previously described. Butyl- and amylacetylene were obtained in the usual manner.[8]

Reaction of Chloromethyl Acetate with Sodium Butylacetylide.—Twelve grams of sodium (0.5 mole) was converted to the amide in 800 cc. of liquid ammonia[9] contained in a 2-liter three-necked flask provided with condenser, mercury-sealed stirrer and dropping funnel. Butylacetylene, 41 g. (0.5 mole), was added dropwise and the ammonia allowed to evaporate through the (dry) condenser and a soda-lime tower. When nearly dry, 500 cc. of anhydrous benzene was added. Dry nitrogen was passed through the flask with vigorous stirring and refluxing for about six hours. After cooling, 54 g. (0.5 mole) of chloromethyl acetate, diluted with an equal volume of dry benzene, was added dropwise. The mixture was then refluxed with stirring for one and one-half hours, cooled and poured into ice-water. The organic layer was washed until neutral to litmus, dried over magnesium sulfate and fractionally distilled. The ester was put through a Whitmore–Fenske column and then redistilled through a modified Podbielniak column, both under vacuum. The yield was 12.7 g. or 16%. When repeated with bromomethyl acetate in ether the yield dropped to 9.7%.

Saponification equivalent calculated for butylpropargyl acetate, $CH_3COOC_7H_{11}$, 154; obs., 155.9.

Reaction of *sym*-Dichloromethyl Ether with Hexynylmagnesium Bromide.—One mole of magnesium turnings was converted to the Grignard reagent with ethyl bromide in the usual manner. Eighty-two grams of butylacetylene diluted with an equal volume of dry ether was added slowly and the mixture refluxed until the evolution of ethane ceased. About 0.1 g. of cuprous chloride was introduced[10] and 57 g. (0.5 mole) of *sym*-dichloromethyl ether (diluted with ether) added slowly. After heating for one-half hour and standing overnight, the product was hydrolyzed with ice and acetic acid. The dibutylpropargyl ether was purified as described above. The yield was 22.3 g. or 21%.

Reaction of Methylene Sulfate with Hexynylmagnesium Bromide.—Approximately 0.5 mole of butylacetylene Grignard reagent was prepared as noted above. About 0.1 g. of cuprous chloride was added to the mixture and 55 g. (0.5 mole) of methylene sulfate extracted into it. This was achieved by placing the solid sulfate in a Soxhlet type extractor and refluxing the solvent ether through it. Complete extraction took about fifty-six hours and at the end of this time the mixture was decomposed with ice and hydrochloric acid. The layers were separated, the aqueous layer extracted with ether and the extracts combined with the organic layer. This was washed, dried and the ether distilled off. The small amount of residue was fractionated twice through a 50 cc. Claisen flask with small Vigreux column. The yield was 5.9 g. or 13% of 5,8-tridecadiyne.

(8) Vaughn, Hennion, Vogt and Nieuwland, *J. Org. Chem.*, **2**, 1 (1937).

(9) Vaughn, Vogt and Nieuwland, THIS JOURNAL, **56**, 2120 (1934).

Summary

Sodium alkylacetylides and the corresponding Grignard reagents have been treated with a number of formaldehyde derivatives to yield various alkylpropargyl compounds. Nine products are described.

(10) Danehy, Killian and Nieuwland, *ibid.*, **58**, 611 (1936).

NOTRE DAME, INDIANA RECEIVED JUNE 1, 1943

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

The Alkaline Degradation of Phenyl-β-lactoside, Phenyl-β-cellobioside and Phenyl-D-gluco-β-D-gulo-heptoside

BY EDNA M. MONTGOMERY, NELSON K. RICHTMYER AND C. S. HUDSON

In an earlier paper[1] it was shown that phenyl-β-D-glucoside and phenyl-β-D-galactoside are degraded readily by the action of hot, aqueous potassium hydroxide to D-glucosan<1,5>β<1,6> and D-galactosan<1,5>β<1,6>, respectively, whereas the corresponding anomeric phenyl-α-hexosides are attacked only very slowly, if at all, under considerably more drastic conditions. It was suggested that the differences in reactivity might be used as a basis for determining the configuration of the glycosidic carbon atom in these compounds, and in the other anomeric glycosides and sugars with which they may be correlated.

Karrer and Smirnoff[2] found that acetobromo-α-D-glucose will add trimethylamine, and that the resulting tetraacetyl-D-glucosido-trimethylammonium bromide is cleaved readily by hot alkali to form D-glucosan<1,5>β<1,6>; the other products are trimethylamine, acetic acid and hydrobromic acid. If the quaternary ammonium halide has the β-configuration, as Micheel[3] has suggested on the basis of its low rotation, the formation of levoglucosan in the two types of degradation may proceed through similar mechanisms.[4]

(1) Montgomery, Richtmyer and Hudson, THIS JOURNAL, **65**, 3 (1943).

(2) Karrer and Smirnoff, *Helv. Chim. Acta*, **4**, 817 (1921).

(3) Micheel, *Ber.*, **62**, 688 (1929); Micheel and Micheel, *ibid.*, **63**, 386 (1930).

(4) See Micheel and Micheel, *ibid.*, **63**, 2862 (1930); **65**, 258 (1932), for additional information in regard to possible mechanisms.

