[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY AND CHEMOTHERAPY, EXPERIMENTAL BIOLOGY AND MEDICINE INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

The Synthesis of 1,5:3,6-Dianhydro-D-galactitol (D-Neogalactide)

BY HEWITT G. FLETCHER, JR., AND C. S. HUDSON

While various optically active dianhydrides of glucitol,[1] mannitol[2] and iditol[3] have been reported in the literature in recent years and while the older literature records an amorphous dianhydrogalactitol (dulcide[4]) which was prepared from galactitol and is therefore optically inactive either by virtue of meso symmetry or because it is racemic, no optically active dianhydride of galactitol has been reported. The recent synthesis of 1,5-anhydro-D-galactitol[5] in this Laboratory through the reductive desulfurization of 2′-naphthyl 1-thio-β-D-galactopyranoside tetraacetate with Raney nickel offered an attractive path for the synthesis of an optically active dianhydrogalactitol of readily demonstrable structure. This synthesis has now been carried out.

The selective monotosylation of 1,5-anhydro-D-galactitol (I) was readily accomplished, a monotosyl-1,5-anhydro-D-galactitol being isolated as its tribenzoate in 62% yield. The well-established selectivity of tosyl chloride for primary, as distinguished from secondary, hydroxyl groups[6] together with the unusually high yield obtained in this instance justify the assumption that the ester is 2,3,4-tribenzoyl-6-tosyl-1,5-anhydro-D-galactitol (II). As was originally pointed out by Oldham and Rutherford,[7] distinction may usually be made between primary tosyl groups and secondary ones by virtue of the fact that substances containing the former group react almost quantitatively to form an iodo derivative when heated with sodium iodide in acetone solution at 100° for two hours. Substances containing secondary tosyl groups on the other hand are, in general, essentially unaffected under these conditions. Although this generalization is of unquestioned utility in the sugar group, a few exceptions to it are well known. Thus a primary tosyl group attached to carbon one of a ketose, as in 1-tosyl-2,3:4,6-diisopropylidene-L-sorbose,[8] is quite stable toward sodium iodide in acetone at 100° while the secondary tosyl groups in what has since been proved[2a,b] to be 2,5-ditosyl-1,4:3,6-dianhydro-D-mannitol were found by Brigl and Grüner[9] to react quantitatively with sodium iodide when heated in acetone solution at 110° for three and one-half hours. Examination of the literature reveals a wide difference in the reactivity of various primary tosyl groups toward sodium iodide. Thus, while methyl 2,3,4-triacetyl-6-tosyl-β-D-glucoside,[10] methyl 2,3,4-tribenzoyl-6-tosyl-α-D-mannoside[11] and methyl 2,3,4-tribenzoyl-6-tosyl-α-D-altroside[12] all react almost quantitatively upon treatment with sodium iodide in acetone under relatively mild conditions, various derivatives of D-galactose having tosyl groups in position six are surprisingly resistant to this reagent. As instances may be cited methyl 2-acetyl-3,4-isopropylidene-6-tosyl-α-D-galactoside[13] which gave only 67% yield of the corresponding iodide after heating in acetone solution with sodium iodide at 120° for six hours; 1,2:3,4-diisopropylidene-6-tosyl-D-galactose,[14] after thirty-six hours at 105–110°, gave an 85% yield of the desired iodide. To cite substances which are very closely related to the 2,3,4-tribenzoyl-6-tosyl-1,5-anhydro-D-galactitol in question it may be noted that methyl 2,3,4-tribenzoyl-6-tosyl-β-D-galactoside[15] was heated at 100° in acetone solution with sodium iodide for forty hours to give a 90% yield of the 6-iodo derivative while methyl 6-tosyl-α-D-galactoside[16] gave a yield of only approximately 50% when heated at 140° for five hours. In the light of these recorded facts it is not surprising that the 2,3,4-tribenzoyl-6-tosyl-1,5-anhydro-D-galactitol prepared in the course of the present research was found to give but a 23% yield of sodium *p*-toluenesulfonate when heated in acetone solution with sodium iodide at 100° for two hours (the conditions recommended by Oldham and Rutherford[7]). While this yield is well above that usually found for substances containing only secondary tosyl groups it falls far short of the nearly quantitative yields found for the majority of primary tosyl derivatives and it would appear that considerable caution ought to be exercised in using the Oldham–Rutherford test to distinguish between primary

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[1] (a) R. C. Hockett, H. G. Fletcher, Jr., E. L. Sheffield and R. M. Goepp, Jr., THIS JOURNAL, **68**, 927 (1946); (b) R. Montgomery and L. F. Wiggins, *J. Chem. Soc.*, 390 (1946).

