[CONTRIBUTION FROM THE SOUTHERN REGIONAL RESEARCH LABORATORY[1]]

The Rearrangement of Acetylated and Benzoylated β-Glucosides Catalyzed by Titanium Tetrachloride[2]

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Titanium tetrachloride catalyzes the formation of an equilibrium mixture of benzoylated non-aromatic glucosides in which the α-isomer greatly predominates over the β-isomer. The reaction provides a convenient method of preparing the α-glucosides from their anomers. The transformation of the benzoylated β-glucosides occurs more readily than that of the corresponding acetates. Application of the isorotation rules has indicated that when benzoates are compared with their corresponding acetates benzoylation is found to have increased the dextrorotation of the C_2–C_6 portion of glucoside molecules and to have decreased the influence of the aglucone upon the rotation. Six new, crystalline glucoside derivatives and a crystalline compound containing *o*-nitrophenol, titanium and chlorine in the ratio 2:1:2 have been prepared.

The activity of titanium tetrachloride in promoting the transformation of fully acetylated alkyl β-glucopyranosides to their α-isomers was first reported by Pacsu.[3] Piel and Purves[4] and more recently, Lindberg[5] also investigated the transformation reactions of fully acetylated glucosides. These workers showed that the transformation proceeds to an equilibrium mixture containing a large proportion of the α-modification of the acetylated glucosides.

This transformation reaction has, apparently, not been studied with glucoside derivatives other than the acetates. In the present report the transformation of glucoside benzoates is discussed.

Experimental

Methyl 2,3,4,6-Tetrabenzoyl-β-D-glucopyranoside. High Melting Form.—This substance was prepared by the method described by Ness, Fletcher and Hudson.[6] Upon recrystallization from a mixed solvent composed of acetone and ether, as recommended by these authors, the product melted at 163–164° and had a specific rotation in chloroform of +29° in agreement with their reported values. Apparently this is also the form which was obtained by Fischer and Helferich.[7]

Low Melting Form.—Upon recrystallization of the above substance from *n*-amyl alcohol a second crystalline form was obtained. This form melted at 138–140°, and upon being further heated to 150° it crystallized and remelted at 162°. The optical rotation of the low melting form was the same as that recorded for the high melting form. Ness, Fletcher and Hudson[6] mentioned a second crystalline form as rhombohedral plates, sp. rot. +29.8° in chloroform, but they did not record the melting point of their crystals. That our low melting form did not contain solvent of crystallization is indicated by its analysis.

Anal. Calcd. for $C_{35}H_{30}O_{10}$ (610.59): C, 68.84; H, 4.95. Found: C, 68.62, 68.63; H, 5.10, 5.08.

Rearrangement to Methyl 2,3,4,6-Tetrabenzoyl-α-D-glucopyranoside.—To a solution containing 980 mg. of the high melting form of methyl tetrabenzoyl-β-glucoside in 20 ml. of absolute chloroform an equimolar amount of titanium tetrachloride, also dissolved in absolute chloroform, was added. The solution turned yellow immediately and the dextrorotation increased during 17 minutes at room temperature (29°) and then remained constant. The solution was washed with aqueous hydrochloric acid, then with water, and dried over anhydrous sodium sulfate. The specific rotation had increased from +29° to +79° indicating 94% conversion to the α-form. After evaporation of the solvent and several recrystallizations of the residue from alcohol 490 mg. (50%) of the pure α-isomer,[6] m.p. 107–109°, $[\alpha]^{29}D$ +82° (in chloroform), was obtained.

The behavior of methyl 2,3,4,6-tetrabenzoyl-α-D-glucopyranoside with titanium tetrachloride was investigated by observing the optical rotation of a solution containing 1:1 mole proportions dissolved in absolute chloroform. The optical rotation of the solution decreased slightly during the first hour at room temperature and remained constant for 4 days thereafter. After the solution was washed free of titanium and chloride ion the specific rotation of the product was +78° corresponding to a mixture containing 92.5% of the α-isomer and 7.5% of the β-isomer.

***n*-Amyl 2,3,4,6-tetrabenzoyl-β-D-glucopyranoside** was prepared from 8.1 g. of tetrabenzoyl-α-glucosyl bromide dissolved in 50 ml. of absolute chloroform and 50 ml. of *n*-amyl alcohol by shaking with 12 g. of silver oxide for 16 hours. After filtration and evaporation of the solvent *in vacuo* the residue crystallized from alcohol, yield 6.46 g. (79%). Recrystallization from alcohol gave stout prisms, m.p. 113–114°, $[\alpha]^{29}D$ +18° (*c* 6.3, in chloroform).

