# Synthesis of D-Galactose Derivatives Substituted at Carbon 3[1]

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Benzyl and methyl 2-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranosides (Bz-VIII and Me-VIII) have been prepared as intermediates for the synthesis of derivatives of D-galactose substituted at C-3. Condensation of these intermediates with tetra-*O*-acetyl-α-D-glucopyranosyl bromide, followed by hydrogenolysis and removal of the acetyl groups, gave, respectively, the disaccharides 3-*O*-(-β-D-glucopyranosyl)-D-galactose (XI) and methyl 3-*O*-(-β-D-glucopyranosyl)-β-D-galactopyranoside (Me-XI). After sulfation of Bz-VIII and Me-VIII, hydrogenolysis of the benzyl and benzylidene substituents was found to be strongly hindered. D-Galactose 3-sulfate (XIV) was prepared by sulfation of 4,6-*O*-ethylidene-1,2-*O*-isopropylidene-D-galactose, followed by mild acid hydrolysis. Methylation of D-galactose 3-sulfate and hydrolysis gave only 2,4,6-tri-*O*-methyl-D-galactose, thus proving the position of the sulfate ester.

A number of naturally occurring carbohydrate-containing substances have been found to be composed partly of D-galactosyl units linked at their C-3 position to a variety of substituents. Particularly in glycolipids gangliosides[2] and sulfatides[3] and in milk oligosaccharides,[4] acidic neuraminyl or sulfate ester groups are located specifically at C-3 of D-galactose. In glyco proteins also, neuraminyl residues have been found to be similarly linked.[5] Consequently, it became of special interest to synthesize simple derivatives of D-galactose selectively substituted at C-3. Such derivatives, with clearly established structures, are necessary as reference compounds, not only for the determination of their chemical and physical properties, but also to study their metabolism and the specificity of action of the enzymes neuraminidase and sulfatases.

Selective substitution at C-3 of D-galactose has been previously accomplished in the syntheses of 3-*O*-methyl-D-galactose and of the disaccharide 3-*O*-(-β-D-galactopyranosyl)-D-galactose, using 4,6-*O*-ethylidene-1,2-*O*-isopropylidene-D-galactose as intermediate.[6] Since, however, acid hydrolysis is necessary for the cleavage of acetals, it appeared desirable to attempt to block temporarily positions 1, 2, 4, and 6 in the galactopyranose ring by substituents removable eventually under neutral conditions. This was expected to be advantageous especially for the synthesis of compounds in which the newly formed linkage at C-3 is very sensitive to acid, as in neuraminyl derivatives, or when migration or elimination could possibly occur under acidic or alkaline conditions, as in sulfate esters. Benzyl and benzylidene substituents have been chosen for that purpose because these groups are, generally, easily removable by catalytic hydrogenolysis under neutral conditions in the presence of palladium on charcoal. Thus, benzyl 2-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside (Bz-VIII) has been synthesized and used as a key compound for the synthesis of derivatives of D-galactose substituted at C-3, namely, 3-*O*-methyl-D-galactose and 3-*O*-(-β-D-glucopyranosyl)-D-galactose. Methyl 2-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside (Me-VIII) was also prepared and was used for the synthesis of methyl 3-*O*-(-β-D-glucopyranosyl)-β-D-galactopyranoside. This illustrates an interesting possibility of obtaining disaccharides having the reducing end engaged in glycosidic linkage.

Sulfation of Me-VIII and Bz-VIII has also been accomplished. However, subsequent removal of benzyl and benzylidene substituents could not be done by catalytic hydrogenolysis. A similar stabilization of benzyl groups, when a sulfate ester is present in the same molecule, has been observed before.[7] Removal of the benzyl substituents was also attempted with boron trichloride;[8] it resulted in the loss of the sulfate group.

The preparation of D-galactose 3-sulfate has, however, been accomplished by sulfation of crystalline 4,6-*O*-ethylidene-1,2-*O*-isopropylidene-D-galactose[9] with chlorosulfonic acid in pyridine, followed by mild acid hydrolysis of the acetal groups.[10] The position of the sulfate group at C-3 has been confirmed by methylation, since only 2,4,6-tri-*O*-methyl-D-galactose was detectable in the hydrolysate of the methylated compound.

The condensation of Bz-VIII and Me-VIII with the methyl ester of acetochloroneuraminic acid[11] is being attempted at present.

The syntheses of Bz-VIII and Me-VIII started, respectively, from benzyl β-D-galactopyranoside and methyl β-D-galactopyranoside and proceeded through the following intermediates.[12]

Methyl 3,4-*O*-isopropylidene-β-D-galactopyranoside[13] (Me-I) was obtained in an improved yield (76%) when anhydrous cupric sulfate with a small amount of $H_2SO_4$ was used as catalyst in the reaction of methyl β-D-galactopyranoside with acetone. Under identical

(1) Presented before the Division of Carbohydrate Chemistry at the 124th Meeting of the American Chemical Society, New York, N. Y., Sept 1966.

(2) (a) L. Svennerholm, *J. Lipid Res.*, **5**, 145 (1964), (b) R. Ledeen, *J. Am. Oil Chemists' Soc.*, **43**, 57 (1966).

(3) P. Stoffyn, *ibid.*, 69 (1966).

(4) R. Kuhn, Proceeding of the Fourth International Congress of Biochemistry, Vienna, 1958, Pergamon Press, Inc., New York, N. Y., p 67.

(5) (a) E. H. Eylar and R. W. Jeanloz, *J. Biol. Chem.*, **237**, 1021 (1962); (b) R. W. Jeanloz and A. Closse, *Federation Proc.*, **22**, 538 (1963); (c) R. G. Spiro, *J. Biol. Chem.*, **239**, 567 (1964).

(6) D. H. Ball and J. K. N. Jones, *J. Chem. Soc.*, 905 (1958).

(7) J. R. Turvey and T. P. Williams, *ibid.*, 2119 (1962).

(8) T. G. Bonner, E. J. Bourne, and S. McNally, *ibid.*, 2929 (1960).