[2] (a) L. F. Wiggins, *J. Chem. Soc.*, 4 (1945); (b) R. C. Hockett, H. G. Fletcher, Jr., E. L. Sheffield, R. M. Goepp, Jr., and S. Soltzberg, THIS JOURNAL, **68**, 930 (1946); (c) R. C. Hockett and E. L. Sheffield, *ibid.*, **68**, 937 (1946).

[3] (a) H. G. Fletcher, Jr., and R. M. Goepp, Jr., THIS JOURNAL, **68**, 939 (1946); (b) L. F. Wiggins, *J. Chem. Soc.*, 1403 (1947).

[4] P. Carré, *Compt. rend.*, **139**, 637 (1904).

[5] H. G. Fletcher, Jr., and C. S. Hudson, THIS JOURNAL, **70**, 310 (1948).

[6] P. A. Levene and A. L. Raymond, *J. Biol. Chem.*, **102**, 317 (1933); R. C. Hockett and M. L. Downing, THIS JOURNAL, **64**, 2463 (1942).

[7] J. W. H. Oldham and J. K. Rutherford, *ibid.*, **54**, 366 (1932).

[8] T. S. Gardner and J. Lee, *J. Org. Chem.*, **12**, 733 (1947).

[9] P. Brigl and H. Grüner, *Ber.*, **67**, 1582 (1934).

[10] J. Compton, THIS JOURNAL, **60**, 395 (1938).

[11] W. T. Haskins, R. M. Hann and C. S. Hudson, *ibid.*, **68**, 628 (1946).

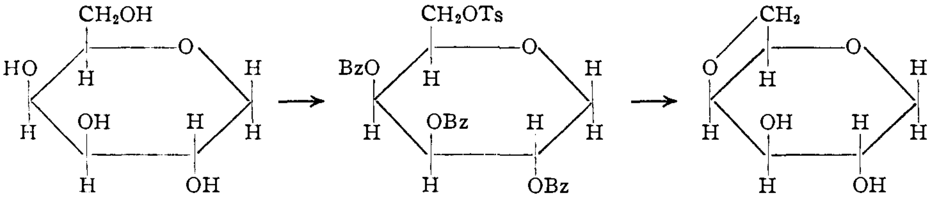
[12] D. A. Rosenfeld, N. K. Richtmyer and C. S. Hudson, *ibid.*, **70**, 2201 (1948).

[13] B. Iselin and T. Reichstein, *Helv. Chim. Acta*, **29**, 508 (1946).

[14] A. L. Raymond and E. F. Schroeder, THIS JOURNAL, **70**, 2785 (1948).

[15] A. Müller, *Ber.*, **64**, 1820 (1931).

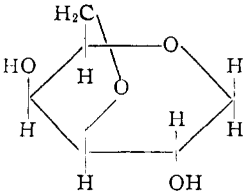
[16] H. B. MacPhillamy and R. C. Elderfield, *J. Org. Chem.*, **4**, 150 (1939).



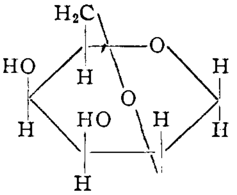
I
1,5-Anhydro-D-galactitol

II
2,3,4-Tribenzoyl-6-tosyl-1,5-anhydro-D-galactitol (Ts = *p*-toluenesulfonyl; Bz = benzoyl)

III
1,5:4,6-Dianhydro-D-galacitol



IV
1,5:3,6-Dianhydro-D-galactitol



V
1,5:2,6-Dianhydro-D-galactitol

and secondary tosyl derivatives in the galactose series.

