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OPTICAL ROTATION AND ATOMIC DIMENSION. VII. THE HALOGENO-HEPTA-ACETYL DERIVATIVES OF GENTIOBIOSE

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In the sixth article of this series, it was reported that the specific rotational values of the halogen hepta-acetyl derivatives of two bioses (cellobiose and glucosido-mannose) deviate from the regular relationship observed for the monose sugars and further that an agreement is obtained by excluding the values for the fluoro derivatives. This conclusion was also supported by the values for the chloro, bromo and iodo compounds of lactose measured by Hudson and Kunz[1] (the fluoro derivative being amorphous). These three bioses possess the same type of carbon attachment in their structural formulas, the two constituent monoses being attached to each other by an oxygen atom in the same way (according to the latest views the *fourth* carbon of the one monose to the *first* carbon of the second).

The preparation and the rotational values of the pure crystalline fluoro, chloro, bromo and iodo derivatives of acetylated gentiobiose are described in the present article. The synthesis of this biose by Helferich and co-workers[2] leaves hardly any doubt that in gentiobiose the *sixth* carbon of the one monose is attached through an oxygen atom to the *first* carbon atom of the other. Gentiobiose is, therefore, a representative of the so-called "straight chain" bioses, the others being representative of the branched chain bioses. The data for the specific rotations compiled in Tables I and II show that both kinds of bioses behave in the same

TABLE I

COMPARISON OF SPECIFIC ROTATIONS OF BIOSE DERIVATIVES WITH REPRESENTATIVE MONOSE DERIVATIVES (INCLUDING FLUORO DERIVATIVES)

	Derivatives of			Respective spec. rot. diff.			Respective spec. rot. diff. reduced			Specific rot. diff. of monose sugars (glucose) reduced to Bragg's atomic diameter difference
	Gentiobiose	Cellobiose	Glucosido-mannose							
F	+ 43.8	+ 30.6	+ 13.6							
				36.7	41.1	37.6	41	41	41	41
Cl	+ 80.5	+ 71.7	+ 51.2							
				20.6	24.1	26.7	23	24	29	17
Br	+101.1	+ 95.8	+ 77.9							
				25.0	29.9	33.6	28	30	37	21
I	+126.1	+125.7	+111.5							

[1] Hudson and Kunz, THIS JOURNAL, **47**, 2052 (1925).

[2] (a) Helferich and others, *Ann.*, **447**, 27 (1926); (b) **450**, 219 (1926).

TABLE II

COMPARISON OF SPECIFIC ROTATIONS OF BIOSE DERIVATIVES WITH REPRESENTATIVE MONOSE DERIVATIVES (EXCLUDING FLUORO DERIVATIVES)

	Derivatives of				Respective spec. rot. diff.				Respective spec. rot. diff. reduced				Spec. rot. diff. of monose sugars (glucose) reduced to Bragg's atomic diameter diff.
	Gentiobiose	Cellobiose	Lactose	Glucosidomannose									
Cl	+ 80.5	+ 71.7	+ 83.9	+ 51.2									
					20.6	24.1	24.8	26.7	17	17	17	17	17
Br	+101.1	+ 95.8	+108.7	+ 77.9									
					25.0	29.9	28.2	33.6	21	21	20	21	21
I	+126.1	+125.7	+136.9	+111.5									

manner: by including the fluoro derivatives a deviation from the regular relationship of the monose sugars is observed, whereas by excluding the fluoro derivatives the *same ratio 17:21* is found again. The ratio 41:17:21 obtained from the specific rotational values of the halogen derivatives of the monose sugars agrees closely with the ratio derived from the calculations of de Boer and van Arkel[3] for distances of the carbon atom to the halogen atoms in carbon compounds. This ratio is 41:17:22.6.