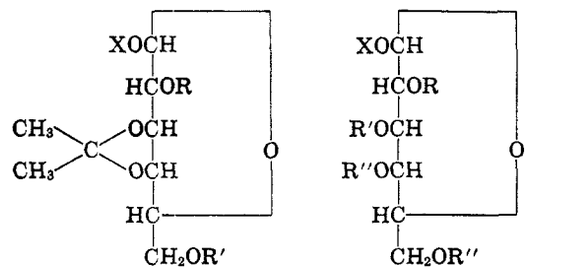
(9) D. H. Ball, *J. Org. Chem.*, **31**, 220 (1966).

(10) Recently, D-galactose 3-sulfate has been prepared by a procedure essentially identical with the one here described [H. Jatzkewitz and G. Nowoczek, *Chem. Ber.*, 100, 1667 (1967)]. The assignment of the structure of the sulfate ester was based on the way of the synthesis and on periodic acid oxidation data which were in agreement with results suggesting a C-3 position for the sulfate group in the minor component of the mixture resulting from random sulfation of D-galactose [J. R. Turvey and T. P. Williams, *J. Chem. Soc.*, 2242 (1963)].

(11) R. Kuhn, P. Lutz, and D. L. MacDonald, *Chem. Ber.*, **99**, 611 (1966).

(12) Derivatives of methyl β-D-galactopyranoside, in which X = methyl, are referred to by the prefix Me; when X = benzyl the prefix used is Bz; for reducing sugars, X = H, no prefix is used.

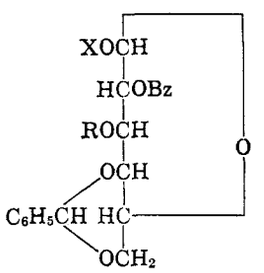
(13) D. J. Bell and S. Williamson, *J. Chem. Soc.*, 1196 (1938).



I, R = R′ = H
II, R = H; R′ = Tr
III, R = Bz; R′ = Tr



IV, R = Bz; R′ = R″ = H
V, R = Bz; R′ = R″ = Me
VI, R = H; R′ = R″ = Me
VII, R = R″ = H; R′ = Me

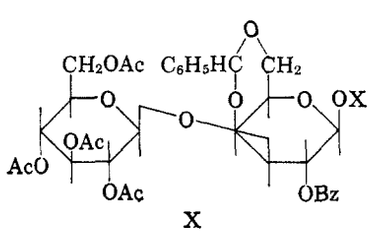


VIII, R = H
IX, R = Me

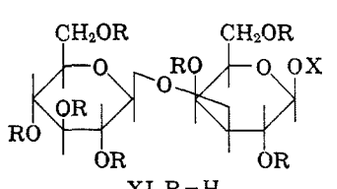
conditions, benzyl 3,4-*O*-isopropylidene-β-D-galactopyranoside (Bz-I) was obtained in 61% yield from benzyl β-D-galactopyranoside. This latter compound, first described by Fisher and Helferich,[14] was prepared in good yield by reacting 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide with benzyl alcohol according to the Reynolds and Evans[15] modification of a Königs–Knorr reaction. Both Me-I and Bz-I were etherified with chlorotriphenylmethane in the usual way. Methyl 3,4-*O*-isopropylidene-6-*O*-trityl-β-D-galactopyranoside[16] (Me-II) was obtained crystalline in 45% yield. Benzyl 3,4-*O*-isopropylidene-6-*O*-trityl-β-D-galactopyranoside (Bz-II) was obtained in good yield also, but did not crystallize. Thin layer chromatography (tlc) showed that triphenylcarbinol still contaminated Bz-II, even after repeated purification by chromatography. Me-II and Bz-II were then converted into the corresponding 2-*O*-benzyl derivatives by a new method inspired by the methylation procedure described by Hakomori,[17] but in which α-bromotoluene was substituted for iodomethane. Thus, methyl 2-*O*-benzyl-3,4-*O*-isopropylidene-6-*O*-trityl-β-D-galactopyranoside (Me-III) was obtained in 87% yield of recrystallized material, whereas benzyl 2-*O*-benzyl-3,4-*O*-isopropylidene-6-*O*-trityl-β-D-galactopyranoside (Bz-III) was obtained in high yield as a syrup. Treatment of Me-III and Bz-III with hot 60% acetic acid removed the isopropylidene and trityl groups giving, respectively, methyl 2-*O*-benzyl-β-D-galactopyranoside (Me-IV) and benzyl 2-*O*-benzyl-β-D-galactopyranoside (Bz-IV). The similarly high yields (73–75%) of recrystallized Bz-IV as well as of Me-IV indicate that, although Bz-III and Bz-II were not obtained in the crystalline state, they were nevertheless quite pure. Confirmation of the position of the benzyl group at C-2 in Bz-IV was obtained by methylation, followed by hydrogenolysis, which gave 3,4,6-tri-*O*-methyl-D-galactose (VI) identical with the product described by Kuhn and Baer.[18] It is interesting to note that of the four possible tri-*O*-methyl-D-galactopyranosides, only the 3,4,6 isomer moves by electrophoresis on paper in borate buffer. This is apparently due to the presence of a vicinal glycol group at C-1 and C-2, which none of the other isomers possess. Thus, a combination of paper electrophoresis and chromatography on thin layer of silica gel[3] allows the complete separation of the four tri-*O*-methyl-D-galactopyranoses.

Both Me-IV and Bz-IV, when reacted with benzaldehyde in the presence of zinc chloride, gave the corresponding crystalline benzylidine derivatives (Me-VIII and Bz-VIII) in fair yield. The structure of Me-VIII and Bz-VIII was established by methylation followed by hydrogenolysis and hydrolysis, giving the known 3-*O*-methyl-D-galactose (VII). For direct comparison, 3-*O*-methyl-D-galactose was prepared from 4,6-*O*-ethylidene-1,2-*O*-isopropylidene-D-galactopyranoside.[6]

Condensation of Bz-VIII with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide was first accomplished by the Reynolds–Evans modification of a Königs–Knorr reaction.[15] The condensation product (Bz-X) was obtained as long needles melting at 167–169°. Catalytic hydrogenolysis of the benzyl and benzylidene groups, followed by deacetylation with barium methoxide, gave the syrupy disaccharide (XI) which was undistinguishable from solabiose[19] on paper chromatograms. Acid hydrolysis of this disaccharide resulted in the liberation of equivalent amounts of glucose and galactose. A better yield was obtained when the condensation of Bz-VIII with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide was carried out in nitromethane in the presence of mercuric cyanide. After hydrogenolysis and deacetylation, the disaccharide was isolated by preparative paper chromatography. It had $[\alpha]^{25}D$ +47° in fair agreement with the value reported for solabiose $[\alpha]^{22}D$ +40.7°.[19] Although XI did not crystallize, it gave a crystalline acetate which, after distillation under vacuum, melted at 71–74°; Kuhn, *et al.*, reported mp 75°.