Anal. Calcd. for $C_{39}H_{38}O_{10}$ (666.69): C, 70.26; H, 5.74. Found: C, 70.24, 70.23; H, 5.76, 5.78.

Debenzoylation with barium methylate in methanol solution gave the known crystalline *n*-amyl β-D-glucoside,[8,9] m.p. 90–92°.

***n*-Amyl 2,3,4,6-tetrabenzoyl-α-D-glucopyranoside** was prepared by rearrangement of the β-isomer under conditions similar to those described for methyl glucoside tetrabenzoate. The rearrangement was complete after 10 minutes at room temperature. The product was twice recrystallized from methanol. It melted at 104–105°, $[\alpha]^{20}D$ +84.1° (*c* 6.5, in chloroform), and the yield of the pure substance was 1.26 g. (33%) from 3.77 g. of starting material.

Anal. Calcd. for $C_{39}H_{38}O_{10}$ (666.69): C, 70.26; H, 5.74. Found: C, 70.09, 70.19; H, 5.73, 5.77.

Cyclohexyl 2,3,4,6-tetrabenzoyl-β-D-glucopyranoside was prepared from 4.05 g. of tetrabenzoyl-α-glucosyl bromide dissolved in 30 ml. of absolute chloroform and 40 ml. of cyclohexanol by shaking for 16 hours at room temperature with 6 g. of silver oxide. The yield was 2.76 g. (64%). Recrystallization from alcohol gave a *high melting form*, m.p. 177–178°, $[\alpha]^{20}D$ +11.5° (*c* 5, in chloroform). Recrystallization from methanol gave a *low melting form* which melted at 142–143° then crystallized again when the temperature was raised to about 150° and remelted at about 172°. The specific rotation of the low melting form was the same as that of the high melting form. The latter crystals were needles with an angle of extinction in polarized light of 18° to 22°; the former were monoclinic prisms with an angle of extinction of 23°.

Anal. Calcd. for $C_{40}H_{38}O_{10}$ (678.7): C, 70.78; H, 5.64. Found high-melting form: C, 70.57, 70.66; H, 5.67, 5.74. Low-melting form: C, 70.58; H, 5.68.

Cyclohexyl 2,3,4,6-tetrabenzoyl-α-D-glucopyranoside was prepared by rearrangement of the β-form with titanium tetrachloride under conditions similar to those described

(1) One of the laboratories of the Agricultural Research Service, U. S. Department of Agriculture. Article not copyrighted.

(2) Presented at the Regional Conclave of the American Chemical Society, New Orleans, La., December, 1953.

(3) (a) E. Pacsu, *Ber.*, **61**, 1508 (1928); (b) THIS JOURNAL, **52**, 2563 (1930); (c) **52**, 2568 (1930).

(4) E. V. Piel and C. B. Purves, *ibid.*, **61**, 2978 (1939).

(5) B. Lindberg, *Acta Chem. Scand.*, **3**, 1153, 1350, 1355 (1949).

(6) R. K. Ness, H. G. Fletcher, Jr., and C. S. Hudson, THIS JOURNAL, **72**, 2200 (1950).

(7) E. Fischer and B. Helferich, *Ann.*, **383**, 90 (1911).

(8) W. W. Pigman and N. K. Richtmyer, THIS JOURNAL, **64**, 369 (1942).

(9) L. C. Kreider and E. Friesen, *ibid.*, **64**, 1482 (1942).

for the methyl glucoside. The rearrangement was complete in about six minutes at room temperature (29°). The product crystallized from alcohol in the form of thin needles less than one micron in width, m.p. 169–170°, $[\alpha]^{20}D$ +84.5° (*c* 5.05, in chloroform). The yield amounted to 0.71 g. (78%) from 0.91 g. of starting material.

Anal. Calcd. for $C_{40}H_{38}O_{10}$ (678.7): C, 70.78; H, 5.64. Found: C, 70.77, 70.55; H, 5.63, 5.60.

The rearrangement of the cyclohexyl glucoside proceeded to the same end-product with only 0.2 mole of titanium tetrachloride. This reaction followed apparent first-order kinetics.