In extending our studies to the disaccharide derivatives, we heated phenyl-β-lactoside with aqueous potassium hydroxide and obtained from the acetylated reaction products an 81% yield of the same hexaacetyllactosan <1,5>β<1,6> which Karrer and Harloff[5] had isolated from the reaction of alkali with heptaacetyllactosidotrimethylammonium iodide, followed by acetylation. More fortunate than those authors, we succeeded in crystallizing the lactosan, or 4-β-D-galactosido-D-glucosan <1,5>β<1,6>, as a monohydrate in large prisms which had $[\alpha]^{20}D$ −50.6° in water, equivalent to −53.4° for the anhydrous substance, as compared with the value $[\alpha]^{18}D$ −44.65° for the crude, amorphous product of Karrer and Harloff. Upon acetolysis, our lactosan was converted in 83% yield to octaacetyl-α-lactose, the 1,6-anhydride ring opening without rupture of the disaccharide union.

Phenyl-β-cellobioside was next prepared, and, by treatment with alkali and subsequent acetylation, converted in 65% yield to the same hexaacetylcellobiosan[6] which had been described by Karrer and Harloff.[5] The deacetylation product, cellobiosan, or 4-β-D-glucosido-D-glucosan <1,5>β<1,6>, was obtained in the form of a hygroscopic, apparently microcrystalline powder of $[\alpha]^{20}D$ −75.0° in water. The crude, amorphous product of Karrer and Harloff was reported to have $[\alpha]^{18}D$ −72.97° in water.

As an example of the alkaline degradation of a phenyl-β-heptoside, we have studied the action of hot, aqueous potassium hydroxide upon phenyl-D-gluco-β-D-gulo-heptoside (I).[7] Phenol was eliminated readily, and the rotation of the solution changed from negative to positive. The carbohydrate moiety was isolated as a colorless, nonreducing sirup which readily formed a crystalline benzoate and a crystalline *p*-nitrobenzoate, each of which had the composition of a tetra-substituted heptosan. Upon debenzoylation of these derivatives, the heptosan itself was obtained in prismatic crystals which melted at 95° and had a specific rotation $[\alpha]^{20}D$ +52.9° in water. Acetolysis converted the heptosan into a mixture of the known α- and β-hexaacetates of the parent D-gluco-D-gulo-heptose.

Although the degradation of phenyl-β-hexosides by alkali had resulted previously in the isolation of 1,6-anhydrides only, an inspection of formula (I), and especially of a molecular model of which (I) is a projection formula, shows that other anhydrides seem possible from phenyl-D-gluco-β-D-gulo-heptoside. The reaction of the heptosan with sodium metaperiodate consumed two equivalents of oxidant and liberated one equivalent of formic acid. The presence of three contiguous carbinol groups is thus proved. From its method of preparation from the stable acetobromoheptose, the phenylheptoside, and also the heptosan, may be presumed to have retained the pyranoside ring. The contiguous hydroxyl groups therefore must be on carbon atoms 2, 3 and 4, and only formulas (II) and (III) need be considered. To distinguish between the 1,6-anhydride (II) and the 1,7-anhydride (III), we might have oxidized the heptosan with periodic acid, followed by bromine water and strontium carbonate, and hydrolyzed the expected strontium salt to known fragments as was done with D-glucosan <1,5>β<1,6>, by Jackson and Hudson.[8] However, we preferred to attempt to prove the presence or absence of the $-CH_2OH$ group in formula (II) by tosylation, followed by treatment with sodium iodide; replacement of a tosyl group by an iodine atom would be expected only if formula (II) is correct.

Tosylation of the heptosan under normal conditions produced a crystalline tritosyl derivative instead of the expected tetratosylheptosan. It was possible, however, to acetylate the remaining hydroxyl group. The action of sodium iodide upon the tritosylacetylheptosan then yielded a ditosylacetylheptosan iodohydrin; the formation of the iodohydrin is good evidence that a $-CH_2OH$ group existed in the heptosan, which can now be represented by formula (II) and designated, by the usual considerations, as D-gluco-D-gulo-heptosan <1,5>β<1,6>.

With the ring structures thus established, the behavior of the heptosan upon tosylation is explained readily. It is well known in the sugar series that a primary hydroxyl group, as on carbon 7, is tosylated in preference to a secondary hydroxyl group. Of the three secondary hydroxyl groups, those on carbons 2 and 3 are above the

(5) Karrer and Harloff, *Helv. Chim. Acta*, **16**, 962 (1933).

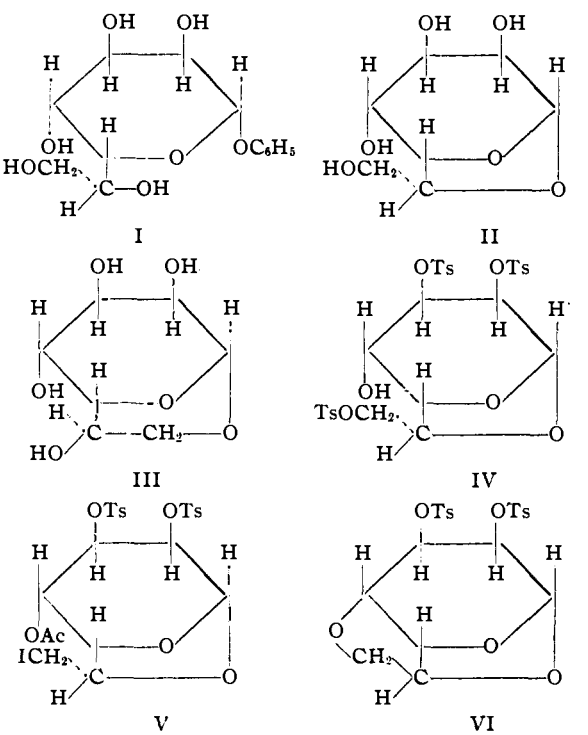
(6) The epimeric hexaacetyl-4-β-D-glucosido-D-mannosan <1,5>β<1,6>, as well as hexaacetyl-4-β-D-galactosido-D-mannosan <1,5>β<1,6>, which is the epimer of hexaacetyllactosan, have been described by Haskins, Hann and Hudson, THIS JOURNAL, **63**, 1725 (1941); **64**, 1854 (1942). The deacetylation products have not yet been obtained in crystalline form (private communication).

