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Synthesis of β-2-Chloroethylgentiobioside and β-2-Chloroethylprimeveroside Acetates

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In connection with investigations on the induced formation of β-glycosides in plants as a result of the absorption of chemicals which serve as aglycons[1] it became necessary to synthesize β-2-chloroethylgentiobioside heptaacetate for identification purposes. The first synthesis was carried out by condensing acetobromogentiobiose with ethylene chlorohydrin in the presence of Ag_2O. The β-gentiobiose octaacetate was obtained by the reaction between acetobromoglucose and β-D-glucose-1,2,3,4-tetraacetate according to the method of Reynolds and Evans.[2] The β-D-glucose-1,2,3,4-tetraacetate was prepared through the 6-trityl compound after the method of Helferich and Klein[3] as improved by Reynolds and Evans.[2]

Since β-2-chloroethyl-D-glucoside can be obtained in good yield[4] it seemed desirable to attempt the preparation of 2,3,4-triacetyl-β-2-chloroethyl-D-glucoside (through the 6-trityl compound) and its condensation with acetobromoglucose to form β-2-chloroethylgentiobioside heptaacetate. Similar reactions have been carried out with a number of glucosides by previous workers.[5] The availability of 2,3,4-triacetyl-β-2-chloroethyl-D-glucoside would greatly facilitate the synthesis of additional disaccharide glycosides of ethylene chlorohydrin in which the linkage occurs between the six position of the glucose molecule and the one position of the other sugar.

Employing conditions similar to those used for the preparation of the corresponding compounds of glucose, 6-trityl-2,3,4-triacetyl-β-2-chloroethyl-D-glucoside and 2,3,4-triacetyl-β-2-chloroethyl-D-glucoside were readily obtained in satisfactory yield. The latter, on condensation with acetobromoglucose, gave β-2-chloroethylgentiobioside heptaacetate. This reaction serves as a proof of the structure of the 2,3,4-triacetyl-β-2-chloroethyl-D-glucoside since the β-2-chloroethylgentiobioside heptaacetate obtained from ethylene chlorohydrin and acetobromogentiobiose was available for comparison with the product of this alternative synthesis.[6]

2,3,4-Triacetyl-β-2-chloroethyl-D-glucoside also was condensed with acetobromo-D-xylose to form β-2-chloroethylprimeveroside hexaacetate.

Experimental

Acetobromogentiobiose.—Acetobromogentiobiose was prepared from β-gentiobiose octaacetate and hydrogen bromide by a procedure differing somewhat from that used by previous workers. The modified procedure, involving the use of toluene to remove the acetic acid, gave a yield of 57% of recrystallized product. Details are given in a previous publication.[1b]

β-2-Chloroethylgentiobioside Heptaacetate.—A mixture of 13 cc. of alcohol-free dry chloroform, 0.84 g. (2 mols) of dry ethylene chlorohydrin, 5.3 g. of Drierite and 1.4 g. of silver oxide was kept at room temperature with occasional shaking for one-half hour. Three-tenths of a gram of iodine[7] was then added followed by 3.68 g. (1 mol) of acetobromoglucose in small portions over a period of one hour. The mixture stood at room temperature overnight, after which it was filtered through Celite and the insoluble material washed well with chloroform. The chloroform solution was washed with water, the chloroform evaporated off *in vacuo* and the product crystallized from absolute ethanol, yield 2.98 g. or 81%. Treatment with Norite and recrystallization from absolute ethanol gave the pure substance. In melting point determinations partial melting was observed at 128–129° (cor.) with the final melting point at 167–168° (cor.). The amount of change noted at the lower temperature was affected by the rate of heating and varied from a barely perceptible change to almost complete melting if the sample in the melting point tube was plunged into a bath at a temperature above 129°. On continuing the heating the sample solidified again and then melted sharply at the higher temperature. Specific rotation was $[\alpha]^{25}\text{D}$ −20.2° (*C*, 3.755; $CHCl_3$).

Anal. Calcd. for $C_{28}H_{39}O_{18}Cl$: Cl, 5.07. Found: Cl, 5.03, 4.98.

6-Trityl-2,3,4-triacetyl-β-2-chloroethyl-D-glucoside.—Trityl chloride (17.05 g., 1 mol) and 14.8 g. (1 mol) of β-2-chloroethyl-D-glucoside[4] were dissolved in 50 cc. of dry pyridine and kept at room temperature for six hours. The solution was then cooled in an ice-bath and 35 cc. of acetic anhydride added. After standing at room temperature overnight the reaction mixture was poured slowly into

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(1) (a) Miller, *Contrib. Boyce Thompson Inst.*, **9**, 425 (1938); (b) **12**, 15 (1941).

(2) Reynolds and Evans, This Journal, **60**, 2559 (1938).

(3) Helferich and Klein, *Ann.*, **450**, 219 (1926).

(4) Compton, *Contrib. Boyce Thompson Inst.*, **11**, 21 (1940).

(5) Helferich, Bredereck and Schneidmüller, *Ann.*, **458**, 111 (1927); Robertson and Waters, *J. Chem. Soc.*, 1881 (1931).

(6) β-2-Chloroethylgentiobioside heptaacetate has also been obtained by acetylating the glycoside formed in tomato plants grown in a nutrient medium containing ethylene chlorohydrin (unpublished results). Although tomato plants are not known to contain gentiobiose normally, absorption of certain chemicals has been shown to lead to the formation of β-gentiobiosides. See (1b) and Miller. *Contrib. Boyce Thompson Inst.*, **11**, 387 (1941).