The interpretation stated and discussed in the preceding article[4] holds also for the gentiobiose derivatives. Besides α-fluoro-, chloro-, bromo- and iodo-hepta-acetylgentiobiose impure β compounds of chloro- and iodo-hepta-acetylgentiobiose can be obtained. Starting from β-octa-acetylgentiobiose in acetic anhydride solution, which is saturated at $-15°$ with hydrochloric acid, the β-chloro derivative is first formed and subsequently converted to the α-chloro compound. On account of this conversion, which is much enhanced by zinc chloride (see experimental part for further information) and which even takes place in a pure chloroform solution, a mixture in which the *β compound* predominated is not easily obtained.[5]

[3] De Boer and van Arkel, *Z. Physik*, **41**, 27 (1927). Also their value for the distance carbon-hydrogen agrees with the respective rotational differences of the salicin derivatives reported in Part V.

[4] That as a result of the complicated structure of the molecule other atoms are situated in the neighborhood of the halogen atoms, whereby these halogen atoms are selectively influenced.

[5] The observed facts may be studied further for the purpose of obtaining more detailed information on the mechanism of substitution. An interesting treatment of this subject is given by Hückel ["Konfigurationsänderungen bei Substitutionsreaktionen," *Z. angew. Chem.*, **39**, 842 (1926)]. The positions of α- and β-hydroxyl, acetyl and halogen in the molecule having been established and correlated, and the nomenclature having therefore been put on a sound basis [Hudson, THIS JOURNAL, **46**, 463 (1924); Böseken, *Ber.*, **46**, 2612 (1913); Pictet, *Helv. Chim. Act.*, **3**, 649 (1920)], the conclusion may be reached that the *Walden inversion* from β-octa-acetyl gentiobiose to

Experimental Part

General Remarks.—For all determinations of the specific rotation U. S. P. chloroform or purified chloroform was used. The volume of the solution was made up in the same flask to 24.9767 cc. at 20°, which must be multiplied by the factor 4.0038 to obtain 100 cc. The reading was made in the same 4dm. tube at 20° and is given in circular degrees.

β-Octa-acetylgentiobiose.—The preparation by Hudson and Johnson[6] was improved, yielding a method similar to the method of Haworth and Wylam.[7] After the method had been tested with small quantities it was found that 4 kg. of powdered gentian root could be worked up at one time. The weevils that infest the root and powder may in some cases reduce the yield to *nil*. A genuine powder yielded originally about 3% of pure octa-acetylgentiobiose, of which 1 kg. was prepared. The remaining powder was kept in tin containers. After one year only about 0.5% yield could be obtained from this powder, and a few months later none was obtained.

Four kilograms of powdered gentian root was mixed with 35 liters of water in a 16-gallon crock; 8 small cakes of bakers' yeast was added and the mixture was allowed to ferment to completion, which required two days, an additional 8 cakes of yeast having been added on the morning of the second day. The mixture was stirred occasionally with a paddle. Lead subacetate solution (1600 cc. of specific gravity 1.25) was added and the mixture was well stirred and filtered on large Büchner funnels and washed with a few liters of water. The filtrate was treated with hydrogen sulfide until all of the lead was precipitated. The excess hydrogen sulfide was blown out with a current of air. The liquid was then filtered on Büchner filters containing a layer of hot decolorizing carbon (heated in a pan with boiling water). The almost colorless filtrate was evaporated in a large distilling apparatus in a vacuum to a sirup of high density, the maximum temperature of the outside bath being 65°. When the gentian powder has undergone deterioration the filtrate is more acid and should be neutralized with sodium bicarbonate.

The sirup was digested under a reflux condenser on a steam-bath with 1200 cc. of absolute methyl alcohol with frequent, vigorous shaking. The mixture was then cooled rapidly to 20° and filtered on a large suction filter. The filtrate was concentrated at low temperature, the thick sirup being poured into two tared 6-liter flasks. One-fourth of its weight of dry sodium acetate and four times its weight of acetic anhydride were added to the sirup and the mixture was slowly heated on the steam-bath with vigorous shaking. As soon as the reaction started and the mixture boiled, it was quickly cooled in ice water to prevent foaming. When the reaction had quieted down the solution was boiled for five minutes and the contents of each flask was poured with constant stirring into about 8 liters of water. At first a dark, sticky reaction product formed which was separated by decantation and allowed to solidify under fresh water. A purer product gradually separated from the decanted solution on standing for a few days. The crude octa-acetate was recrystallized first from 50% alcohol and then from absolute methyl alcohol (with the aid of decolorizing carbon) until a pure product was obtained.