Examination of the structure of 2,3,4-tribenzoyl-6-tosyl-1,5-anhydro-D-galactitol (II) shows that the alkaline treatment could conceivably convert it to one or more of three different dianhydrides. On steric grounds, formation of the 1,5:4,6-dianhydride (III) and the 1,5:2,6-dianhydride (V) is rather unlikely. The 1,5:3,6-dianhydro-D-galactitol (IV) is sterically acceptable and, indeed, bears a close resemblance to methyl 3,6-anhydro-α-D-galactopyranoside which has been synthesized from methyl 6-tosyl-α-D-galactoside.[17]

Treatment of 2,3,4-tribenzoyl-6-tosyl-1,5-anhydro-D-galactitol with sodium methoxide readily gave in 90% yield a dianhydride which proved to be unattacked by periodate and therefore possesses structure IV since, of the three possible dianhydrides, only this lacks a pair of vicinal hydroxyl groups.[18] By analogy with 1,5:3,6-dianhydro-D-mannitol which was designated as neomannide by Hockett and Sheffield[2c] the new dianhydride may be called D-neogalactide.

The 1,5:3,6-dianhydro-D-galactitol was further characterized through the crystalline dibenzoate and ditosylate; attempts to obtain a crystalline bis-(N-phenylcarbamate) have thus far failed.

Acknowledgment.—The authors are indebted to Mrs. Margaret M. Ledyard and Mrs. Evelyn G. Peake for combustion analyses.

Experimental[19]

2,3,4-Tribenzoyl-6-tosyl-1,5-anhydro-D-galactitol (II).—1,5-Anhydro-D-galactitol, m. p. 113–114° and specific rotation +78.0° in water (*c*, 0.83), was prepared through the reductive desulfurization of 2′-naphthyl 1-thio-β-D-galactopyranoside tetraacetate by Raney nickel in a manner similar to that described recently.[5] The anhydride (3.429 g., 0.0209 mole), dissolved in 20 ml. of anhydrous pyridine, was cooled to 0° and with vigorous stirring treated over the course of twenty minutes with a solution of 3.982 g. (0.0209 mole) of tosyl chloride in 15 ml. of pyridine. After one hour at 0°, one hour at room temperature and one-half hour at 40°, the reaction mixture was cooled to 0° and treated with 10 ml. (0.0862 mole) of benzoyl chloride over the course of fifteen minutes; it was then held a further ten minutes at 0° and finally at 50° for thirty minutes. The resulting solution was diluted with chloroform and washed successively with ice water, cold 3 *N* sulfuric acid and saturated aqueous sodium bicarbonate. Water was removed with sodium sulfate and the solution then filtered through decolorizing carbon. Removal of solvent *in vacuo* at 55° (bath) gave a sirup which was dissolved in 20 ml. of absolute alcohol; during concentration of this solution *in vacuo* at 55° crystallization began spontaneously. The resulting magma was dissolved in 800 ml. of ethanol (95%) by prolonged boiling, the solution concentrated to a volume of approximately 300 ml., seeded while warm and then left at room temperature. A feathery mass of needles (8.12 g., 62%) melting at 179–184° was obtained. Recrystallized once from a mixture of 4 parts of benzene and 1.2 parts of pentane and then twice from 5 parts of a 1:1 mixture of 2-butanone and 95% ethanol, the pure material melted at 187° and rotated +165° in chloroform (*c*, 1.293).

2,3,4-Tribenzoyl-6-tosyl-1,5-anhydro-D-galactitol is soluble in acetone, ethyl acetate and hot alcohol, insoluble in cold alcohol, pentane and water.

Anal. Calcd. for $C_{34}H_{30}O_{10}S$: C, 64.75; H, 4.80; S, 5.08. Found: C, 64.95; H, 5.06; S, 4.75.

Reaction of 2,3,4-Tribenzoyl-6-tosyl-1,5-anhydro-D-galactitol with Sodium Iodide in Acetone Solution.—The procedure of Oldham and Rutherford[7] was employed. 2,3,4-Tribenzoyl-6-tosyl-1,5-anhydro-D-galactitol (0.9940 g.) and 1.0413 g. of sodium iodide were dissolved in 4.5 ml. of dry acetone and heated in a sealed tube at 100° for two hours. After cooling, the flaky precipitate was removed by filtration and washed with acetone; 70.4 mg. (23% yield). In a similar experiment a 21% yield of sodium *p*-toluenesulfonate was obtained. From the mother liquor 0.68 g. of 2,3,4-tribenzoyl-6-tosyl-1,5-anhydro-D-galactitol, representing 68% of the starting material, was recovered.