Debenzoylation of this tetrabenzoate with barium methylate in methanol yielded cyclohexyl α-D-glucopyranoside, m.p. 124–125°, $[\alpha]^{20}D$ +137.5° (*c* 1.44, in water). Pacsu[3c] reported the m.p. to be 125–126°, and the sp. rot., +133.5° (water?) for this substance.

Phenyl 2,3,4,6-Tetrabenzoyl-α-D-glucopyranoside.—Phenyl α-D-glucopyranoside (160 mg.) was dissolved in 3 ml. of pyridine and 1 ml. of benzoyl chloride was added. The solution was heated to 100° for 3 hours after which it was poured into water. The precipitate crystallized upon stirring, and after one recrystallization from alcohol the product weighed 260 mg. (64%) and melted at 168–170°. Successive recrystallizations from alcohol, *n*-butanol and alcohol raised the melting point to 172–174°. The specific rotation of the pure substance was $[\alpha]^{28}D$ +84° (*c* 1.6, in chloroform). It was dried at 100° over P_2O_5 for analysis.

Anal. Calcd. for $C_{40}H_{32}O_{10}$ (672.66): C, 71.42; H, 4.80. Found: C, 70.99; H, 4.87.

This substance also was obtained in 10% yield by rearrangement of the β-isomer. Phenyl 2,3,4,6-tetrabenzoyl-β-D-glucopyranoside (2.58 g.) was heated under reflux for 3 hours with 5 molar proportions of titanium tetrachloride in 87 ml. of absolute chloroform. The product from the titanium rearrangement, after several recrystallizations, had a specific rotation of $[\alpha]^{25}D$ +86° (*c* 1.3, in chloroform), and melted at 168–170°. The melting point was not depressed upon mixing with the substance prepared by benzoylation of phenyl α-D-glucopyranoside. A more dextrorotatory substance which may have been tetrabenzoyl-α-D-glucopyranosyl chloride was removed during the recrystallizations.

Phenyl 2,3,4,6-tetrabenzoyl-β-D-glucopyranoside did not rearrange rapidly under the mild conditions which were successful in the case of the methyl glucoside. After standing for one month at room temperature with one mole proportion of titanium tetrachloride a 2% yield of phenyl tetrabenzoyl-α-glucoside was obtained.

***o*-Nitrophenyl 2,3,4,6-tetrabenzoyl-β-D-glucopyranoside** was prepared by mixing a solution containing 1.5 g. of *o*-nitrophenol and 0.6 g. of sodium hydroxide dissolved in 15 ml. of water with a solution containing 6.3 g. of tetrabenzoyl-α-glucosyl bromide dissolved in 40 ml. of acetone. The product was isolated by the procedure employed by Glaser and Wulwek[10] in the preparation of the analogous tetraacetyl compound. The yield was 2.6 g. corresponding to 38% of the amount of tetrabenzoylglucosyl bromide used. After recrystallization from alcohol the product melted at 183–184°. Its specific rotation in chloroform solution was strongly and reversibly influenced by temperature, ranging from +65.7° at a temperature of 20 to +54.3° at 45° (*c* 4.4).

Anal. Calcd. for $C_{46}H_{31}O_{12}N$ (717.66): C, 66.94; H, 4.35; N, 1.95. Found: C, 66.96, 67.06; H, 4.32, 4.37; N, 1.94, 1.98.

Debenzoylation of this compound was accomplished by shaking the crystals until solution was complete with methanol saturated with ammonia. The solution was then concentrated to a small volume, and upon addition of ether the product crystallized. When first prepared the *o*-nitrophenyl β-D-glucopyranoside melted at 140–141°, but after standing for several weeks over phosphoric anhydride it melted at 168–170°, in agreement with the value observed by Montgomery, Richtmyer and Hudson.[11] Its specific rotation was $[\alpha]^{23}D$ −94.5° (*c* 2.48, in water).

The reaction between titanium tetrachloride and *o*-nitrophenyl 2,3,4,6-tetrabenzoyl-β-D-glucopyranoside was investigated under both mild and relatively drastic conditions, but attempts to isolate the α-isomer of the starting material were not successful. The only products isolated were tetrabenzoyl-α-D-glucosyl chloride (in 44% yield), and ruby-red crystals which were, apparently, bis-*o*-nitrophenyl dichlorotitanate.

