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THE ALPHA AND BETA 1,3,4,6-TETRAACETYL-D-GLUCOPYRANOSES AND THEIR CHLOROACETYL DERIVATIVES[1]

By R. U. Lemieux and G. Huber[2]

ABSTRACT

Reaction of 3,4,6-triacetyl-β-D-glucopyranosyl chloride with silver acetate in acetic acid gave 1,3,4,6-tetraacetyl-α-D-glucopyranose, m.p. 97–98°C., $[\alpha]_D$ +145° (chloroform). 3,4,6-Triacetyl-α-D-glucopyranosyl chloride, m.p. 93–94°C., $[\alpha]_D$ +185° (chloroform), prepared from the β-anomer by isomerization in acetone, with silver acetate in acetic acid gave 1,3,4,6-tetraacetyl-β-D-glucopyranose, m.p. 137–138°C., $[\alpha]_D$ +26° (chloroform). The structures of these glucose tetraacetates were established by the interconversion of chloroacetyl derivatives.

Our studies of the properties of the pentaacetylglucopyranoses (16, 17, 18) have established the strong activating effect of C2-acetoxy group participation in dissociation of the Cl to acetoxy group bond of the 1,2-*trans*-β-anomer. It was now of interest to examine the effect of altering the C2-substituent on the ease of dissociation and for this the anomeric 1,3,4,6-tetraacetyl-D-glucopyranoses were desirable starting materials.

In 1921, Brigl (5) reported the preparation of 2-trichloroacetyl-triacetyl-β-D-glucopyranosyl chloride (I) by reaction of pentaacetyl-β-D-glucopyranose with phosphorus pentachloride. Ammonia in ether was shown to preferentially remove the trichloroacetyl group to yield 3,4,6-triacetyl-β-D-glucopyranosyl chloride (II). The chloride (II) was shown to mutarotate in acetone solution to yield a strongly dextrorotatory sirupy product presumed to be the α-anomer (III). In re-examining these reactions we have found the yield of I to be much more reproducible and substantially increased by lengthening the reaction time from 2.5 hr. to 5 hr. and by adding carbon tetrachloride to hasten attainment of homogeneity. Further, we have crystallized III, and its chemical properties agree with the structure proposed by Brigl.

Later, Brigl (6) reported the preparation of triacetyl-D-glucosan ⟨1,5⟩ α ⟨1,2⟩ (Brigl's anhydride) (IV) by treating the β-chloride (II) with an excess of ammonia in dry benzene. Brigl (6) discovered that the anhydride (IV) reacts with methanol at room temperature to yield methyl 3,4,6-triacetyl-β-D-glucopyranoside (VII). Hardegger and de Pascual (10) found that reaction of the anhydride (IV) with acetic acid gave a glucose tetraacetate, m.p. 131°C., $[\alpha]_D$ +28° (chloroform), which was presumed to be 1,3,4,6-tetraacetyl-β-D-glucopyranose (VI). We have obtained the same substance, m.p. 137–138°C., $[\alpha]_D$ +26° (chloroform), in high yield by reaction of the 3,4,6-triacetyl-α-D-glucopyranosyl chloride (III) with silver acetate in acetic acid. Gakhokidze (8) has reported the preparation of 1,3,4,6-tetraacetyl-β-D-glucopyranose with melting point 138°C. The rotation

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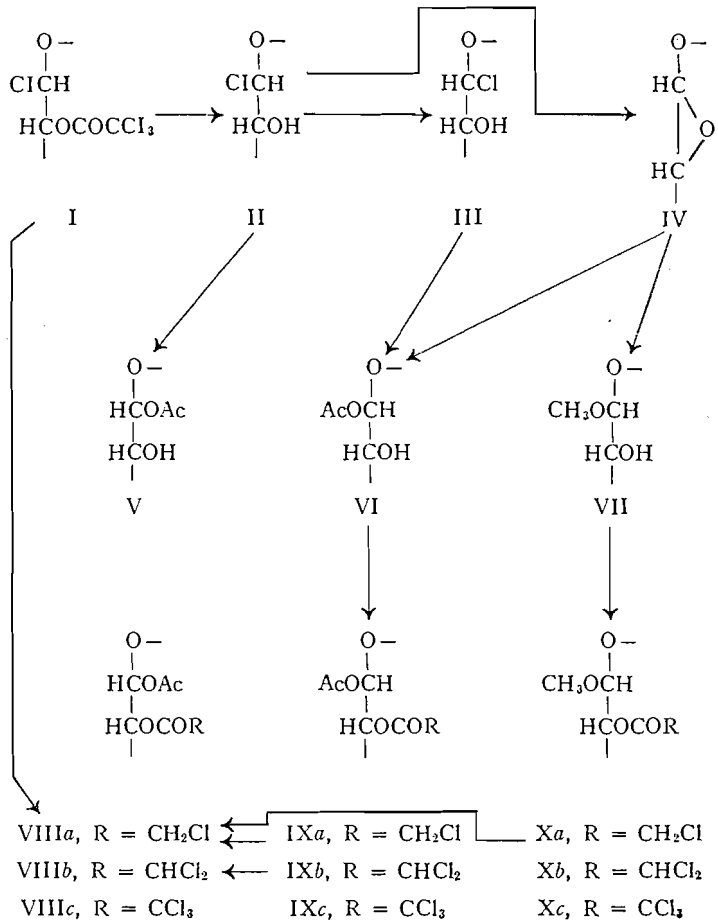