(7) Originally named phenyl-β-D-glucoheptoside. For the nomenclature of the heptoses see Hudson, THIS JOURNAL, **60**, 1537 (1938). This compound is now designated phenyl-D-gluco-β-D-gulo-heptoside to indicate that the configuration of the first five carbon atoms is that of a β-D-gulosido.

(8) Jackson and Hudson, THIS JOURNAL, **62**, 958 (1940).

plane of the pyranoside ring, whereas the hydroxyl group on carbon 4 is below the plane of the pyranoside ring and appears to lie in close proximity to carbon 7 which already is substituted by a large tosyl group capable of hindering the entrance of another tosyl group. Formula (IV) represents the 2,3,7-tritosyl-D-gluco-D-gulo-heptosan $<1,5>\beta<1,6>$. The failure of the hydroxyl group on carbon 4 to be tosylated recalls the inability of Müller, Móricz and Verner[9] to introduce a tosyl group at carbon 4 in their methyl-2,3-diacetyl-6-trityl-β-D-galactoside, as well as in the anomeric α-derivative, but they also were able to acetylate successfully. Their free hydroxyl group was likewise below the plane of the ring where its tosylation could be hindered sterically by the large, neighboring triphenylmethyl residue. On the other hand, methyl-2,3-dibenzoyl-6-trityl-α-D-glucoside has been tosylated with ease[10]; the hydroxyl group on carbon 4 in this compound is above the plane of the ring and away from the sphere of influence of the 6-triphenylmethyl group.

When the tritosylheptosan (IV) was heated at 70° with sodium iodide in acetonylacetone, one *p*-toluenesulfonyl group was eliminated. The resulting crystalline compound contained no iodine, and had the composition of a ditosylanhydroheptosan. It was suspected that the tosyl group on carbon 7 had actually been replaced by an iodine atom, and that hydrogen iodide had then been eliminated to form an ethylenic linkage between carbons 6 and 7. The absence of an ethylenic linkage was demonstrated by failure of the new compound to add bromine, hydrogen or ozone; furthermore, the compound could not be acetylated, as would be expected if the hydroxyl on carbon 4 were still present. In the 2,3-ditosyl-4-acetyl-heptosan-7-iodohydrin (V) the iodine atom had remained in the molecule as long as the acetyl group was attached to carbon 4; on deacetylation, however, both the acetyl and iodine were eliminated, and the ditosylanhydroheptosan crystallized from the cold deacetylating solution. The combined evidence makes it extremely probable that the iodine on carbon 7 has united with the hydrogen of the hydroxyl on carbon 4, eliminating hydrogen iodide and forming a third ring. The new compound accordingly is designated 2,3-ditosyl-4,7-anhydro-D-gluco-D-gulo-heptosan $<1,5>\beta<1,6>$. Formula (VI) thus represents a pyranoside ring with two five-membered rings fused to it, and to each other. The five-membered rings are pictured below the pyranoside ring, and more or less at right angles to it and to each other. The formation of a 4,7-anhydride ring in this heptose series is analogous to the formation of the well-known 3,6-anhydride of methyl-β-D-glucoside by the action of barium hydroxide on methyl - 2,3,4 - triacetyl - β - D - glucoside - 6 - bromohydrin.[11] In fact, the configurations of the respective four carbon atoms which are contained in the 3,6- and the 4,7-anhydride rings are identical.



Experimental Part

4-β-D-Galactopyranosido-D-glucosan $<1,5>\beta<1,6>$ (= Lactosan).—As starting material for this preparation, **phenyl-heptaacetyl-β-lactoside**, of m. p. 161° and $[\alpha]^{20}D$ −23.4° in chloroform (*c*, 2), was obtained in 52% yield by the condensation of acetobromolactose with phenol by means of potassium hydroxide in aqueous acetone, according to the directions of Helferich and Griebel.[12] Upon deacetylation, it yielded pure **phenyl-β-lactoside**, of m. p. 192° and $[\alpha]^{20}D$ −36.0° in water (*c*, 1). These data are in agreement with those reported by Helferich and Griebel.