Bis-*o*-nitrophenyl Dichlorotitanate.—Upon mixing 2.74 g. of titanium tetrachloride dissolved in absolute chloroform with 8 g. (4 mole proportions) of *o*-nitrophenol dissolved in the same solvent a dark red solution was obtained which quickly deposited beautiful ruby-red crystals. The same product also was obtained, in smaller yields, when the mole ratios of the reactants were 1:1, 1:2 and 1:3. The red crystals were filtered and rinsed with absolute chloroform. Upon drying *in vacuo* over phosphoric anhydride they changed in color to reddish-brown. Neither the red nor the brown form of the crystals was appreciably soluble without decomposition in any solvent tested. The brown crystals did not melt on heating; upon exposure to moisture they slowly decomposed liberating *o*-nitrophenol. For analysis the substance was decomposed with ether and dilute nitric acid. *o*-Nitrophenol was recovered by evaporation of the ether solution, and the aqueous solution was analyzed for titanium dioxide and chloride.

Anal. Calcd. for $C_{12}H_8O_6N_2Cl_2Ti$ (395.01): TiO_2, 20.22; Cl, 17.95; *o*-nitrophenol, 70.9. Found: TiO_2, 20.55; Cl, 18.05; *o*-nitrophenol, 68.8.

The Rearrangement of Methyl 2,3,4,6-Tetraacetyl-β-D-glucopyranoside with Titanium Tetrachloride in Absolute Chloroform at Room Temperature.—This glucoside gives a chloroform-insoluble precipitate with titanium tetrachloride. Tubes containing 0.2555 g. of the glucoside, one mole proportion of titanium tetrachloride and 5 ml. of absolute chloroform were allowed to stand at 28° for various lengths of time. The titanium and chloride ions were then washed from the chloroform solutions, and the optical rotations of these solutions were measured. The calculated specific rotations and percentage conversions were, respectively: 5 minutes, −16°, 1.4%; 1 hr., +7°, 17%; 6 hr., +92°, 74%; 16 hr., +98°, 78%.

The rearrangement of cyclohexyl 2,3,4,6-tetraacetyl-β-D-glucopyranoside also was investigated at room temperature. This substance forms a yellow, chloroform-soluble complex with one mole of titanium tetrachloride. The rearrangement was followed by the same method employed with the preceding substance. The calculated specific rotations and per cent. conversions were, respectively: 5 minutes, +13.3°, 26%; 20 minutes, +56.9°, 56%; 1 hr., +109.3°, 92%; 2 hr., +120.6°, 99%.

Discussion

It was observed that fully benzoylated β-glucosides are transformed to their anomers more readily than are the corresponding acetates. Under comparable conditions the tetrabenzoate of methyl β-glucoside required only 17 minutes while the tetraacetate required more than 6 hours to reach equilibrium. The corresponding times for the cyclohexyl derivatives were 6 minutes and 2 hours, respectively.

Unsuccessful attempts to carry out the rearrangement of phenyl tetraacetyl-β-D-glucoside are mentioned in the literature[12]; however, the benzoylated derivative gave the α-isomer in small yield. That aromatic glucosides are prone to undergo glycosic cleavage was indicated by the experiments with *o*-nitrophenyl tetrabenzoyl-β-D-glucoside.

Sufficient data are now available to allow the consideration of the optical rotation of glucoside tetrabenzoates in terms of the isorotation rules as was done by Pigman and Isbell[13] in the case of the tetraacetates. The glucoside tetrabenzoates for which specific rotation values have been recorded are listed in Table I. In the four instances where both

(10) E. Glaser and W. Wulwek, *Biochem.*, [2] **145**, 516 (1924).

(11) E. M. Montgomery, N. K. Richtmyer and C. S. Hudson, THIS JOURNAL, **65**, 6 (1943).

(12) C. M. Montgomery, N. K. Richtmyer and C. S. Hudson, *ibid.*, **64**, 690 (1942).

(13) W. W. Pigman and H. S. Isbell, *J. Research Natl. Bur. Standards*, **27**, 9 (1941).

enantiomorphs are listed the $2A$ and $2B$ values have been calculated. The $2A$ value represents the difference between, $2B$, the sum of, the molecular rotations of the α- and β-forms. The most striking fact brought out by Table I is that all of these glucoside tetrabenzoates are dextrorotatory, save that of cholesterol.