X



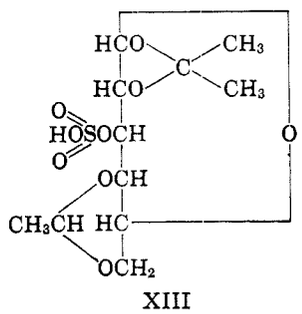
XI, R = H
XII, R = $CH_3$

Condensation of Me-VIII with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide was also carried out either in a modified Königs–Knorr reaction or in the presence of mercuric cyanide in nitromethane. The nonreducing disaccharide (Me-XI), obtained after hydrogenolysis and deacetylation, was isolated by pre-

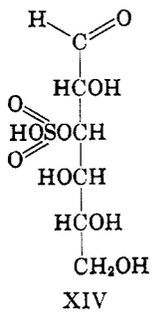
(14) E. Fisher and B. Helferich, *Ann.*, **383**, 68 (1911).
(15) D. D. Reynolds and W. L. Evans, *J. Am. Chem. Soc.*, **60**, 2559 (1938).
(16) D. Grant and A. Holt, *J. Chem. Soc.*, 5026 (1960).
(17) S. Hakomori, *J. Biochem.* (Tokyo), **55**, 205 (1964).
(18) R. Kuhn and H. H. Baer, *Chem. Ber.*, **88**, 1537 (1955).
(19) R. Kuhn, I. Low, and H. Trischmann, *ibid.*, 1492 (1955).

parative paper chromatography. For complete characterization, Me-XI was methylated and the permethylated disaccharide (Me-XII), which crystallized readily, was hydrolyzed. Chromatography of this hydrolyzate on thin layer of silica gel G showed that 2,4,6-tri-*O*-methyl-D-galactose and 2,3,4,6-tetra-*O*-methyl-D-glucose had been liberated, thus giving unequivocal proof of the structure of Me-XI.

4,6-*O*-Ethylidene-1,2-*O*-isopropylidene-D-galactose 3-sulfate (XIII), resulting from the sulfation of 4,6-*O*-ethylidene-1,2-*O*-isopropylidene-D-galactose,[9] was purified using a charcoal column on which the sulfated material was retained strongly and from which it was later eluted with ammonia containing solvent as the readily crystallizing ammonium salt. It is interesting to note that retention on charcoal is a general property of sulfate esters of carbohydrates,[20] including the sulfatides, which has been advantageously used for their isolation.[21] Hydrolysis of XIII with 1% acetic acid for 3 hr[22] gave a mixture of D-galactose and D-galactose 3-sulfate (XIV) as indicated by paper electrophoresis in borate buffer at pH 10. Isolation of XIV was achieved by chromatography on a column of charcoal on which the sulfate ester was retained until eluted with ammonia. Compound XIV was methylated,[23] and chromatography of the hydrolysate of the methylated product on thin layer of silica gel G[3] indicated that it contained only 2,4,6-tri-*O*-methyl-D-galactose.



XIII



XIV

## Experimental Section[24]

**Methyl 3,4-*O*-Isopropylidene-β-D-galactopyranoside (Me-I).**—To a solution of 1.25 ml of $H_2SO_4$ in 1.5 l. of acetone were added 25 g of methyl β-D-galactopyranoside and 75 g of anhydrous cupric sulfate, and the mixture was shaken for 8 hr at room temperature. The solid was collected on a filter and washed with acetone. The filtrate was neutralized with gaseous ammonia, and the precipitated ammonium sulfate was separated by filtration through a pad of Celite analytical filter aid. The filtrate was concentrated under vacuum to a syrup which crystallized. Recrystallization from a mixture of acetone, ether, and hexane afforded 23 g, 76%, of prisms melting at 132–134°, $[\alpha]^{24}D$ + 21° (*c* 1.1, water).

**Methyl 3,4-*O*-Isopropylidene-6-*O*-trityl-β-D-galactopyranoside (Me-II).**—To a solution of 5 g of Me-I in 70 ml of dry pyridine was added 4.75 g of chlorotriphenylmethane. The solution was kept for 18 hr at room temperature and then heated at 70° for 1 hr. After cooling to room temperature, about 1 g of ice was added, the mixture was kept 1 hr and then poured on ice. The semisolid precipitate was collected on a Celite pad, washed with water, and then dissolved on the filter in a mixture of chloroform–methanol (2:1, v/v). The filtered solution was concentrated under vacuum and the residue, dissolved in benzene, was chromatographed on 250 g of silica gel using benzene as eluent. Triphenylcarbinol was eluted first, followed by the product which crystallized in clusters of thick needles. Recrystallization of the crude material (7.7 g) from benzene–ether–hexane afforded 4.6 g (45%) of the trityl ether in the form of prismatic needles melting at 162–164°, $[\alpha]^{25}D$ −20.4° (*c* 1.65, chloroform).

*Anal.* Calcd for $C_{29}H_{32}O_6$: C, 73.09; H, 6.78. Found: C, 73.05; H, 6.61.