was not reported and an error may have been made (7, p. 40) in reporting the preparative procedure. Reaction of 3,4,6-triacetyl-β-D-glucopyranosyl chloride (II) with silver acetate in acetic acid gave 1,3,4,6-tetraacetyl-α-D-glucopyranose (V), m.p. 97–98°C., $[\alpha]_D$ +145° (chloroform), in high yield. The yield was much lower when ether was used as solvent. Proofs for the structures of these glucose tetraacetates (V and VI) are described below.

Trichloroacetylation of the α-tetraacetate (V) yielded a trichloroacetyl-tetraacetyl-α-D-glucose (VIII*c*) which was identical to that obtained on reaction of 2-trichloroacetyl-triacetyl-β-D-glucopyranosyl chloride (I) with silver acetate in acetic acid. Therefore, the substance (V) must be 1,3,4,6-tetraacetyl-α-D-glucopyranose. Monochloroacetylation of V gave a product (VIII*a*) which was also obtained by anomerization of the product from the monochloroacetylation of the β-tetraacetate (VI). Therefore, the latter substance (VI) must be 1,3,4,6-tetraacetyl-β-D-glucopyranose. These conclusions were substantiated in a variety of ways. Trichloroacetylation of VI yielded a

product (IX*c*) with the physical constants reported by Brigl (5) for 2-trichloroacetyl-tetraacetyl-β-D-glucopyranose. Dichloroacetylation of VI yielded 2-dichloroacetyl-tetraacetyl-β-D-glucopyranose (IX*b*) and anomerization of this product gave a substance identical to that (VIII*b*) obtained on dichloroacetylation of the α-tetraacetate (V). Finally, the 2-monochloroacetyl-tetraacetyl-β-D-glucopyranose (IX*a*) was shown to be different to the monochloroacetyl-tetraacetyl-β-D-glucopyranoses which contain the monochloroacetyl group at positions 1, 4, or 6. This precaution seemed warranted since acetyl migrations are known (12, 13) which involve positions 1, 2, 4, and 6 of the glucopyranose molecule.

The 2-monochloroacetyl, 2-dichloroacetyl, and 2-trichloroacetyl derivatives (X*a*, X*b*, and X*c*, respectively) of methyl 3,4,6-triacetyl-β-D-glucopyranoside were prepared (see Table I). The structure of the monochloroacetyl derivative (X*a*) was corroborated by acetolysis to the 2-monochloroacetyl-tetraacetyl-α-D-glucopyranose (VIII*a*).

THEORETICAL CONSIDERATIONS

Lemieux (16) has pointed out that participation of the C2-acetoxy group in replacement of the C1-acetoxy group of pentaacetyl-β-D-glucopyranose affords a reasonable account for the preferential chlorination of the C2-acetoxy group by phosphorus pentachloride to yield 2-trichloroacetyl-triacetyl-β-D-glucopyranosyl chloride (I). Abramovitch (1) has suggested that the preferential chlorination of the C2-acetoxy group may be due to the −I effect of a chlorine atom at C1.