Thirty grams of phenyl-β-lactoside in 1500 ml. of 2.6 *N* aqueous potassium hydroxide was boiled gently under a reflux condenser. The rotation changed from $[\alpha]^{20}D$ −36.0°, calculated as the lactoside, to −44.0°, calculated

(9) Müller, Móricz and Verner, *Ber.*, **72**, 745 (1939).
(10) Oldham and Robertson, *J. Chem. Soc.*, 688 (1935).
(11) Fischer and Zach, *Ber.*, **45**, 456 (1912).
(12) Helferich and Griebel, *Ann.*, **544**, 201 (1940).

as a lactosan, during the first eight hours, and did not change during an additional sixteen hours. From the nearly colorless solution the product was isolated as a sirup by the procedure outlined in a previous publication.[1] Acetylation of the sirup with acetic anhydride and pyridine produced an 81% yield of the known **hexaacetyl-4-β-D-galactopyranosido-D-glucosan** < 1,5 > β < 1,6 >. After recrystallization from ethyl alcohol, this hexaacetyllactosan melted at 206–208°, and showed $[\alpha]^{20}D$ −40.8° in chloroform (*c*, 2); Karrer and Harloff[5] reported m. p. 206° and $[\alpha]^{18}D$ −38.9° in chloroform. The deacetylation of this compound with barium methylate catalytically, followed by several recrystallizations of the product from aqueous methyl alcohol, yielded pure **4-β-D-galactopyranosido-D-glucosan** < 1,5 > β < 1,6 > **monohydrate** as large, clear prisms which melted at 128–130° and showed $[\alpha]^{20}D$ −50.6° in water (*c*, 2). It did not reduce Fehling solution. The air-dried material remains hydrated under the ordinary conditions of temperature and pressure. Dried to constant weight *in vacuo* at 110°, the anhydrous lactosan had a m. p. 140–144° and $[\alpha]^{20}D$ −53.5° in water.

Anal. Calcd. for $C_{12}H_{20}O_{10}\cdot H_2O$: C, 42.10; H, 6.48; H_2O, 5.26. Found: C, 42.18; H, 6.38; H_2O, 5.35.

Partial Acetolysis of 4-β-D-Galactopyranosido-D-glucosan < 1,5 > β < 1,6 >.—A solution of 1.00 g. of lactosan hydrate in a total volume of 50 ml. of 2:1 acetic anhydride-acetic acid containing 2.5% by volume of concentrated sulfuric acid changed in $[\alpha]^{20}D$ to +53.7° within thirty minutes at 20°, then remained constant for forty-eight hours. From the reaction mixture was isolated an 83% yield of pure octaacetyl-α-lactose of m. p. 152° and $[\alpha]^{20}D$ +53.8° in chloroform. The acetylation of lactose under the same conditions gave nearly identical results. This acetolysis of the lactosan opens the 1,6 ring but does not rupture the disaccharide linkage.

Phenyl-heptaacetyl-β-cellobioside.—The condensation of acetobromocellobiose with phenol was carried out by the same directions which were used for the corresponding lactoside.[12] The product was isolated in a 75% yield. After several recrystallizations from chloroform and isopentane the pure phenyl-heptaacetyl-β-cellobioside had a m. p. 206–208° and $[\alpha]^{20}D$ −36.0° in chloroform (*c*, 2). The compound described by Zemplén[13] melted at 193° and may have contained some of the anomeric form; no rotation was reported.

Anal. Calcd. for $C_{32}H_{40}O_{19}$: C, 53.93; H, 5.66. Found: C, 54.03; H, 5.77.

Phenyl-β-cellobioside.—Catalytic deacetylation of the heptaacetate with barium methylate produced phenyl-β-cellobioside; the long, flexible needles which crystallized from methyl alcohol solution lost their transparency on exposure to the air at room temperature. Pure phenyl-β-cellobioside melted at 211–213° and showed $[\alpha]^{20}D$ −59.5° in water (*c*, 1).

Anal. Calcd. for $C_{18}H_{26}O_{11}$: C, 51.67; H, 6.26. Found: C, 51.82; H, 6.35.

4-β-D-Glucopyranosido-D-glucosan < 1,5 > β < 1,6 > **(= Cellobiosan).**—A solution of 34 g. of phenyl-β-cellobioside in 1700 ml. of 2.6 *N* aqueous potassium hydroxide was heated to gentle boiling (110–115°) for a period of forty-eight hours. The rotation changed from $[\alpha]^{20}D$ −59°, calculated as phenylcellobioside, to −57°, calculated as a cellobiosan, during the first twenty-four hours and remained constant thereafter. The product was isolated in the usual manner as a colorless sirup which was then acetylated with acetic anhydride and pyridine. The hexaacetate was purified by several recrystallizations from ethyl alcohol, as rosets of needles. The melting point of the **hexaacetyl-4-β-D-glucopyranosido-D-glucosan** < 1,5 > β < 1,6 > was 145–146°, and the $[\alpha]^{20}D$ −54.4° in chloroform (*c*, 2); identical values were obtained upon deacetylation and subsequent reacetylation. Karrer and Harloff[5] reported m. p. 144° and $[\alpha]^{17}D$ −46.24° in chloroform (*c*, 3.2) for their hexaacetylcellobiosan.

Deacetylation of the hexaacetylcellobiosan produced a sirup which could be transformed to a granular hygroscopic powder by concentration *in vacuo* of its solution in a 1:1 mixture of methyl and *n*-butyl alcohols. Under a polarizing microscope the material appeared to be at least partly crystalline. The **4-β-D-glucopyranosido-D-glucosan** < 1,5 > β < 1,6 > was dried to constant weight over calcium chloride in an evacuated desiccator; it did not reduce Fehling solution; the m. p. was 122°, and $[\alpha]^{20}D$ −75.0° in water (*c*, 2).