TABLE I

THE OPTICAL ROTATIONS OF SOME GLUCOSIDE 2,3,4,6-TETRABENZOATES

Aglucone	C_1 configuration	Optical rotation, in degrees $[\alpha]_D$($CHCl_3$)	$2A$	$2B$
Methanol	α	+84[a]	33,600	69,000
	β	+29[a]		
n-Amyl alcohol	α	+84[b]	44,000	67,000
	β	+18[b]		
Cyclohexanol	α	+84.5[b]	49,500	65,100
	β	+11.5[b]		
Phenol	α	+82[b]	36,500	73,500
	β	+27[c]		
o-Nitrophenol	β	+66[b]		
Cetyl alcohol	β	+15.4[d]		
Cholesterol	β	−18.3[a]		
β-Sitosterol	β	+15.9[e]		
β-Sitosterol	β	+18.3[d]		

[a] See footnote 6. [b] This work. [c] B. Helferich and F. Strauss, *J. prakt. Chem.*, **142**, 13 (1935). [d] A. H. Salway, *J. Chem. Soc.*, **103**, 1022 (1913). [e] L. J. Swift, THIS JOURNAL, **74**, 1099 (1952).

There are three glucoside pairs for which data are available for both anomers in the acetylated and benzoylated states. These are the methyl, cyclohexyl and phenyl glucosides. In each instance the $2A$ value is greater for the tetraacetate[13] than for the tetrabenzoate. This indicates that the aglucone has less influence upon the rotation of the benzoylated glucosides than upon that of the acetylated glucosides.

Pigman and Isbell found that the acetylated *aliphatic* glucosides had $2B$ values of approximately 40,000. For the acetylated *aromatic* glucosides the $2B$ values were higher, 62,000 in the case of the phenyl glucosides. As is shown by the table the $2B$ values for the benzoylated glucosides are higher ranging from 65,000 to 73,500, the highest value being that of the phenyl glucoside. The higher $2B$ values for the benzoylated glucosides indicate that the portion of the glucoside molecule composed of carbon atoms 2 to 6 is rendered more dextrorotatory by benzoylation than by acetylation.

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Structure of Galactosylglycerol from *Irideae laminarioides*

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The non-reducing galactoside is hydrolyzed with yeast α-galactosidase to yield D-galactose and glycerol. Complete methylation of the compound produces a hexamethylgalactoside, which on hydrolysis yields 2,3,4,6-tetra-*O*-methyl-D-galactopyranose and 1,3-di-*O*-methylglycerol. When the galactosylglycerol is oxidized with sodium periodate, two moles of periodate are consumed with the production of one mole of formic acid; no formaldehyde is produced. These results show that the structure of the compound is α-D-galactopyranosyl-2-glycerol.

A study of the carbohydrates that occur in the marine alga *Irideae laminarioides* revealed that this plant contains from 1 to 4% of an alcohol-soluble galactoside, consisting of galactose and glycerol. Colin and co-workers[1,2] previously showed that a galactosylglycerol (fluoridoside) occurs in many of the red algae. They isolated the compound and showed that it can be hydrolyzed with α-galactosidase, yielding equimolar quantities of D-galactose and glycerol. From this they concluded that the galactoside possessed an α-linkage. Colin[3] also showed that the galactoside was oxidized with difficulty by bromine, and that it was not attacked by *Acetobacter;* whereas the hydrolysis products were readily oxidized when treated with bromine or when inoculated with *Acetobacter*. On the basis of these results he concluded that the galactosidic linkage in the compound occurs through the secondary alcohol group of the glycerol.

Inasmuch as these data do not afford conclusive proof for the structure of this galactoside, we have undertaken a thorough investigation of its constitution, using the methylation and periodate oxidation procedures.

The galactoside was acetylated and the product methylated first with methyl sulfate and sodium hydroxide, and finally with methyl iodide and silver oxide. Methanolysis of the hexamethylgalactoside produced 2,3,4,6-tetra-*O*-methyl-D-galactose and 1,3-di-*O*-methylglycerol. These data, therefore, show that the galactose is linked through position 2 of glycerol.

Additional evidence for the support of the galactosylglycerol structure was obtained from periodate oxidation data on the original compound. On treatment of the galactosylglycerol with sodium periodate it consumed two moles of periodate and produced one mole of formic acid. No formaldehyde could be found in the reaction mixture. These data are consistent only with a structure in which the D-galactopyranosyl moiety is linked to the secondary alcohol of glycerol.

It can be concluded that the structure of the

(1) H. Colin and E. Guéguen, *Compt. rend.*, **191**, 163 (1930).
(2) H. Colin and J. Augier, *ibid.*, **195**, 1042 (1933).
(3) H. Colin, *Bull. soc. chim.*, [5] **4**, 277 (1937).