1,5:3,6-Dianhydro-D-galactitol (IV).—Twenty grams (0.0317 mole) of pure 2,3,4-tribenzoyl-6-tosyl-1,5-anhydro-D-galactitol, dissolved in 58 ml. of U. S. P. chloroform was poured into 200 ml. of anhydrous methanol in

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[17] W. N. Haworth, J. Jackson and F. Smith, *J. Chem. Soc.*, 630 (1940).

[18] As far as the authors are aware only three substances possessing vicinal hydroxyl groups have been found to be resistant to the action of periodate: D-glucosan<1,4>β<1,6> [R. J. Dimler, H. A. Davis and G. E. Hilbert, THIS JOURNAL, **68**, 1377 (1946)], 1,2,3,4-tetraacetylmesoinositol [G. Dangschat, *Naturwissenschaften*, **30**, 146 (1942)] and diphenylacenaphthenediol [R. Criegee, *Sitzber. Ges. Beförder. ges. Naturw. Marburg*, **69**, 25 (1934)].

[19] Melting points were taken with an Anschütz-type thermometer completely immersed in the bath liquid. Rotations are specific rotations for sodium light at 20°, concentration being expressed in g. of substance per 100 ml. of solution.

which 3.0 g. (0.130 mole) of sodium had previously been dissolved. After three days at room temperature (25°) the solution was made neutral to phenolphthalein with 1 *N* sulfuric acid and then concentrated *in vacuo*, the residue being held at 55° and a pressure of 1.0 mm. to remove the major part of the methyl benzoate. The white, crystalline mass was then extracted with four successive 400-ml. portions of boiling ethyl acetate. The combined extracts were concentrated to a volume of approximately 80 ml. and refiltered to remove a slight turbidity. On cooling, the filtrate deposited radial masses of needles amounting to 3.63 g.; a further 0.55 g. of material was obtained on concentration of the mother liquor, giving a total yield of 90%. Recrystallized thrice from ethyl acetate and once from a mixture of 2-butanone and benzene the 1,5:3,6-dianhydro-D-galactitol formed either hair-like needles or feathery masses melting at 145–146° and showing in water a rotation of +40.2° (*c*, 2.054).

The dianhydride is readily soluble in water, alcohol, hot ethyl acetate and hot 2-butanone; insoluble in benzene and pentane. A sample was found to sublime slowly at a pressure of approximately 1 mm. and a temperature of 117°.

Anal. Calcd. for $C_6H_{10}O$: C, 49.31; H, 6.90. Found: C, 49.47; H, 7.07.

The Stability of 1,5:3,6-Dianhydro-D-galactitol toward Sodium Metaperiodate.—The technique of Jackson and Hudson[20] was employed. 1,5:3,6-Dianhydro-D-galactitol (0.2047 g.) was dissolved in a few ml. of water, treated with 5 ml. of approximately 0.45 *M* sodium metaperiodate solution and the mixture diluted with water to 25.0 ml. After seventeen hours at room temperature (27°) a 5.0-ml. aliquot was titrated for acid and oxidant; 0.07 ml. of 0.1 *N* alkali was required both for the solution and for a blank. Similarly, the aliquot required 5.84 ml. of 0.1 *N* iodine while the blank needed 5.85 ml.

2,4-Dibenzoyl-1,5:3,6-dianhydro-D-galactitol.—Benzoylation of 1.04 g. of 1,5:3,6-dianhydro-D-galactitol with benzoyl chloride in pyridine in the usual fashion furnished 2.05 g. (81%) of the dibenzoate as fine needle-like crystals. Recrystallized three times from 3 parts of 95% ethanol the substance melted at 103° and showed in chloroform a rotation of +101° (*c*, 2.04). The 2,4-dibenzoyl-1,5:3,6-dianhydro-D-galactitol is soluble in acetone and hot ethanol; insoluble in pentane, water and cold alcohol.

Anal. Calcd. for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 67.85; H, 5.40.