Acetobromo-D-gluco-α-D-gulo-heptose.—Fifty grams of hexaacetyl-D-gluco-β-D-gulo-heptose,[14] of m. p. 134–135° and $[\alpha]^{20}D$ +4.8° in chloroform (*c*, 2), was made into a paste with 25 ml. of glacial acetic acid; to this was added 40 ml. of a 30% solution of hydrobromic acid in glacial acetic acid and the mixture kept in the dark at room temperature for ninety minutes. The mixture was then diluted with chloroform, and the solution washed successively with ice-water, aqueous sodium bicarbonate, and water, dried with granular calcium chloride, and concentrated *in vacuo* to a sirup. The product crystallized readily. After several recrystallizations from ethyl alcohol, in rosets of prisms, the pure acetobromo-D-gluco-α-D-gulo-heptose melted at 111° and showed $[\alpha]^{20}D$ +187° in chloroform (*c*, 2). The melting point is in agreement with the value 110° reported both by Glaser and Zuckermann,[15] and by Haworth, Hirst and Stacey.[16] The rotation was reported by the latter investigators as $[\alpha]^{20}D$ +156° in chloroform (*c*, 0.9). It seems probable that this low value is incorrect because of a typographical error, inasmuch as Hartley and Hudson[17] found the purified acetobromo compound to have $[\alpha]^{20}D$ +186°, and m. p. 111°.

(13) Zemplén, *Ber.*, **53**, 1003 (1920).

(14) Fischer, *Ann.*, **270**, 64 (1892); Hudson and Yanovsky, THIS JOURNAL, **38**, 1575 (1916).

(15) Glaser and Zuckermann, *Z. physiol. Chem.*, **166**, 103 (1927).

(16) Haworth, Hirst and Stacey, *J. Chem. Soc.*, 2864 (1931).

(17) Unpublished results of Miss Olive Pierce Hartley, working under the direction of one of us (C. S. H.) at the National Bureau of Standards, 1926–1928. A thesis entitled "Some New Derivatives of α-D-Glucoheptose" was presented by her to the Faculty of the Graduate College in the University of Nebraska in partial fulfillment of the requirements for the degree of Master of Science, which was conferred upon her in February, 1929. Miss Hartley died August 27, 1938. The following additional data are reported in the thesis: **methyl-D-gluco-β-D-gulo-heptoside**, m. p. 167–169°, $[\alpha]^{20}D$ −74.7° in water. Fischer [*Ber.*, **28**, 1156 (1895)] found 168–170° and −74.9°; Isbell and Frush [*J. Research Natl. Bur. Standards*, **24**, 125 (1940)] found 170° and −74.7°.

Methyl-pentaacetyl-D-gluco-β-D-gulo-heptoside, m. p. 153–154°, $[\alpha]^{20}D$ −21.3° in chloroform. The compound was prepared by acetylation of the pure β-glycoside and also, in an 80% yield, from the acetobromoheptose by the action of methyl alcohol and silver car-

Anal. Calcd. for $C_{17}H_{23}O_{11}Br$: Br, 16.57. Found (by Miss Hartley): Br, 16.41.

Phenyl-D-gluco-β-D-gulo-heptoside (I).—The condensation of acetobromo-D-gluco-D-gulo-heptose with phenol was effected in benzene solution by the silver carbonate procedure for phenolic glycosides described by Carter.[18] The phenyl-heptaacetyl-D-gluco-β-D-gulo-heptoside was isolated in a 55% yield, with m. p. 99° and $[\alpha]^{20}D$ +8.0° in chloroform (*c*, 2). Deacetylation with barium methylate catalytically produced phenyl-D-gluco-β-D-gulo-heptoside, of m. p. 168° and $[\alpha]^{20}D$ −90.0° in water (*c*, 1). These data for the two compounds are in agreement with the values reported by Pigman and Isbell.[19]

D-Gluco-D-gulo-heptosan < 1,5 > β < 1,6 > (II).—A solution of 20.00 g. of phenyl-D-gluco-β-D-gulo-heptoside in one liter of 2.6 *N* aqueous potassium hydroxide was boiled gently under a reflux condenser for forty-eight hours. Determination of the liberated phenol by titration with iodine indicated that the degradation was complete after eight hours. During that time the specific rotation changed from −90.0°, calculated as the phenylheptoside, to +38.0°, calculated as a heptosan, and remained constant thereafter. The clear, yellow solution was cooled, neutralized to methyl orange with 3 *N* sulfuric acid, and concentrated *in vacuo* to dryness. The product was extracted from the potassium sulfate with alcohol, and any remaining potassium ions were precipitated by the cautious addition of dilute sulfuric acid to the cold, alcoholic solution. The 14 g. of sirup obtained by concentration *in vacuo* failed to crystallize over a period of several weeks.

Benzoylation of 8 g. of the heptosan sirup in 80 ml. of pyridine and 25 g. of benzoyl chloride overnight, followed by decomposition of the mixture with ice-water containing 22 g. of sodium bicarbonate, resulted in the separation of a gelatinous product. The material could be crystallized from acetone-isopentane in rosets of fine needles. A 60% yield of pure **tetrabenzoyl-D-gluco-D-gulo-heptosan** < 1,5 > β < 1,6 > was obtained, with m. p. 154–155°, and $[\alpha]^{20}D$ +144.4° in chloroform (*c*, 2). The benzoate is readily soluble in acetone, chloroform and ethylene dichloride, slightly soluble in alcohol and ether.

Anal. Calcd. for $C_{35}H_{28}O_{10}$: C, 69.07; H, 4.64. Found: C, 68.93; H, 4.78.