**Methyl 2-*O*-Benzyl-3,4-*O*-isopropylidene-6-*O*-trityl-β-D-galactopyranoside (Me-III).**—Sodium hydride (250 mg) (56% in oil) was dissolved with stirring, under a stream of dry nitrogen, in 50 ml of dimethyl sulfoxide at 70°. To this mixture, cooled to 20°, was added, under continued stirring, a solution of 1.0 g of Me-II in 80 ml of dimethyl sulfoxide. After 10 min, 0.6 ml of α-bromotoluene was added dropwise, and the mixture was kept stirring for 0.5 hr. Benzene was added (300 ml), and the solution was washed four times with 1.5 l. of a saturated solution of sodium bicarbonate. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated under vacuum. Crystallization of the residue from hexane gave a total of 1.024 g (87%) of rectangular platelets melting at 170–171°, $[\alpha]^{25}D$ +4.28° (*c* 0.87, chloroform).

*Anal.* Calcd for $C_{36}H_{38}O_6$: C, 76.30; H, 6.78. Found: C, 76.08; H, 6.80.

**Methyl 2-*O*-Benzyl-β-D-galactopyranoside (Me-IV).**—A solution of 971 mg of Me-III in 28 ml of glacial acetic acid was heated on a boiling water bath, and 14 ml of water was added progressively in 1 hr. The solution was evaporated under vacuum and the remaining acid and water were eliminated by repeated codistillation with ethanol–toluene (1:1, v/v). The crystalline residue, dissolved in benzene, was chromatographed on 20 g of silica gel. Triphenylcarbinol was eluted with benzene–ether mixtures, and the desired product was eluted with ether–ethyl acetate. Recrystallization from acetone–hexane gave 368 mg (75%) of diamond-shaped platelets, mp 148–149°, $[\alpha]^{24}D$ +9.24° (*c* 0.73, methanol).

*Anal.* Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.25; H, 7.09.

**Methyl 2-*O*-Benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside (Me-VIII).**—A mixture of 200 mg of Me-IV, 200 mg of freshly fused and pulverized zinc chloride, and 2 ml of benzaldehyde was shaken for 1 hr at room temperature, and the solution was further kept for 24 hr. It was then poured in a beaker containing 40 ml of water and 40 ml of pentane. The microcrystalline precipitate that formed upon stirring was collected on a filter and washed with water and pentane. For purification, the product was dissolved in benzene and the solution was passed through a column of 4 g of neutral Alumina (Woelm activity III). Recrystallization from methanol gave 164 mg, 63%, of needles. The product melted first at 55–60°, then recrystallized, and melted again sharply at 118–119°, $[\alpha]^{24}D$ +22.4° (*c* 0.84, chloroform).

*Anal.* Calcd for $C_{21}H_{26}O_6$: C, 67.64; H, 6.51. Found: C, 67.84; H, 6.44.

**Methyl 2-*O*-Benzyl-4,6-*O*-benzylidene-3-*O*-methyl-β-D-galactopyranoside (Me-IX).**—A suspension of 200 mg of silver oxide in a solution of 150 mg of Me-VIII in 10 ml $CH_3I$ was stirred for 7 hr. Another portion of 200 mg of silver oxide was added, and the mixture was kept stirring for 18 hr. After filtration through a Celite pad, the solution was evaporated to dryness leaving a syrup which crystallized readily. Recrystallization from methanol gave 145 mg of clusters of very fine needles melting at 140–141°, $[\alpha]^{26}D$ +45° (*c* 0.4, chloroform).

*Anal.* Calcd for $C_{22}H_{26}O_6$: C, 68.37; H, 6.78. Found: C, 68.54; H, 6.81.

**Benzyl β-D-Galactopyranoside.**—A mixture of 14.8 g of dry benzyl alcohol, 34.4 g of silver oxide, and 137 g of Drierite in 137 ml of dry, alcohol-free chloroform was stirred for 1 hr in the dark. Then 6.7 g of iodine was added, followed by a solution of 56.7 g of 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide in 206 ml of chloroform which was added dropwise in the course of 1 hr. Stirring was continued for 24 hr. The suspension was filtered through a Celite pad which was rinsed with chloroform. The filtrate was evaporated to a syrup which was dissolved in 350 ml of anhydrous methanol and 40 ml of a

(20) A. Stoffyn and P. Stoffyn, unpublished data.

(21) M. Malone and P. Stoffyn, *Biochem. Biophys. Acta*, **98**, 218, (1965).

(22) S. Peat, J. R. Turvey, M. J. Clancy, and T. P. Williams, *J. Chem. Soc.*, 4761 (1960).

(23) R. Kuhn and H. Trischmann, *Chem. Ber.*, **96**, 284 (1963).

(24) Corrected melting points were determined between glass slides under the microscope. Specific optical rotation values were measured with a 80Q3 O. C. Rudolph & Sons, Inc., photoelectric polarimeter. Silica gel (Davison, grade 950, 60–200 mesh) was used for column chromatography. Thin layer chromatography was done on Silica gel G (E. Merck, Darmstadt). Elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

0.4 *N* solution of barium methoxide in methanol was added at 0°. The solution was kept at 4° for 24 hr. Carbon dioxide was passed through the solution which, after neutralization, was evaporated under vacuum. A solution of the remaining oil in acetone was filtered through Celite to retain inorganic salts and was then applied on a column containing 500 g of silica gel. Elution was carried out with acetone. The crystalline fractions were combined, and the product was crystallized from methanol–ether in the form of needles melting at 106–107°. The melted substance recrystallized on further heating and melted again at 117–118°. By further recrystallization the melting point was raised to 125°, $[\alpha]^{27}D$ −25.3° (*c* 1.2, water). The yield was 60–65%.

**Benzyl 3,4-*O*-Isopropylidene-β-D-galactopyranoside (Bz-I).**—A mixture of 20 g of benzyl β-D-galactopyranoside and 60 g of anhydrous cupric sulfate in 1.2 l. of acetone containing 1 ml of $H_2SO_4$ was shaken for 10 hr. The solid was collected on a filter and washed with acetone. The filtrate was neutralized with $NH_3$, and the precipitated ammonium sulfate was separated by filtration through a pad of Celite. The filtrate was concentrated under vacuum, and the remaining oil was chromatographed on 500 g of silica gel. The product was eluted with chloroform–ether (1:1 v/v) and crystallized in fine needles from acetone–ether. Upon heating the needles changed at 113–115° into a stable rhombic form melting at 123–124°, $[\alpha]^{25}D$ −1.47° (*c* 1.12, chloroform), yield 61%.