α-chloro-hepta-acetyl gentiobiose *proceeds at least in two definite steps*. Preliminary experiments showed that α-octa-acetylgentiobiose and β-penta-acetylglucose seem to follow the same procedure in this reaction. Schlubach [*Ber.*, **59**, 840 (1926)] and Brigl and Keppler [*Ber.*, **59**, 1588 (1926)] have already prepared β-chloro-acetyl glucose and similar β derivatives by other methods.

[6] Hudson and Johnson, THIS JOURNAL, **39**, 1274 (1917).

[7] Haworth and Wylam, *J. Chem. Soc.*, **123**, 3122 (1923).

α-Fluoro-hepta-acetylgentiobiose was prepared from β-octa-acetylgentiobiose in the manner previously described.[8] It is important to finish the distillation as quickly as possible (in twenty minutes instead of half an hour). The sirup was crystallized by stirring with some methyl alcohol, the yield of impure crystals being 7 g. from 15 g. of β-octa-acetate. It was recrystallized several times by dissolving in boiling methyl alcohol with addition of decolorizing carbon, filtering through hardened paper with the aid of a hot-water funnel and allowing the filtrate to cool gradually. The pure product crystallizes in small needles and is stable, colorless and tasteless. It is fairly soluble in benzene, slightly soluble in petroleum ether, water and cold methyl alcohol; m. p. 168–169° (Helferich, Bäuerlein and Wiegand, 162–163°).[9] The determination of the specific rotation in chloroform gave the following result.

Rotation. Third recrystallization. Subs., 0.6358: $\alpha = +4.325°$; $[\alpha]_D^{20} = +42.48°$. Fourth recrystallization. Subs., 0.6015: $\alpha = +4.142°$; $[\alpha]_D^{20} = +42.99°$. Fifth recrystallization. Subs., 0.6303: $\alpha = +4.384°$; $[\alpha]_D^{20} = +43.43°$. Sixth recrystallization. Subs., 0.6251: $\alpha = +4.384°$; $[\alpha]_D^{20} = +43.79°$. Seventh recrystallization. Subs., 0.6142: $\alpha = +4.280°$; $[\alpha]_D^{20} = +43.51°$.

Therefore, +43.80° is taken as the specific rotation of the pure substance, since another preparation gave as the final rotation +43.85°.

Anal. Subs., 0.2091: CO_2, 0.3738; H_2O, 0.1017. Subs., 0.5168: CaF_2, 0.0299. Subs., 0.5000: 100.00 cc. of 0.25 *N* H_2SO_4, 312.10 cc. of 0.1 *N* NaOH. Subs., 0.0516, 0.0866: C_6H_6, 100 g., Δf, 0.028°, 0.040°. Calcd. for $C_{26}H_{35}O_{17}F$: C, 48.88; H, 5.53; F, 2.97; 62.67 cc. of 0.1 *N* NaOH for AcOH + F; mol. wt., 638. Found: C, 48.76; H, 5.44; F, 2.81; 62.10 cc. of 0.1 *N* NaOH; mol. wt., 554, 651.

α-Chloro-hepta-acetylgentiobiose.—Many experiments were made before suitable conditions were found to obtain this derivative. The use of zinc chloride in the reaction is especially essential. Besides the two reactions mentioned in the introduction, another reaction is noticeable in which probably a dichloro compound is formed. This dichloro compound is not easily separated from the monochloro compound, the best means found being recrystallization from methyl alcohol. In order to prevent its formation as far as possible, it is necessary to follow exactly the description of the preparation as to time and temperature.