The formation of the 1,2-*cis*-α-anomer (VIII*c*) as the main product from the reaction of 2-trichloroacetyl-triacetyl-β-D-glucopyranosyl chloride (I) with silver acetate in acetic acid should be contrasted with the usual tendency for acetohalogenosugars to yield 1,2-*trans*-acetates under these reaction conditions (19). This result is in agreement with the conclusion (17) that the trichloroacetyl group has little tendency for participation in replacements at a neighboring carbon atom. Hickinbottom (14) has prepared α-glucosides by reaction of 2-trichloroacetyl-triacetyl-β-D-glucopyranosyl chloride (I) under the conditions of the Koenigs-Knorr reaction. The formation of the α-tetraacetate (V) from the β-chloride (II) in 81% yield by reaction with silver acetate in acetic acid was to be expected on the basis of the conclusion reached by Winstein and Grunwald (20) that neighboring hydroxyl groups show little tendency for participation in replacement reactions. The formation of the β-tetraacetate (VI) from the α-chloride (III) in 79% yield under the same reaction conditions indicates that this reaction was also free of appreciable neighboring group participation. This result could not be predicted since evidence exists (2) that the C6-oxygen atom of glucose can participate in replacement reactions at the anomeric center. It is of interest to note that Hardegger and Montavon (11) have prepared ethyl α-D-isorhamnoside from 3,4-diacetyl-β-D-isorhamnosyl chloride and ethyl β-D-isorhamnoside from 3,4-diacetyl-α-D-isorhamnosyl chloride. The high yields of the Walden inversion products obtained in these reactions suggest that the transformations took

TABLE I
SOME DERIVATIVES OF D-GLUCOPYRANOSES

Compound	M.p., °C.	$[\alpha]_D^a$	$[M]_D$	A^b	B^b	% Carbon		% Hydrogen		Reference
						Calc.	Found	Calc.	Found	
Derivatives of tetraacetyl-D-glucopyranoses										
α-1,3,4,6- (V)	97–98	145°	50,500	±20,700	29,800	48.27	48.57	5.78	5.82	
β-1,3,4,6- (VI)	137–138	26	9000							*c*
α-2-Monochloroacetyl (VIII*a*)	143–144	98	41,600	±18,700	22,900	45.23	45.19	4.98	5.01	
β-2-Monochloroacetyl (IX*a*)	118–118.5	9.8	4200				45.03		5.02	
α-2-Dichloroacetyl (VIII*b*)	128–129	97	44,500	±18,800	25,700	42.00	41.87	4.38	4.39	
β-2-Dichloroacetyl (IX*b*)	134–135	15.3	6900				41.84		4.36	
α-2-Trichloroacetyl (VIII*c*)	121–123	93	45,900	±18,600	27,400	38.92	39.08	3.88	3.89	*d*
β-2-Trichloroacetyl (IX*c*)	165–166	17.9	8800				38.99		3.88	*e*
β-1-Monochloroacetyl	134–134.5	−1.39								(4)
β-4-Monochloroacetyl	117–118	3				45.23	44.98	4.98	4.93	
β-6-Monochloroacetyl	145–145.5	10				45.23	45.03	4.98	4.95	
Derivatives of methyl triacetyl-β-D-glucopyranoside										
2-Monochloroacetyl (X*a*)	97.5–98	−5.3				45.40	45.63	5.34	5.32	
2-Dichloroacetyl (X*b*)	101–102	4.4				41.77	41.55	3.72	4.68	
2-Trichloroacetyl (X*c*)	108.5–109	8				38.68	38.57	4.11	4.11	

[a] *Unless otherwise stated the rotations were measured in chloroform, (c, 0.8–1 in the temperature range 22–26°C).* [b] *Values calculated on the basis of Hudson's rules of isorotation.* [c] *Lit. (10), m.p. 131°C.,* $[\alpha]_D$ *+28° (c, 1.3 in chloroform).* [d] *Lit. (5), m.p. 120°C.,* $[\alpha]_D^{14}$ *+101.5° (c, 2.5 in nitrobenzene).* [e] *Lit. (5), m.p. 167°C.,* $[\alpha]_D^{15}$ *+28.8° (c, 3 in nitrobenzene).*

place by the S_N2 type of mechanism proposed by Isbell and Frush (15) for the reaction of α-acetobromoglucose with methanol in the presence of silver carbonate.

EXPERIMENTAL

Methods

The specific rotations were measured at room temperature, 22–26°C. The melting points are corrected.