*Anal.* Calcd for $C_{16}H_{22}O_6$: C, 61.91; H, 7.01. Found: C, 62.12; H, 7.13.

**Benzyl 3,4-*O*-Isopropylidene-6-*O*-trityl-β-D-galactopyranoside (Bz-II).**—Bz-I (5 g) and chlorotriphenylmethane (4.84 g) were dissolved in 50 ml of pyridine, and the solution was kept at room temperature for 60 hr and then heated at 70° for 1 hr. After cooling, a small piece of ice was added and, after 1 hr, the solution was poured on ice. The semisolid mass was collected on a Celite pad, washed with water, and then dissolved on the filter in chloroform–methanol (2:1). The filtrate was evaporated under vacuum. The residue, dissolved in 200 ml of benzene–petroleum ether (1:1), was chromatographed on 200 g of silica gel. Triphenylcarbinol was eluted with 4 l. of benzene and the trityl ether was eluted with benzene–ether (9:1 and 4:1). After evaporation of the solvents, the syrupy product was further purified by a repeated chromatography under identical conditions, $[\alpha]^{25}D$ −22.4° (*c* 1.08, chloroform), yield about 75%. Examination of this product by thin layer chromatography on silica gel G using benzene–ether (9:1) or ethanol–water (1:1) as solvents indicated that it was still contaminated with a small proportion of triphenylcarbinol.

**Benzyl 2-*O*-Benzyl-3,4-*O*-isopropylidene-6-*O*-trityl-β-D-galactopyranoside (Bz-III).**—With stirring, and under a stream of dry nitrogen, 1.5 g of sodium hydride (56% in oil) was dissolved in 125 ml of dimethyl sulfoxide at 70°. After cooling to 20°, 7.62 g of Bz-II dissolved in 125 ml of dimethyl sulfoxide was added. Then 4.5 ml of α-bromotoluene was added slowly, and the mixture was kept for 20 min at room temperature. The solution was diluted with 500 ml of benzene and washed five times with 2 l. of a saturated solution of sodium bicarbonate. The benzene solution was dried over anhydrous sodium sulfate and evaporated under vacuum. The syrupy residue was chromatographed on 200 g of silica gel. Mixtures of petroleum ether (bp 30–60°) and benzene, followed by pure benzene, slowly eluted the product, $[\alpha]^{24}D$ −29.1° (*c* 0.86, chloroform). Chromatography on thin layer of silica gel, using benzene–ether (9:1) as solvent and anthrone–$H_2SO_4$ as spray reagent, was used to monitor the effluent of the column. Fractions containing only Bz-III and migrating much faster than the starting material were combined and evaporated to dryness giving the syrupy product in a 79–89% yield.

**Benzyl 2-*O*-Benzyl-β-D-galactopyranoside (Bz-IV).**—To a solution of 5 g of Bz-III in 10 ml of glacial acetic acid at 100°, 5 ml of water was added slowly. The mixture was kept at 100° for 1 hr. The liberated triphenylcarbinol was collected on a filter, and the filtrate was evaporated under vacuum; the remaining water and acid were codistilled with toluene–ethanol (1:1). The crystalline residue was recrystallized from benzene–hexane giving 1.72 g of very small needles melting at 138–139°. Chromatography of the mother liquors on 20 g of silica gel, with benzene as solvent, gave an additional 0.32 g of product: total yield 73%, $[\alpha]^{26}D$ −3.48° (*c* 0.79, chloroform).

*Anal.* Calcd for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71. Found: C, 66.74; H, 6.87.

**Benzyl 2-*O*-Benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside (Bz-VIII).**—A mixture of 200 mg of Bz-IV and 250 mg of freshly fused and pulverized zinc chloride in 2 ml of benzaldehyde was shaken at room temperature for 1 hr. The homogeneous solution was further kept for 24 hr, poured in 100 ml of water, and shaken with 100 ml of pentane. The crystalline precipitate was collected on a filter, washed with water and pentane, and dried. The product, in solution in benzene, was passed through a column (15 × 2 cm) of neutral alumina (Woehlm activity III). After evaporation of the solvent, the residue crystallized from methanol in clusters of long needles changing in a few hours into clusters of very small needles melting at 143.5–144°. The yield was 150 mg, 60%, $[\alpha]^{25}D$ −10.4° (*c* 0.68, chloroform).

*Anal.* Calcd for $C_{27}H_{28}O_6$: C, 72.30; H, 6.29. Found: C, 72.05; H, 6.22.

**Benzyl 2-*O*-Benzyl-4,6-*O*-benzylidene-3-*O*-methyl-β-D-galactopyranoside (Bz-IX).**—A mixture of 50 mg of Bz-VIII and 200 mg of silver oxide in 3 ml of iodomethane was stirred at room temperature for 7 hr. Another portion of 200 mg of silver oxide was added, and stirring was continued for 15 hr. The slurry was filtered through a Celite pad, and evaporation of the filtrate left a crystalline residue. Recrystallization from methanol gave 37 mg of very long fine needles melting at 159–160°, $[\alpha]^{26}D$ −3.3° (*c* 0.9, chloroform).

*Anal.* Calcd for $C_{28}H_{30}O_6$: C, 72.70; H, 6.54. Found: C, 72.96; H, 6.73.

**3-*O*-Methyl-D-galactose (VII). A. From Bz-IX.**—Bz-IX (27 mg) in solution in 8 ml of ethanol was hydrogenated at atmospheric pressure over 50 mg of 5% palladium on charcoal. After filtration and evaporation of the solvent, 3-*O*-methyl-D-galactose was obtained as a syrup. It was characterized by its electrophoretic migration on paper in borate buffer at pH 10 ($M_{glucose}$ 0.64–0.66).[25]

**B. From Me-IX.**—Hydrogenation of 50 mg of Me-IX, under the same conditions as indicated above, gave a syrupy material which was shown to be homogeneous by tlc on silica gel G with acetone as solvent, $R_f$ 0.45. For comparison, methyl 6-*O*-methyl-α-D-galactopyranoside had $R_f$ 0.43. The material was then hydrolyzed for 18 hr at 100° with 2 ml of 2 *N* $H_2SO_4$. The solution was passed through a column containing 8 ml of Amberlite CG-45 acetate. Evaporation of the effluent left a syrup which had $M_{glucose}$ 0.64–0.66, in borate buffer at pH 10. For reference, 3-*O*-methyl-D-galactose was prepared by methylation of crystalline 4,6-*O*-ethylidene-1,2-*O*-isopropylidene-D-galactose with $CH_3I$ and $Ag_2O$ in the usual way, followed by hydrolysis of the acetal groups with 2 *N* $H_2SO_4$. 3-*O*-Methyl-D-galactose so obtained was identical with the products described above.