2,4-Ditosyl-1,5:3,6-dianhydro-D-galactitol.—Pure 1,5:3,6-dianhydro-D-galactitol (0.5393 g., 0.00369 mole) was dissolved in 5 ml. of dry pyridine and treated with 2.0 g. (0.0105 mole) of pure *p*-toluenesulfonyl chloride. After standing overnight at room temperature and for one hour at 45° the excess tosyl chloride was decomposed with a chip of ice and the reaction mixture diluted with chloroform. The solution was washed successively with water, 3 *N* sulfuric acid, aqueous sodium bicarbonate and then dried over anhydrous sodium sulfate. After filtration through carbon and concentration *in vacuo* at 50° to a colorless sirup, the material was twice dissolved in absolute ethanol and concentrated *in vacuo*. Repeated cooling and scratching of a solution of the residue in 15 ml. of ethanol eventually induced the crystallization of 1.40 g. (84%) of product. Two recrystallizations from 9 parts of ethanol gave well-formed needles melting at 97% and showing in chloroform a rotation of +5.6° (*c*, 2.14). The 2,4-ditosyl-1,5:3,6-dianhydro-D-galactitol is readily soluble in ethyl acetate, acetone and hot alcohol; insoluble in cold alcohol, pentane and water.

Anal. Calcd. for $C_{20}H_{22}O_8S_2$: C, 52.85; H, 4.88. Found: C, 52.67; H, 4.98.

Summary

2,3,4 - Tribenzoyl - 6 - tosyl - 1,5 - anhydro - D-galactitol has been synthesized from 1,5-anhydro-D-galactitol and the unusual stability of its primary tosyloxy group toward sodium iodide in acetone discussed. Alkaline treatment of this ester gives 1,5:3,6-dianhydro-D-galactitol, the position of the newly introduced ring being proven by the stability of the substance to the action of periodate. 1,5:3,6-Dianhydro-D-galactitol has been further characterized through its dibenzoate and ditosylate.

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[20] E. L. Jackson and C. S. Hudson, THIS JOURNAL, **59**, 994 (1937).

[CONTRIBUTION FROM THE WM. H. CHANDLER CHEMISTRY LABORATORY, LEHIGH UNIVERSITY]

Studies in the Sulfone Series. V.[1] 2,8-Diaminophenothiazine-5-dioxide

BY J. G. MICHELS AND E. D. AMSTUTZ

The investigation of compounds structurally similar to 4,4′-diaminodiphenyl sulfone has been under way in this Laboratory for several years. The compounds previously prepared and studied[1,2,3,4] include sulfones with a direct linkage between the *o,o*′-positions and several with an *o,o*′-carbonyl bridge. The present paper describes the preparation and proof of structure of another member of this series, namely, 2,8-diaminophenothiazine-5-dioxide (VIII).

Baltzly, Harfenist and Webb[5] reported that the Friedel–Crafts reaction between phenothiazine and acetyl chloride in carbon disulfide led to an acetylphenothiazine. These authors have discussed the evidence which indicates that substitution took place at the 2-position.[6]

By increasing the ratio of reactants, it has been found possible to utilize this reaction in the preparation of 2,8-diacetylphenothiazine (II). The conversion of this compound to the desired diamino compound is represented in the chart.

The yields in the Friedel–Crafts reaction varied between 35 and 50%. These variations are probably due to the grain size of the aluminum chloride used and to the gummy nature of the reaction product which always enclosed some unreacted aluminum chloride. From the crude reaction product could also be separated some of the 2-acetylphenothiazine as reported above.[1] Oxidation of the triacetylphenothiazine (I) to the di-

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[1] For the preceding paper in this series see Amstutz, Fehnel and Hunsberger, THIS JOURNAL, **70**, 133 (1948).

[2] Neumoyer and Amstutz, *ibid.*, **69**, 1920 (1947).

[3] Amstutz, Fehnel and Woods, *ibid.*, **69**, 1922 (1947).

[4] Amstutz and Neumoyer, *ibid.*, **69**, 1925 (1947).

[5] Baltzly, Harfenist and Webb, *ibid.*, **68**, 2673 (1946).

[6] See also Gilman, Van Ess and Shirley, *ibid.*, **66**, 1214 (1944).