A tube 25 cm. long and 5 cm. in diameter was closed at one end and sealed at the other end to a tube 1 cm. in diameter and 7 cm. long. This tube was used as a container for saturating with hydrochloric acid a suspension of 10 g. of dry β-octa-acetylgentiobiose in a solution of 3 g. of zinc chloride in 100 cc. of pure acetic anhydride. The hydrochloric acid was washed by passage through sulfuric acid and then through acetic anhydride, after which it was passed through a glass spiral tube provided with a bulb pocket at the lower end for condensing acetic anhydride vapor (by cooling the spiral in an ice-and-salt mixture). A slow stream of hydrogen chloride thus prepared was passed through the described solution of gentiobiose octa-acetate, the container being cooled in ice and salt. Saturation was completed in about three hours. The tube was sealed and kept for twenty-two hours at 3 to 5°. It was opened after cooling in ice and salt. The solution, after being concentrated by means of a current of dry air under a bell jar for one hour, was poured into a separatory funnel containing ice water, crushed ice and chloroform and was shaken out 4 times with water. The chloroform solution was dried with calcium chloride and concentrated at low temperature to a sirup which crystallized readily when stirred with ether. The crystals were separated on a suction filter. Recrystallization was first performed by adding ether to a concentrated

[8] Brauns, THIS JOURNAL, **45**, 834 (1923).

[9] Ref. 2a, p. 36.

chloroform solution. Repeated recrystallizations did not remove all impurities, as the chlorine content was always found to be too high. Good results were obtained by making a concentrated solution in hot methyl alcohol, adding some decolorizing carbon, filtering through hardened paper with the aid of a hot-water funnel and cooling the solution in ice and afterwards in ice and salt.

The crystals were separated on a suction filter and dried in a vacuum desiccator; m. p. 148°. The determination of the specific rotation in chloroform gave the following results.

Rotation. First recrystallization. Subs., 0.4434: $\alpha = +5.684°$; $[\alpha]_D^{20}$ +80.04°. Second recrystallization. Subs., 0.4642: $\alpha = +5.961°$; $[\alpha]_D^{20}$ +80.18°. Third recrystallization. Subs., 0.6431: $\alpha = +8.276°$; $[\alpha]_D^{20}$ +80.36°. Fourth recrystallization. Subs., 0.6476: $\alpha = +8.370°$; $[\alpha]_D^{20}$ +80.70°. Fifth recrystallization. Subs., 0.6289: $\alpha = +8.117°$; $[\alpha]_D^{20}$ +80.59°. Sixth recrystallization. Subs., 0.6491: $\alpha = +8.370°$; $[\alpha]_D^{20}$ +80.51°; 0.6185: $\alpha = +7.978°$; $[\alpha]_D^{20}$ +80.54°; 0.6495: $\alpha = +8.373°$; $[\alpha]_D^{20}$ +80.50°.

The average of the last crystallization, +80.52°, is taken as the specific rotation of the pure substance. The pure solution crystallizes in needles and is tasteless, colorless and stable. It is readily soluble in ordinary solvents except water, petroleum ether and ether.

Anal. Subs., 0.2377: CO_2, 0.4172; H_2O, 0.1134. Subs., 0.2477, 0.2501: AgCl, 0.0535, 0.0523. Subs., 0.5000: 310.53 cc. of 0.1 *N* NaOH; 249.25 cc. 0.1 *N* H_2SO_4. Subs., 1.3392, 2.5513: C_6H_6, 100 g., Δf, 0.114°, 0.202°. Calcd. for $C_{26}H_{55}O_{17}Cl$: C, 47.65; H, 5.39; Cl, 5.41; 61.10 cc. of 0.1 *N* NaOH; mol. wt., 655. Found: C, 47.50; H, 5.33; Cl, 5.34; 5.17; 61.28 cc. of 0.1 *N* NaOH; mol. wt., 588, 631.