**3,4,6-Tri-*O*-methyl-D-galactose (VI).**—A suspension of 50 mg of Bz-IV and 200 mg of silver oxide in 10 ml of $CH_3I$ was stirred for 4 hr. Another portion of 200 mg of silver oxide was added, and stirring was continued for 18 hr. The mixture was filtered through a Celite pad, and the syrupy residue, obtained by evaporation of the filtrate, was methylated again as described. The syrupy material in solution in 20 ml of methanol was then hydrogenated for 24 hr at atmospheric pressure over 100 mg of 5% palladium on charcoal. This operation was repeated over a fresh portion of catalyst, and after filtration and evaporation, the syrup was examined by chromatography on Whatman No. 1 paper using the upper phase of 1-butanol–ethanol–water (5:1:4) as solvent and aniline phthalate as spray reagent. This showed that the main product had a migration identical with the one of 2,3,4-tri-*O*-methyl-D-galactose and was contaminated by small amounts of dimethyl-D-galactoses. Compound VI was purified by preparative chromatography on Whatman 3MM paper in the above-mentioned solvent system. Chromatography on thin layer of silica gel G with acetone–water–concentrated ammonium hydroxide (250:3:1.5) as solvent, and aniline phthalate as spray reagent, indicated that the material had an $R_f$ value almost undistinguishable from the one of 2,3,4-tri-*O*-methyl-D-galactose but different from the $R_f$ value of the 2,4,6 and 2,3,6 isomers. By paper electrophoresis in borate buffer at pH 10, VI had $M_{glucose}$ of 0.18 and was thus different from the other three isomeric tri-*O*-methyl-D-galactoses which do not migrate under these conditions.

**3-*O*-(-β-D-Glucopyranosyl)-D-galactose (XI). A. By Königs-**

(25) H. Bouveng and B. Lindberg, *Acta. Chem. Scand.*, **10**, 1283 (1956).

**Knorr.**—A mixture of 75 mg of Bz-VIII, 165 mg of powdered Drierite, 60 mg of silver oxide, and 0.4 ml of ethanol-free chloroform was stirred in the dark for 1 hr. Then 8 mg of iodine was added and, under continuous stirring, a solution of 70 mg of tetra-*O*-acetyl-α-D-glucopyranosyl bromide in 0.3 ml of chloroform was added progressively in 1 hr. The mixture was kept stirring for 24 hr and was then filtered through a Celite pad. The syrup left upon evaporation of the solvent crystallized when a small amount of methanol was added. Crystallization from methanol gave 36 mg of starting material as clusters of small needles. By concentration of the mother liquors 27 mg of Bz-X was obtained as very long and fine needles melting at 167–169, $[\alpha]^{26}D$ 0.0° (*c* 0.7, chloroform).

*Anal.* Calcd for $C_{41}H_{46}O_{15}$: C, 63.1; H, 5.95. Found: C, 63.2; H, 6.0.

A solution of 10 mg of this material in 1 ml of methanol containing a catalytic amount of barium methoxide was kept at 4° for 24 hr. After deionization by filtration through a column containing 2 ml of each Amberlite CG 45 acetate and Dowex 50 ($H^+$) and evaporation to dryness, the syrupy residue was hydrogenated in ethanol for 24 hr at room temperature and atmospheric pressure in the presence of 50 mg of 5% palladium on charcoal. After filtration and evaporation of the solvent, the syrupy disaccharide XI had $R_{glucose}$ 0.41 when chromatographed on Whatman No. 1 paper in 1-butanol–pyridine–water (10:3:3). After hydrolysis with 2 ml of 2 *N* $H_2SO_4$ in a sealed tube at 100° for 8 hr and deionization with Amberlite CG 45 acetate, paper chromatography indicated that the disaccharide had been split liberating equal amounts of glucose and galactose.

**B. In Nitromethane with Mercuric Cyanide.**—A solution of 100 mg of Bz-VIII in 4 ml of nitromethane and 3 ml of benzene was made anhydrous by distillation of 3 ml of solvent. Then the temperature was maintained at 70°, and 55 mg of mercuric cyanide and 91 mg of tetra-*O*-acetyl-α-D-glucopyranosyl bromide were added with stirring. The solution was kept for 20 hr at 70°, diluted with 10 ml of benzene, and washed with cold saturated sodium bicarbonate and water, dried over anhydrous sodium sulfate, and evaporated. Tlc on silica gel G using benzene–ether (4:1) as solvent showed that the product was a mixture of starting material and of the disaccharide Bz-X obtained above. The whole mixture was deacetylated with barium methoxide and then hydrogenated on palladium–charcoal as described above. Chromatography on Whatman No. 1 paper indicated the presence of the disaccharide with $R_f$ 0.41 and of glucose and galactose. The disaccharide was isolated by preparative chromatography on a sheet of Whatman No. 3MM paper in 1-butanol–pyridine–water (10:3:3) as solvent. The zone of the paper containing the disaccharide was cut out, and the sugar was recovered by washing the paper with 50% methanol. The syrupy product weighed 36 mg, $[\alpha]^{25}D$ +47° (*c* 1.05, water). A solution of 20 mg of this product in 0.3 ml of pyridine and 0.3 ml of acetic anhydride was kept 24 hr at room temperature and was then poured on ice. The syrup, which had separated, was extracted with 5 ml of chloroform, and the solution was washed with saturated copper sulfate and sodium bicarbonate. After drying over $Na_2SO_4$ and evaporation of the solvent, the residue was distilled in a microsublimator. The syrup, which had distilled at a bath temperature of 270° and under a pressure of 0.2 mm, crystallized slowly. It melted at 71–74°.