(7) Helferich, Bohm and Winkler, *Ber.*, **63**, 989 (1930).

750 cc. of ice water. After several hours the product was separated by centrifugation, dissolved in a mixture of acetone and absolute ethanol and crystallized at −7°. The crude product melted over a wide range (100–132°) but after four recrystallizations from 95% ethanol 17.45 g. of the pure compound was obtained; m. p. 158–159° (cor.); $[\alpha]^{25}D$ +30.2° (*C*, 2.545; $CHCl_3$); yield 47%.

Anal. Calcd. for $C_{33}H_{35}O_9Cl$: Cl, 5.80. Found: Cl, 5.80, 5.74.

2,3,4-Triacetyl-β-2-chloroethyl-D-glucoside.—6-Trityl-2,3,4-triacetyl-β-2-chloroethyl-D-glucoside (12 g.) was dissolved with slight warming in 75 cc. of glacial acetic acid. The solution was then cooled in an ice-bath and 5 cc. of a 40% solution of hydrogen bromide in glacial acetic acid added and the mixture shaken. A voluminous precipitate formed at once and this was immediately filtered off and washed with glacial acetic acid. The filtrate was poured into 100 cc. of ice water and the mixture extracted with chloroform. Most of the chloroform was evaporated off under vacuum, with the bath temperature not over 40°, and on the addition of ether and petroleum ether the product crystallized. For recrystallization the substance was dissolved in a minimum of chloroform and precipitated by the addition of ether and petroleum ether. After two such recrystallizations, 4.0 g. melting at 120–121° (cor.), $[\alpha]^{28}D$ −17.6° (*C*, 3.375; $CHCl_3$), was obtained; yield, 55%.

Anal. Calcd. for $C_{14}H_{21}O_9Cl$: Cl, 9.62. Found: Cl, 9.70, 9.82.

To form the tetraacetate 300 mg. was acetylated in 5 cc. of pyridine and 3 cc. of acetic anhydride. After standing overnight at room temperature the mixture was poured into 80 cc. of ice water and the crystalline product separated by filtration and washed with water; yield, 300 mg. Recrystallization from absolute ethanol did not change the melting point of 118–119° (cor.). In a mixed melting point determination with the tetraacetate obtained from ethylene chlorohydrin and acetobromoglucose no depression was observed.

β-2-Chloroethylgentiobioside Heptaacetate from 2,3,4-Triacetyl-β-chloroethyl-D-glucoside and Acetobromoglucose.—A mixture of 1.5 g. of 2,3,4-triacetyl-β-2-chloroethyl-D-glucoside, 1.1 g. of silver oxide, 4.5 g. of Drierite and 15 cc. of alcohol-free dry chloroform was shaken mechanically for one hour. A small quantity of iodine (0.25 g.) was then added followed by 1.67 g. (1 mol) of acetobromoglucose in small portions over a period of one hour. The mechanical shaking was continued for a further two hours, after which the reaction mixture stood at room temperature overnight. The solution was then filtered through Celite, the residue washed well with chloroform, the chloroform removed *in vacuo* and the product crystallized from absolute ethanol; yield, 1.39 g. or 49%. For analysis a 0.5-g. portion was recrystallized twice from absolute ethanol. It had the same melting point behavior as described above for this compound obtained from ethylene chlorohydrin and acetobromogentiobiose with final melting at 167–168° (cor.). A mixed melting point determination gave no depression. The optical rotation was found to be $[\alpha]^{27}D$ −20.2° (*C*, 2.875; $CHCl_3$).

Anal. Calcd. for $C_{28}H_{39}O_{18}Cl$: Cl, 5.07. Found: Cl, 5.13, 5.07.

β-2-Chloroethylprimeveroside Hexaacetate.—Following the same procedure used for the preparation of β-2-chloroethylgentiobioside heptaacetate, 1.5 g. of 2,3,4-triacetyl-β-2-chloroethyl-D-glucoside was condensed with 1.36 g. (1 mol) of acetobromo-D-xylose to form β-2-chloroethylprimeveroside hexaacetate. The yield of crude product was 1.05 g. (41%), m. p. 175.5–176.5°. For analysis 0.50 g. was recrystallized twice from absolute ethanol to give 0.40 g., m. p. 176.5–177.5° (cor.); $[\alpha]^{27}D$ −39.9° (*C*, 4.105; $CHCl_3$).

Anal. Calcd. for $C_{25}H_{35}O_{16}Cl$: Cl, 5.66. Found: Cl, 5.77, 5.60.

Summary

β-2-Chloroethylgentiobiose heptaacetate was synthesized from ethylene chlorohydrin and acetobromogentiobiose and by condensing 2,3,4-triacetyl-β-2-chloroethyl-D-glucoside with acetobromoglucose. The 2,3,4-triacetyl-β-2-chloroethyl-D-glucoside was prepared from β-2-chloroethyl-D-glucoside through the 6-trityl-2,3,4-triacetyl derivative.

2,3,4-Triacetyl-β-2-chloroethyl-D-glucoside was condensed with acetobromo-D-xylose to give β-2-chloroethylprimeveroside hexaacetate.

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