α-Bromo-hepta-acetylgentiobiose.—Thirty grams of octa-acetylgentiobiose was dissolved in 300 cc. of purified chloroform and cooled to about 0° in an ice-and-salt mixture, 75 cc. of a saturated solution of hydrogen bromide in acetic acid (also cooled to 0°) being added. The mixture was kept in a stoppered Erlenmeyer flask in ice water for one and one-half hours, then was poured into a separatory funnel containing ice water and cracked ice and shaken out 4 times with ice water. The chloroform extract was dried with calcium chloride, filtered and evaporated to a sirup at low temperature. Dry ether was added and by evaporating and stirring, the sirup was brought to crystallization. The crystals were filtered by suction and recrystallized by dissolving in a small amount of purified chloroform and gradually adding ether to the filtered solution. The first separation contained most of the impurities. The recrystallization was repeated until a constant rotation was obtained; m. p. 144°. The solutions for the rotations were prepared with purified chloroform.

Rotation. First recrystallization. Subs., 0.6049: $\alpha = +9.770°$; $[\alpha]_D^{20}$ +100.85°. Second recrystallization. Subs., 0.6061: $\alpha = +9.808°$; $[\alpha]_D^{20}$ +101.04°. Third recrystallization. Subs., 0.6113: $\alpha = +9.895°$; $[\alpha]_D^{20}$ +101.06°; 0.6343: $\alpha = +10.269°$; $[\alpha]_D^{20}$ +101.08°. Fourth recrystallization. Subs., 0.6301: $\alpha = +10.206°$; $[\alpha]_D^{20}$ +101.14°; 0.6383: $\alpha = +10.328°$; $[\alpha]_D^{20}$ +101.03°.

Therefore, +101.08° is taken as the specific rotation of the pure substance. It is not stable but can be kept in a desiccator over sodium hydroxide in an ice box. It crystallizes in colorless needles and is tasteless. It is soluble in ordinary solvents except water, petroleum ether and ether. Zemplén,[10] who first described crystalline bromo-hepta-acetylgentiobiose, found m. p. 132–133.5° and $[\alpha]_D^{19}$ +111.8°. Probably Zemplén's preparation contained some dibromo derivative, as is also indicated by the bromine determination (found 12.06% Br).

[10] Zemplén, *Ber.*, **57**, 702 (1924).

Anal. Subs., 0.2757: CO_2, 0.4530; H_2O, 0.1207. Subs., 0.3146, 0.3126: AgBr, 0.0864, 0.0859. Subs., 0.5000: 306.44 cc. of 0.1 *N* NaOH; 249.25 cc. of 0.1 *N* H_2SO_4. Subs., 1.0431, 1.7316: C_6H_6, 100 g., Δf, 0.082°, 0.135°. Calcd. for $C_{26}H_{35}O_{17}Br$: C, 44.62; H, 5.05; Br, 11.43; 57.20 cc. of 0.1 *N* NaOH; mol. wt., 699. Found: C, 44.81; H, 4.90; Br, 11.68, 11.69; 57.19 cc. of 0.1 *N* NaOH; mol. wt., 636, 641.

α-Iodo-hepta-acetylgentiobiose.—Five grams of gentiobiose octa-acetate was dissolved in 10 cc. of methylene chloride in a Pyrex test-tube and a minute amount of zinc iodide was added. The solution was cooled in an ice-and-salt bath. Hydriodic acid (which was first passed through asbestos mixed with red phosphorus, then through a calcium chloride tower, then through a phosphorus pentoxide tube and finally through a spiral tube cooled in ice and salt) was passed in a slow stream through the gentiobiose octa-acetate solution for ten to fifteen minutes. The solution was poured into a dish and evaporated with a dry current of air under a bell jar. The residue was stirred with petroleum ether, the solution was poured off and this process repeated until crystallization started. The crystals were mixed with dry ether, filtered by suction and washed with small amounts of ether. Recrystallization was produced by dissolving in a small amount of purified chloroform and gradually adding ether. The first separation contains most of the colored impurities. The recrystallization was repeated until a constant rotating substance was obtained.