Another 8-g. portion of the glucoheptosan sirup was heated with 80 ml. of pyridine and 38 g. of *p*-nitrobenzoyl chloride on the steam-bath for one hour. The reaction mixture was poured into two liters of ice-water, and the solid, crystalline product was filtered and washed well with water. In order to remove the pyridine *p*-nitrobenzoate it was necessary to triturate the solid material with 15% aqueous acetic acid followed by 10% aqueous sodium bicarbonate. The residue was recrystallized from 10 parts of pyridine, then from 200 parts of acetone, as colorless needles. The yield was 55%. The pure **tetra-*p*-nitrobenzoyl-D-gluco-D-gulo-heptosan** < 1,5 > β < 1,6 > melted at 268° and showed $[\alpha]^{20}D$ +218° in pyridine (*c*, 2). It is readily soluble in pyridine, slightly soluble in ethyl acetate, chloroform and acetone, and practically insoluble in water, alcohol, ether, benzene and isopentane.

Anal. Calcd. for $C_{35}H_{24}N_4O_{18}$: C, 53.31; H, 3.07; N, 7.11. Found: C, 53.40; H, 3.08; N, 7.12.

Removal of the benzoyl or *p*-nitrobenzoyl groups from the corresponding derivative was accomplished with barium methylate catalytically; the methyl benzoate or *p*-nitrobenzoate which was produced was extracted with chloroform from the aqueous alcohol solution of the liberated heptosan. The barium ions were removed as sulfate in the usual manner. The product separated from methyl alcohol as a jelly which was transformed, in the course of two weeks, first to microscopic needles and later to heavy prisms. Recrystallized from methyl alcohol by the addition of ethyl acetate, pure **D-gluco-D-gulo-heptosan** < 1,5 > β < 1,6 > was obtained in rosets of shining, acicular prisms of m. p. 95°, and $[\alpha]^{20}D$ +52.9° in water (*c*, 2). The yield was nearly quantitative. The crystalline heptosan is very soluble in water, soluble in methyl alcohol, less soluble in ethyl alcohol, and slightly soluble in ethyl acetate and ether. It does not reduce Fehling solution.

Anal. Calcd. for $C_7H_{12}O_6$: C, 43.75; H, 6.30. Found: C, 43.70; H, 6.27.

An addition compound, of the composition 2 **heptosan·1 NaCl**, was obtained by concentrating an aqueous solution of 0.87 g. of D-gluco-D-gulo-heptosan < 1,5 > β < 1,6 > and 0.13 g. of sodium chloride, and crystallizing the resulting sirup from methyl alcohol by the addition of ethyl acetate. The yield was quantitative. The product could be recrystallized readily, as clusters of shining, approximately rectangular prisms, of m. p. 165–167° and $[\alpha]^{20}D$ +48.6° in water (*c*, 2). One gram was soluble in 15 ml. of hot methyl alcohol.

Anal. Calcd. for $C_{14}H_{24}O_{12}·NaCl$: C, 37.97; H, 5.47; Cl, 8.01; NaCl, 13.20. Found: C, 37.92; H, 5.49; Cl (titratable with silver nitrate), 7.91; NaCl (residue from combustion), 13.1.

Acetolysis of D-Gluco-D-gulo-heptosan < 1,5 > β < 1,6 >.—To 1.00 g. of crystalline heptosan was added sufficient 2:1 mixture of acetic anhydride and acetic acid, containing 2.5% by volume of concentrated sulfuric acid, to make 50 ml. of solution. After eighteen hours at 20° all of the heptosan had dissolved, and the $[\alpha]^{20}D$ value, calculated as

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bonate. Haworth, Hirst and Stacey [*J. Chem. Soc.*, 2864 (1931)] reported 150° and −16°.

Methyl-pentaacetyl-D-gluco-α-D-gulo-heptoside, m. p. 174–175°, $[\alpha]^{20}D$ +105.5° in chloroform. Haworth, Hirst and Stacey found 169° and +91°; Isbell and Frush found 174–175° and +107.4°.

A crystalline solvate of methyl-D-gluco-α-D-gulo-heptoside with a half molecule of ethyl acetate of crystallization was obtained by cooling a hot solution of the heptoside in ethyl acetate. The fluffy needles were very hygroscopic. After complete removal of the ethyl acetate *in vacuo* at 100° the sirupy heptoside showed $[\alpha]^{20}D$ +111.3° in water. Isbell and Frush, who were the first to crystallize the heptoside, found m. p. 106–107° and $[\alpha]^{20}D$ +111.5°.

A crystalline double salt of **cadmium D-gluco-D-ido-heptonate** (originally named *d*-β-glucoheptonate) with cadmium bromide, the analysis of which corresponds to the formula $(C_7H_{13}O_8)_2Cd·CdBr_2·H_2O$. It was obtained readily in 70% yield from a 50% aqueous alcohol solution of its components plus some excess cadmium bromide. The new salt shows $[\alpha]^{20}D$ −5.7° in water; it is soluble to the extent of 6 g. in 100 ml. of hot water, and almost insoluble in 50% alcohol. It begins to discolor at 190° and decomposes without melting. The configuration of carbon atoms 2, 3 and 4 of the heptonic acid is the same as in xylonic and idonic acids, which have been found by Bertrand [*Bull. soc. chim.*, [3] **5**, 556 (1891)], and by Fischer [*Ber.*, **28**, 1975 (1895)], respectively, to yield similar double salts of easy crystallization.

(18) Carter, *Ber.*, **63**, 586 (1930).