2-Trichloroacetyl-triacetyl-β-D-glucopyranosyl Chloride (I) (*5*)

Pentaacetyl-β-D-glucopyranose, 78 gm., phosphorus pentachloride, 177 gm., and 40 ml. of carbon tetrachloride were heated under reflux for five hours. The mixture was evaporated in the vacuum of a water aspirator to a bath temperature of about 85°C. The sirupy residue was dissolved in 160 ml. of dry ether and the clarified solution was left overnight at −10°C. The crystalline deposit was washed first with 20 ml. of cold methanol then with 20 ml. of dry ether. The yield was 38 gm., 40%, of material, m.p. 132–138°C., $[\alpha]_D$ +14° (chloroform). After two recrystallizations from ether, the substance, $[\alpha]_D$ +8.9° (*c*, 1.4 in chloroform) melted at 140–142°C. Brigl (5) has reported m.p. 142°C., $[\alpha]_D$ +2.95° (*c*, 7.4 in benzene).

3,4,6-Triacetyl-α-D-glucopyranosyl Chloride

3,4,6-Triacetyl-β-D-glucopyranosyl chloride (5), 4.00 gm., was dissolved in 250 ml. of dry acetone. After four days at room temperature (5), the solution was evaporated *in vacuo* to sirup which was dissolved in ether. Hexane was added to near turbidity and the solution was left at 0°C. for several days. There was deposited 3.70 gm., 92.5% yield, of crystalline compound, m.p. 90–91.5°. Four recrystallizations from ether–hexane mixture raised the melting point to 93–94°C. with $[\alpha]_D$ +185° (*c*, 1.2 in chloroform). Calc. for $C_{12}H_{17}O_8Cl$: C, 44.38; H, 5.28; Cl, 10.9%. Found: C, 44.18; H, 5.22; Cl, 11.0%.

1,3,4,6-Tetraacetyl-α-D-glucopyranose (V)

3,4,6-Triacetyl-β-D-glucopyranosyl chloride (II), m.p. 156–158°C., $[\alpha]_D$ +28.7° (*c*, 1.1 in chloroform) (5), 1.95 gm., and silver acetate, 1.08 gm., were shaken with 20 ml. of acetic acid for six hours. The silver salts were removed by filtration and the acetic acid by distillation *in vacuo* to yield a sirup which was dissolved in a little ether. The solution was clarified and left overnight at −10°C. A crystalline product, m.p. 90–96°C., 1.40 gm., was formed. A second crop, 0.30 gm., was obtained from the mother liquor to raise the yield to 81%. The purified material is reported in Table I. Reaction of 3,4,6-triacetyl-β-D-glucopyranosyl chloride (II) 1 mM., with silver acetate, 3 mM., in 5 ml. ether for two hours gave the same material in 43% yield. Gakhokidze (8) has reported the use of silver carbonate instead of silver acetate under these conditions to yield 1,3,4,6-tetraacetyl-β-D-glucopyranose. It has been suggested (7, p. 40) that silver acetate was probably the reagent actually used. However, Gakhokidze's product melted at 138°C. and was probably of low specific rotation since he believed the substance to be a β-D-anomer.

1,3,4,6-Tetraacetyl-β-D-glucopyranose (VI) (10)

(*a*) The following reaction conditions are essentially those reported by Hardegger and de Pascual (10). Pure Brigl anhydride (IV), m.p. 59–60°C., $[\alpha]_D$ +73° (*c*, 0.8 in chloroform), was prepared by the method of Gladding and Purves (9). The anhydride, 5.8 gm., was dissolved at 20°C. in 50 ml. of pure acetic acid. After five hours, the acetic acid was removed by distillation *in vacuo* at 30°C. The sirupy product crystallized from ether at −10°C. to yield 5.2 gm., 74%, of product, m.p. 128–130°C. Several recrystallizations from ethanol gave a pure substance, m.p. 136–137°C., $[\alpha]_D$ +26° (*c*, 0.8 in chloroform). Hardegger and de Pascual have reported, m.p. 131°C., $[\alpha]_D$ +28° (*c*, 1.3 in chloroform).

(*b*) A mixture of 650 mgm. 3,4,6-triacetyl-α-D-glucopyranosyl chloride, 350 mgm. silver acetate and 10 ml. of acetic acid was shaken at room temperature for six hours. Benzene, 10 ml., was added, the silver salts were removed by filtration, and the filtrate was evaporated *in vacuo* to a crystalline residue. The substance was dissolved in ether and hexane was added to turbidity. On standing at 0°C., 550 mgm., 79% yield, of a crystalline substance, m.p. 133–134°C., was deposited. Five recrystallizations from ethanol–hexane mixture raised the melting point to 137–138°C., $[\alpha]_D$ +26° (*c*, 0.9 in chloroform). The substance did not depress the melting point of the above described preparation and gave the same monochloroacetyl derivative (IX*a*).