The pure compound decomposes at 134° forming a dark brown liquid. The determination of the specific rotation in chloroform gave the following results.

Rotation. First recrystallization. Subs., 0.4524: $\alpha = +9.080°$; $[\alpha]_D^{20}$ +125.32°. Second recrystallization. Subs., 0.5555: $\alpha = +11.212°$; $[\alpha]_D^{20}$ +126.02°. Third recrystallization. Subs., 0.5270: $\alpha = +10.640°$; $[\alpha]_D^{20}$ +126.06°.

Therefore, +126.10° is taken as the specific rotation of the pure substance. The pure compound crystallizes in long needles and is tasteless and colorless. It is not stable but can be kept in a pure condition for many months in a desiccator over sodium hydroxide in an ice box. It is readily soluble in the ordinary solvents except water, petroleum ether and ether.

Anal. Subs., 0.2477: CO_2, 0.3788; H_2O, 0.1092. Subs., 0.2157: AgI, 0.0688. Calcd. for $C_{26}H_{35}H_{17}I$: C, 41.82; H, 4.73; I, 17.02. Found: 41.71; H, 4.94; I, 17.24.

α- and β-Chloro-hepta-acetylgentiobiose.—Two grams of β-octa-acetylgentiobiose was dissolved in 20 cc. of acetic anhydride and saturated in an ice-and-salt bath with hydrochloric acid in the manner described for the preparation of the α-chloro derivative, except that no zinc chloride was added. The tube was sealed and kept for three hours at 15°; then it was cooled in an ice-and-salt bath and opened, the solution being poured into an evaporating dish and evaporated for half an hour with a current of dry air. The remaining solution was diluted with purified chloroform and poured into a separatory funnel containing ice water and cracked ice. The chloroform solution was quickly shaken out 3 times with ice water, dried with calcium chloride and evaporated with a rapid dry current of air to a sirup which was stirred with ether and soon solidified to a crystalline mass which was then thinned with ether, the crystals were filtered on a suction filter and dried in a vacuum desiccator. The determination of the specific rotation of 0.4651 g. of substance in purified chloroform gave the results shown in Table III. The tabulation shows a change from a negative to a positive rotation. A Carius determination gave the following result. Subs., 0.2458: AgCl, 0.0597; calcd. for a monochloro-derivative, $C_{26}H_{35}O_{17}Cl$, 5.42% Cl. Found: 6.0% Cl. A small amount of dichloro-derivative is therefore present in the reaction product. Calculated according to Hudson's method [Hudson, THIS JOURNAL, **46**, 462, 476, 2600 (1924)] taking the specific rotation of α-chloro-hepta-acetylgentiobiose (mol. wt. 655, $[\alpha]_D = +80.5$) and Hudson's coefficient $B_{gentiobiose} = +15{,}900$ as a basis, the specific rotation of

TABLE III

SPECIFIC ROTATION

Time after solution	α	$[\alpha]_D^{20}$
10 min.	−0.520	− 7.0°
30 min.	−0.450	− 6.0
1 hr.	−0.398	− 5.3
2 hr.	−0.312	− 4.2
5 hr.	−0.03	− 0.5
45 hr.	+1.473	+19.8

β-chloro-hepta-acetylgentiobiose should be $(B_{gentiobiose} - A_{Cl})/655 = 15{,}900 - [(80.5(655) - 15{,}900)]/655 = -32$, from which it is concluded that at least three-fourths of the reaction product is β-chloro-hepta-acetylgentiobiose. This indicates that the β-chloro derivative is formed first and is then converted into the α-chloro derivative. A preliminary experiment was made for the purpose of converting the impure β-chloro-hepta-acetylgentiobiose with silver carbonate and methyl alcohol into the α-methyl derivative. A colorless sirup which could not be brought to crystallization was obtained.