(19) Pigman and Isbell, *J. Research Natl. Bur. Standards*, **27**, 23 (1941).

a hexaacetylheptose, had become constant at +24°. After an additional thirty hours the reaction mixture was decomposed in the usual manner, and from it was isolated a 20% yield of hexaacetyl-D-gluco-α-D-gulo-heptose, of m. p. 164° and $[\alpha]^{20}D$ +87.0° in chloroform (*c*, 1), and a 60% yield of hexaacetyl-D-gluco-β-D-gulo-heptose, of m. p. 135° and $[\alpha]^{20}D$ +4.8° in chloroform (*c*, 2). The acetylation of D-gluco-D-gulo-heptose under similar conditions gave nearly identical results. The values of the α- and β-hexaacetates agree with those previously reported.[20]

Oxidation of D-Gluco-D-gulo-heptosan < 1,5 > β < 1,6 > with Sodium Metaperiodate.—To an aqueous solution of 0.3593 g. of pure heptosan was added 10 ml. of 0.4145 *M* aqueous sodium periodate (2.22 equivalents), and the solution was diluted exactly to 50 ml. with water. In the course of ten days at 20° the $[\alpha]^{20}D$ value changed from +53°, calculated as the heptosan, to −58.7° (constant), calculated as the expected dialdehyde $C_6H_8O_6$. Titrations showed that 2.02 equivalents of periodate had been consumed and that 0.98 mole of formic acid had been produced by the oxidation.

2,3,7-Tritosyl-D-gluco-D-gulo-heptosan < 1,5 > β < 1,6 > (IV).—To 5 g. of crystalline heptosan in 40 ml. of dry pyridine was added 25 g. (5 equivalents) of tosyl chloride, and the mixture was allowed to stand either twenty-four or forty-eight hours at room temperature before it was decomposed with ice-water and the product isolated in the usual manner; the yield was 76%. The tritosyl-D-gluco-D-gulo-heptosan was recrystallized from methyl alcohol as glittering prisms of m. p. 157° and $[\alpha]^{20}D$ +34.6° in chloroform (*c*, 2); it is readily soluble in chloroform and acetone, less soluble in methyl alcohol, ethyl acetate and ether, and insoluble in water.

Anal. Calcd. for $C_{28}H_{36}O_{12}S_3$: C, 51.36; H, 4.62; S, 14.69. Found: C, 51.57; H, 4.72; S, 14.56, 14.67.

2,3,7-Tritosyl-4-acetyl-D-gluco-D-gulo-heptosan < 1,5 > β < 1,6 >. Acetylation of the tritosyl heptosan with acetic anhydride and pyridine for twenty-four hours at room temperature produced a 90% yield of the monoacetyl derivative. The acetate was recrystallized from a mixture of acetone and isopentane in glittering prisms which appeared to contain a molecule of acetone of crystallization. The air-dried material melted at 105°, with foaming, and showed $[\alpha]^{20}D$ +55.2° in chloroform (*c*, 2), equivalent to $[\alpha]^{20}D$ +59.8° for the acetone-free compound. An iodoform test was positive. Material which had been kept in a desiccator for a week seemed to have lost part of its acetone content, the loss in weight at 110° being only 6.4% instead of the 7.7% calculated for one molecule of acetone.

Anal. Calcd. for $C_{36}H_{32}O_{13}S_3 \cdot CH_3COCH_3$: C, 52.51; H, 5.07. Found (air-dried): C, 52.41; H, 5.12. Calcd. for $C_{36}H_{32}O_{13}S_3$: C, 51.71; H, 4.63. Found (dried at 110°): C, 51.65; H, 4.64.

2,3-Ditosyl-4-acetyl-D-gluco-D-gulo-heptosan<1,5>β<1,6>-7-iodohydrin (V).—Five grams of sodium iodide was dissolved in a solution containing 5 g. of the acetyltritosylheptosan in 40 ml. of dry, freshly distilled acetonylacetone. The solution, kept at 70° for eighteen hours, remained light in color and deposited about one equivalent of sodium *p*-toluenesulfonate, which was removed by filtration. The product crystallized readily when the filtrate was diluted with water and was recrystallized several times from a mixture of acetone and isopentane. The pure iodohydrin had a m. p. 135° and $[\alpha]^{20}D$ −4.0° in chloroform (*c*, 2). The yield was 83%.

Anal. Calcd. for $C_{23}H_{25}IO_{10}S_2$: C, 42.34; H, 3.86; I, 19.45. Found: C, 42.29; H, 3.94; I, 19.56.

2,3-Ditosyl-4,7-anhydro-D-gluco-D-gulo-heptosan<1,5>β<1,6> (VI).—Deacetylation of 5 g. of the acetylditosylheptosan iodohydrin with barium methylate at room temperature produced clusters of feathery needles which crystallized within ten minutes from the 200 ml. of methyl alcohol solution. The product was isolated in 85% yield after several recrystallizations from methyl alcohol. The pure ditosylanhydroheptosan had a m. p. of 180–182°, and $[\alpha]^{20}D$ −37.0° in chloroform (*c*, 2); it is readily soluble in chloroform and acetone, less soluble in methyl and ethyl alcohols, ether and ethyl acetate and practically insoluble in water and isopentane.

Anal. Calcd. for $C_{21}H_{22}O_9S_2$: C, 52.27; H, 4.60. Found: C, 52.23; H, 4.67.

The ditosylanhydroheptosan was obtained also directly from the 2,3,7-tritosylheptosan in several attempts which were made to replace the 7-tosyl group by heating with sodium iodide. No intermediate iodohydrin could be isolated when the hydroxyl group on carbon 4 was not protected by previous acetylation.