Methyl 3,4,6-Triacetyl-β-D-glucopyranoside (VII)

This substance, m.p. 94–95°C., $[\alpha]_D$ +19° (*c*, 1 in chloroform), was prepared in the manner described by Gladding and Purves (9).

Monochloroacetylations

The glucose derivative, 4 mM., was dissolved in 15 ml. of dry benzene and 2 ml. of dry pyridine. Monochloroacetic anhydride, 10 mM., was added to the solution cooled to 0°C. After one hour, the mixture was left at room temperature for two hours. Chloroform, 50 ml., was added and the solution washed twice with ice-cold 20% hydrochloric acid, once with cold water, and finally with aqueous sodium bicarbonate solution. The colorless chloroform solution was evaporated *in vacuo* to a sirupy residue which was crystallized from ethanol. The yields of crude crystalline product were in the range 85–95%. The purified products from the monochloroacetylations of IV, V, VI, 1,2,3,6-tetraacetyl-β-D-glucopyranose (13) and 1,2,3,4-tetraacetyl-β-D-glucopyranose (13) are reported in Table I.

Dichloroacetylations

Dichloroacetyl chloride, b.p. 107–108°C., n_D^{25} 1.481, was used as acylating agent. The reaction conditions were essentially the same as described above for the monochloroacetylations. The reaction mixtures developed a dark reddish brown coloration. Consequently, the chloroform extract, freed from pyridine, was decolorized by percolation through Magnesol before concentration. The yields of crude crystalline product were in the range 75–80%. The purified compounds derived from IV, V, and VI are reported in Table I.

Trichloroacetylations

Trichloroacetyl chloride, b.p. 116–118°C., n_D^{25} 1.468, was used as acylating agent and the reaction conditions were essentially as described above for the monochloroacetylations. The yields of crude crystalline product were in the range 80–95%. The purified derivatives obtained from IV, V, and VI are reported in Table I.

Anomerizations and Acetolyses

The substance, 1 mM., was dissolved in 10 ml. of 50: 50 acetic acid – acetic anhydride mixture 0.5 *M* with respect to sulphuric acid (3). The solution was kept at 25°C. for the specified time and then poured into ice-water mixture which contained sufficient sodium acetate to combine with the sulphuric acid. In each case, a crystalline precipitate formed on allowing the solution to stand overnight at 4°C.

2-Monochloroacetyl-tetraacetyl-β-D-glucopyranose (IX*a*), 0.425 gm., after 7.5 hr. reaction time gave 0.32 gm., 78%, of material, m.p. 138–139°C. After several recrystallizations from ethanol the melting point was 142–144°C. This melting point was not depressed by admixture of the 2-monochloroacetyl-tetraacetyl-α-D-glucopyranose (VIII*a*).

Acetolysis of methyl 2-monochloroacetyl-triacetyl-β-D-glucopyranoside (X*a*), 400 mgm., for 6.5 hr. gave 0.21 gm., 48%, of material, m.p. 138–140°C. and this melting point was not depressed by 2-monochloroacetyl-tetraacetyl-α-D-glucopyranose (VIII*a*).

2-Dichloroacetyl-tetraacetyl-β-D-glucopyranose (IX*b*), 460 mgm., after 24 hr. reaction time gave 300 mgm., 65%, of material, m.p. 114–120°C. Several recrystallizations from ethanol raised the melting point to 127–129°C. and this melting point was unchanged by 2-dichloroacetyl-tetraacetyl-α-D-glucopyranose (VIII*b*).

2-Trichloroacetyl-tetraacetyl-α-D-glucopyranose

2-Trichloroacetyl-triacetyl-β-D-glucopyranosyl chloride (I), 4.7 gm., was shaken with silver acetate, 1.8 gm., in 100 ml. of acetic acid for 14 hr. at room temperature. The product, isolated in the usual manner, was crystallized from ethanol to yield 4.8 gm., 82%, of material, m.p. 114–118°C. After several recrystallizations from ether, the melting point was 120–122°C. and $[\alpha]_D$ +93° (*c*, 0.8 in chloroform). The melting point was not changed by admixture of 2-trichloroacetyl-tetraacetyl-α-D-glucopyranose (VIII*c*) (see Table I).

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