**Methyl 3-*O*-(-β-D-Glucopyranosyl)-β-D-galactopyranoside (Me-XI).**—Under experimental conditions essentially identical with those described above, 300 mg of Me-VIII was treated with tetra-*O*-acetyl-α-D-glucopyranosyl bromide in nitromethane with mercuric cyanide as catalyst. The crude condensation product was deacetylated and hydrogenolyzed. Paper chromatography indicated the presence of glucose, methyl β-D-galactopyranoside, and the disaccharide (Me-XI) having $R_{glucose}$ 0.74 in 1-butanol–pyridine–water (10:3:3). Me-XI, isolated by preparative paper chromatography in the same solvent system, was obtained in a 23% yield as a syrup, $[\alpha]^{25}D$ +8.3° (*c* 0.6, methanol). It was characterized by methylation as follows. The dry syrup (71 mg), dissolved in 2 ml of dimethyl sulfoxide, was added to a solution of 10 mg of NaH in 3 ml of dimethyl sulfoxide, previously prepared by stirring at 70° for 1 hr and maintained at 20°. Then 0.5 ml of $CH_3I$ was added slowly, and after stirring for 0.5 hr the solution was diluted with 30 ml of water; the excess of iodomethane was eliminated by bubbling nitrogen through the solution which was then filtered through a column (3 × 1.2 cm) of Norit A–Celite 535 (2:1, w/w) prepared in water. Washing with water and methanol eluted the solvents, salts, and by-products of the reaction. The methylated carbohydrate was then eluted with chloroform–methanol (2:1) and crystallized readily in long needles. After recrystallization from hexane, 55 mg of product was obtained: mp 95–97°, $[\alpha]^{24}D$ −7.4° (*c* 0.6, chloroform).

*Anal.* Calcd for $C_{22}H_{38}O_{11}$: C, 52.84; H, 8.43; O, 38.72; $OCH_3$, 54.6. Found: C, 52.77; H, 8.28; O, 38.83; $OCH_3$, 55.4.

The methylated disaccharide was hydrolyzed with 4 ml of 2 *N* $H_2SO_4$ at 100° for 16 hr. After deionization with Amberlite CG-45 acetate, the solution was evaporated, and the residue was chromatographed on thin layer of silica gel G using acetone–water–ammonia (250:3:1.5) as solvent system and aniline phthalate as spray reagent. This indicated, by comparison with authentic standards, that the hydrolysate contained 2,4,6-tri-*O*-methyl-D-galactose and 2,3,4,6-tetra-*O*-methyl-D-glucose.

**D-Galactose 3-Sulfate (XIV).**—A 10% v/v solution (1 ml) of chlorosulfonic acid in alcohol-free chloroform was added dropwise to a stirred solution, cooled to −15°, of 50 mg of crystalline 4,6-*O*-ethylidene-1,2-*O*-isopropylidene-D-galactose[9] in 3 ml of dry pyridine. Stirring was continued for 1 hr at room temperature. The mixture was then cooled again to −15°, and 1 drop of water was added. After 1 min, the mixture was diluted with water to 30 ml. The solution was evaporated partially under vacuum to eliminate chloroform, and the clear solution was loaded onto a column (6 cm × 1.2 mm diameter) containing a mixture of Norit A–Celite 535 (2:1, w/w) prepared in water. Elution was subsequently carried out with 50 ml each of water, water–methanol (50:50), methanol, and methanol containing 10% concentrated ammonium hydroxide. Upon evaporation to dryness under vacuum, this last fraction left a residue crystallizing in the form of rosettes of needles which was redissolved readily in 5 ml of chloroform–methanol (2:1) leaving a small insoluble residue of inorganic matter. The solution was filtered through a Celite pad and evaporated to dryness under a stream of nitrogen leaving a crystalline residue weighing 44.5 mg. When chromatographed on thin layer of silica gel G using 1-propanol–water–concentrated ammonium hydroxide (160:26:30) as solvent, and anthrone–$H_2SO_4$ as spray reagent, the sulfated compound (XIII) had a migration value of 0.6 compared to the starting material. Hydrolysis of 172 mg of the above material with 15 ml of 1% aqueous acetic acid for 3 hr at 100° in a sealed tube, followed by evaporation of the solvent under vacuum and drying in a desiccator over NaOH, left a glassy residue which was shown to be a mixture of D-galactose and of D-galactose 3-sulfate (XIV) ($M_{glucose}$ 1.30–1.35) by electrophoresis in borate buffer pH 10 on Whatman paper No. 3MM. D-Galactose 3-sulfate was separated by dissolving this mixture in water and applying on a charcoal–Celite column from which galactose was eluted with water and galactose 3-sulfate with 2 *N* $NH_4OH$.

**Methylation of D-Galactose 3-Sulfate.**—A solution of 150 mg of XIV in 2.5 ml of dimethyl sulfoxide was diluted with 2.5 ml of *N*,*N*-dimethyl formamide, and the mixture was cooled to 0° and stirred under a stream of dry nitrogen. Pulverized BaO (0.85 g) and $Ba(OH)_2 \cdot 8H_2O$ (0.85 g) were added. Then 1.75 ml of dimethylsulfate was added dropwise. The mixture was kept stirring 24 hr at room temperature. After decomposition of the excess of the dimethyl sulfate by stirring for 0.5 hr at room temperature with 10 ml of concentrated $NH_4OH$, the methylated product was extracted with 20 ml of chloroform and the chloroform solution was washed with a saturated aqueous solution of NaCl until neutral. The chloroform extract was dried over $Na_2SO_4$ and evaporated to dryness under vacuum. The residue weighed 88 mg. A portion of 30 mg of this product was hydrolyzed in a sealed tube with 2 ml of 2 *N* $H_2SO_4$ at 100° for 18 hr. The solution was deionized by passage through a column containing 6 ml of Amberlite CG-45 acetate and then evaporated to dryness. The residue was chromatographed on thin layer of silica gel G with acetone–water–concentrated $NH_4OH$ (250:3:1.5) and compared with authentic samples of 2,3,4-, 2,4,6-, 2,3,6-, and 3,4,6-tri-*O*-methyl-D-galactoses. Spraying with aniline phthalate showed that 2,4,6-tri-*O*-methyl-D-galactose only resulted from the methylation of D-galactose 3-sulfate.