The ditosylanhydroheptosan did not decolorize a solution of bromine in carbon tetrachloride, did not absorb hydrogen at room temperature and atmospheric pressure in the presence of palladium black, and was not appreciably attacked by ozone in chloroform solution at 0°. The compound was recovered unchanged after attempted acetylations with acetic anhydride and pyridine for twenty-four hours at room temperature, and with acetic anhydride and fused sodium acetate for three hours on the steam-bath, indicating that it contains no hydroxyl group.

The authors wish to thank Dr. Arthur T. Ness for carrying out the microchemical analyses, and Mr. Charles G. Remsburg for the sulfur determinations.

Summary

Phenyl-β-lactoside and phenyl-β-cellobioside have been degraded readily by the action of hot, aqueous potassium hydroxide to lactosan (4-β-D-galactopyranosido-D-glucosan<1,5>β<1,6> and cellobiosan (4-β-D-glucopyranosido-D-glucosan<1,5>β<1,6>), respectively.

Phenyl-D-gluco-β-D-gulo-heptoside has been degraded similarly to a crystalline anhydride, to which has been assigned, on strong evidence, the structure D-gluco-D-gulo-heptosan<1,5>β<1,6>. The heptosan has been characterized by means of an addition compound of the composition 2 heptosan·1NaCl, a tetrabenzoate, a tetra-*p*-nitrobenzoate, a 2,3,7-tritosyl derivative, a 2,3,7-tritosyl-4-acetyl derivative, and a 2,3-ditosyl-4-acetyl-7-iodohydrin. The last-named compound on de-

(20) Hudson and Yanovsky, THIS JOURNAL, **38**, 1575 (1916).

acetylation is transformed smoothly to 2,3-di-tosyl-4,7-anhydro-D-gluco-D-gulo-heptosan <1,5> β<1,6>, a sugar derivative containing one six-atom ring and two five-atom rings fused together in a novel manner.

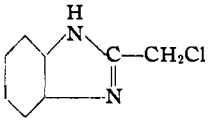
BETHESDA, MARYLAND RECEIVED JUNE 24, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

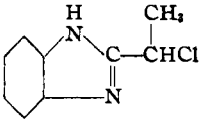
The Allylic Character of 2-(α-Chloroalkyl)-benzimidazoles[1]

BY HERMAN SKOLNIK,[2] JOHN G. MILLER AND ALLAN R. DAY

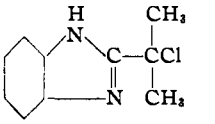
Previous work[3] has indicated that the chlorine atoms in 2-chloromethylbenzimidazole and 2-(α-chloroethyl)-benzimidazole are highly reactive. This was shown by the extreme ease with which these compounds reacted with primary or secondary amines. Structurally they are similar to allyl chloride and benzyl chloride, and so might be expected to show some similarity in chemical behavior. The fact that they appeared to be more active prompted the present study of the activating effect of the benzimidazole group on the chlorine atom in several types of 2-(α-chloroalkyl)-benzimidazoles.



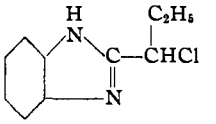
I
2-Chloromethyl-benzimidazole



II
2-(α-Chloroethyl)-benzimidazole



III
2-(α-Chloroisopropyl)-benzimidazole



IV
2-(α-Chloro-*n*-propyl)-benzimidazole

This selection of 2-α-chloroalkyl derivatives not only permitted a study of the labilizing influence of the benzimidazole nucleus but the effect of the nature of the α-carbon atoms as well. It will be noted that compound I is a primary halide, II and IV are secondary halides, while III is a tertiary halide.

Numerous studies have been published concerning the effect of labilizing groups on halogen atoms. In many cases only qualitative information has been reported, such as the conditions under which certain metathetic reactions occur or whether the reaction proceeds at all. In other cases quantitative data resulting from reaction studies have been reported. In the present investigation both the qualitative and quantitative methods have been employed. The results from both methods point to the fact that the 2-α-chloroalkyl benzimidazoles are more reactive than the usual allyl halide type. No work has been reported previously on this grouping, $-N=\overset{|}{C}-\overset{|}{C}HCl$. Only the qualitative data are included in this paper.

It was no great surprise to encounter certain anomalies in the chemical investigation undertaken to establish the allylic character of compounds I, II, III and IV. These derivatives have more functional groups than allyl chloride, which results in greater complexity of activity. For example, the benzimidazole ring system contains two nitrogen atoms, one a tertiary basic nitrogen and the other attached to an active hydrogen atom. In solution such compounds are probably highly associated through hydrogen bonding.[4]

Since allyl chloride is known to react with Grignard reagents, it was expected that 2-chloromethylbenzimidazole would react similarly with phenylmagnesium bromide. However, no identifiable products could be isolated.

Greater success resulted from a study of hydrolysis reactions. The 2-chloromethyl compound was hydrolyzed almost quantitatively by boiling with water for thirty to sixty minutes. The 2-(α-chloroethyl) and 2-(α-chloro-*n*-propyl) compounds gave similar results in a somewhat shorter time and the 2-(α-chloroisopropyl) derivative was completely hydrolyzed by water at room temperature. The greater ease of hydrolysis of the secondary and tertiary chlorides was to be expected, but it must

(1) Presented at the Detroit meeting of the American Chemical Society in April, 1943.

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(3) Bloom and Day, *J. Org. Chem.*, **4**, 14 (1939); Roeder and Day, *ibid.*, **6**, 25 (1941).

(4) Hunter and Marriot, *J. Chem. Soc.*, 777 (1941).