of the residue from methanol, pure **11** (7.8 g, 44%), m.p. 80–82°, $[\alpha]_D^{20}$ −55°; ^{1}H-n.m.r. data: δ 5.95 (d, $J_{1,2}$ 4 Hz, H-1), 5.00 (d, $J_{3,4}$ 2, $J_{3,2}$ 0 Hz, H-3), 4.85 (d, $J_{2,1}$ 4 Hz, H-2), 3.25 (d, *J* 8, O_2SCH_2), 1.45 (t, *J* 8, CH_2-CH_3), and 1.32, 1.32, 1.43, and 1.51 (s, 2 CMe_2).

Anal. Calc. for $C_{14}H_{24}O_8S$: C, 47.71; H, 6.86; S, 9.10. Found: C, 47.64; H, 6.80; S, 9.21.

After elution of compound **11** from the column, the elution was continued with ethyl acetate, affording unreacted starting-material (6.8 g, 40%).

Reaction of compound **8** *with an excess of methyl iodide.* — A solution of compound **8** (3.4 g) in *N,N*-dimethylformamide (80 mL) was treated with methyl iodide (3 mL) and powdered potassium hydroxide (20 g) at 35–38°, as described for compound **1**. The crude product was separated by column chromatography, using solvent *B* for elution. The fractions having R_F 0.4 gave, according to their ^{1}H-n.m.r. data, a 4:1 mixture (1.8 g) of **11** (mono-*C*-methylation) and **12** (di-*C*-methylation); ^{1}H-n.m.r. data for **11**: δ 5.95 (d, $J_{1,2}$ 4 Hz, H-1), 5.00 (d, $J_{3,4}$ 2, $J_{3,2}$ 0 Hz, H-3), 4.85 (d, $J_{2,1}$ 4 Hz, H-2), 3.25 (q, *J* 8 Hz, $O_2SCH_2CH_3$), 1.45 (t, *J* 8 Hz, $O_2SCH_2CH_3$), and 1.32, 1.32, 1.43, and 1.51 (s, 2 CMe_2); and, for **12**: δ 5.80 (d, $J_{1,2}$ 4 Hz, H-1), 4.80 (d, $J_{3,4}$ 2, $J_{3,2}$ 0 Hz, H-3), 4.55 (d, $J_{2,1}$ 4 Hz, H-2), 3.37 (m, *J* 7.5 Hz, OSO_2CHMe_2), 1.46 (d, *J* 7.5 Hz, $CHMe_2$), and 1.33, 1.33, 1.41, and 1.49 (s, 2 CMe_2).

*Reaction of 3-*O*-(ethylsulfonyl)-1,2:5,6-di-*O*-isopropylidene-α-*D*-glucofuranose* (**11**) *with an excess of benzyl chloride.* — A solution of compound **11** (3.5 g) in *N,N*-dimethylformamide (80 mL) was treated with benzyl chloride (6.8 mL) and powdered

potassium hydroxide (20 g) at 30–35°, as described for compound **1**. The crude product was separated by column chromatography, using solvent *B* for elution. The fraction having R_F 0.75 gave, on evaporation, pure **14** as a colorless syrup (0.25 g), $[\alpha]_D^{20}$ −33.88° (*c* 1.8, chloroform); ^{1}H-n.m.r. data: δ 5.80 (d, $J_{1,2}$ 4 Hz, H-1), 4.93 (d, $J_{3,4}$ 3, $J_{3,2}$ 0 Hz, H-3), 4.70 (d, $J_{2,1}$ 4 Hz, H-2), 3.35 and 3.15 (2 d, J_{AB} 13 Hz, 2 Ph-CH_2), 1.26 (s, C-CH_3), and 1.26, 1.34, 1.40, and 1.43 (s, 2 CMe_2).

REFERENCES

1 G. Medgyes and J. Kuszmann, *Carbohydr. Res.*, 92 (1981) 225–237.
2 R. S. Tipson, *Adv. Carbohydr. Chem.*, 8 (1953) 107–216.
3 H. Moskowitz, J. Blanceguenee, and M. Miocque, *C. R. Acad. Sci., Ser. C*, 267 (1968) 898–899.
4 H. Tsukasa, and S. Saito, *Yukagaku*, 24 (1975) 659–664.
5 K. Kondo and D. Tunemoto, *Tetrahedron Lett.*, (1975) 1007–1010.
6 J. Kuszmann, P. Sohár, Gy. Horváth, and Zs. Méhesfalvi-Vajna, *Tetrahedron*, 30 (1974) 3905–3910.