**Registry No.**—Me-I, 14897-47-3; Bz-I, 14897-51-9; Me-II, 14897-52-0; Bz-II, 15038-68-3; Me-III, 14897-

51-1; Me-IV, 15038-69-4; Bz-IV, 15038-70-7; Me-VIII, 15038-71-8; Bz-VIII, 14897-54-2; Me-IX, 14897-55-3; Bz-IX, 14897-56-4; Bz-X, 15038-75-2; Me-XI, 15038-72-9; XI, 15038-73-0; benzyl β-D-galactopyranoside, 14897-46-2.

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# Chlorination of Unsymmetrical Benzylic Sulfides with N-Chlorosuccinimide[1]

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The chlorination of eight unsymmetrical benzylic sulfides with N-chlorosuccinimide has been investigated. The resulting mixtures of α-chloro sulfides have been analyzed using nmr spectrometry. The results of these internal competitions are correlated by the Hammett treatment: $\rho$ for the reaction is 1.05 ± 0.04.

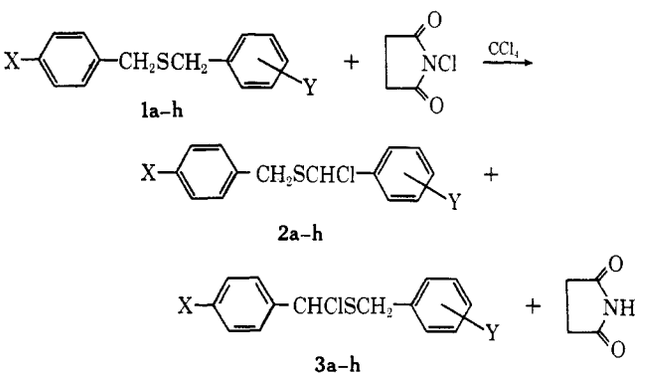
The reaction between benzylic sulfides and N-chlorosuccinimide (NCS) in carbon tetrachloride has previously been shown[2,3] to yield α-chloro sulfides, with no cleavage or ring halogenation. Chlorination of benzyl *p*-chlorobenzyl sulfide (**1d**) with NCS produced a mixture of the two α-chloro sulfides, benzyl α,*p*-dichlorobenzyl sulfide (**2d**) and α-chlorobenzyl *p*-chlorobenzyl sulfide (**3d**); the major component of the mixture was chloro sulfide **2d**. A more complete study of such internal competitive chlorination has now been performed on a series of unsymmetrical benzylic sulfides.

Sulfides **1a–h** were synthesized from the appropriate benzylic halides and potassium mercaptides in ethanol. Nmr spectra of the sulfides were consistent with their structure; satisfactory elemental analyses were obtained on those which have not been previously reported.

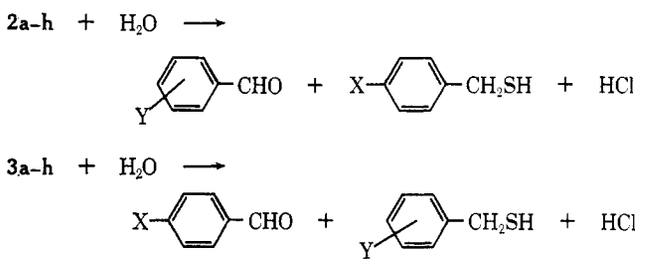
Chlorination of each of the sulfides with NCS at room temperature in carbon tetrachloride afforded a mixture of α-chloro sulfides **2** and **3** (Scheme I). The nmr spectra of these mixtures displayed in addition to aromatic multiplets two singlets corresponding to the methinyl hydrogens. The methylene protons of the α-chloro sulfide products are rendered nonequivalent by the asymmetric center at the site of chlorination; they appear in these spectra as two doublets of doublets.

The relative amounts of **2** and **3** in these mixtures was generally assessed by evaluation of the relative areas of the methinyl hydrogen singlets. These peaks appear in the region of 5.65–5.8 ppm and are shifted downfield by 2.2–2.3 ppm relative to the methylene groups of the starting sulfides.[4] The methinyl singlets of the products resulting from the chlorination of **1a** and **1b** were not resolved by the 60-Mc spectrometer employed. The relative amounts of chloro sulfides in these product mixtures was determined by evaluation of the relative areas of the singlets due to the methyl groups.

SCHEME I




| | Ratio 2:3[a] |
|---|---|
| a, X = H, Y = *p*-$OCH_3$ | 0.51 |
| b, X = H, Y = *p*-$CH_3$ | 0.75 |
| c, X = H, Y = *m*-$CH_3$ | 0.91 |
| d, X = H, Y = *p*-Cl | 1.6 |
| e, X = H, Y = *m*-F | 2.1 |
| f, X = Cl, Y = *p*-CN | 3.0 |
| g, X = Cl, Y = *m*-$NO_2$ | 3.5 |
| h, X = Cl, Y = *p*-$NO_2$ | 4.4 |




[a] Averaged values of several traces of the nmr spectra. Peak areas were determined using a Keuffel and Esser planimeter, Model 620005.

The identity of the predominant component of each mixture of α-chloro sulfides was established by hydrolysis. Aldehydes, produced in the hydrolyses, were identified by examination of the nmr spectra and augmentation with authentic samples. The predom-

(1) Presented in part at the Southeastern Regional Meeting of the American Chemical Society, Louisville, Ky., Oct 1966.

(2) D. L. Tuleen and T. B. Stephens, *Chem. Ind.* (London), 1555 (1966).

(3) D. L. Tuleen and V. C. Marcum, *J. Org. Chem.*, **32**, 204 (1967).

(4) A shielding constant of 2.53 for chlorine has been reported for disubstituted methylenes: R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1964, p 87.