α- and β-Iodo-hepta-acetylgentiobiose.—Eight grams of β-gentiobiose octa-acetate was dissolved in 16 cc. of methylene chloride and the solution was saturated in an ice-and-salt bath with hydriodic acid in the manner described for the preparation of the α-iodo derivative, no zinc chloride being added. The light brown solution was quickly evaporated in a current of dry air. On stirring with petroleum ether the residue solidified to a mass of needles which was dissolved in a small quantity of purified chloroform. Ether was added until crystallization started. The crystals which separated were washed with ether on a suction filter. They were sticky and contained iodine. Probably the recrystallization had partly converted the α- into the β-iodo derivative. The determination of the specific rotation of 0.1674 g. of substance in purified chloroform gave the following result.

Time after solution	α	$[\alpha]_D^{20}$
6 min.	−0.381	−14.2°
10 min.	−0.268	−10.3
20 min.	−0.208	− 7.7
30 min.	−0.173	− 6.5
1 hr.	−0.035	− 1.3
24 hr.	+2.045	+76.3
48 hr.	+2.530	+94.4
72 hr.	+2.634	+98.3

After twenty-four hours the solution gradually turned brown. Calculated according to Hudson's method, taking the specific rotation of α-iodo-hepta-acetylgentiobiose (mol. wt. 746, $[\alpha]_D = +126.1$) and Hudson's coefficient $B_{gentiobiose} = +15{,}900$ as a basis, the specific rotation of β-iodo-hepta-acetylgentiobiose should be $(B_{gentiobiose} - A_I)/746 = (15{,}900 - [(126.1)(746) - 15{,}900)]/746 = -83$, from which it is concluded that at least 67% of the reaction product is β-iodo-hepta-acetylgentiobiose. This supports the conclusion reached in the case of the chloro derivative that in this reaction the β halogen derivative is formed first and is subsequently converted into the α-halogen derivative.

Summary

The α-fluoro-, chloro-, bromo- and iodo-hepta-acetyl derivatives of gentiobiose have been prepared and described. A comparison of the

specific rotational values of these halogen derivatives shows that these straight chain biose derivatives behave the same as the branched chain biose derivatives investigated in the previous article, as agreement with the regular relationship observed for the corresponding derivatives of the monose sugars is obtained only by excluding the values for the fluoro derivatives.

Besides the pure α-halogen derivatives of gentiobiose, impure β-chloro and iodo compounds were obtained.

The Walden inversion from β-octa-acetylgentiobiose to α-chloro- and iodo-hepta-acetyl gentiobiose by the action of hydrochloric and hydriodic acids proceeds at least in *two* definite steps, β-chloro- or iodo-hepta-acetyl-gentiobiose being intermediately formed.

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ACYL ISO-UREAS

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The chemistry of methyl- and ethyl-*iso*-ureas (oxygen ethers of urea) and their acyl derivatives has been studied mainly by Stieglitz and his collaborators,[1,2,3] and by Wheeler and Johnson.[4]

More recently E. A. Werner[5] has made important contributions to this field of study.

In an investigation of the pharmacological properties of acyl *iso*-ureas, it was observed by one of us[6] that carbethoxy-ethyl-*iso*-urea was mildly depressing to the central nervous system and caused a large and rapid fall of body temperature. Later it was shown that dicarbethoxy-ethyl-*iso*-urea possessed similar properties but in greater degree[7] while carbo-*n*-butoxy-ethyl-*iso*-urea had only slight physiological action.[8]

In view of these results, the preparation of a greater variety of acyl *iso*-ureas was undertaken. Since only methyl- and ethyl-*iso*-ureas and their derivatives have been prepared up to the present, a study of the possibility of obtaining propyl-, butyl-, phenyl-, benzyl- and phenylethyl-*iso*-ureas was commenced, preliminary results of which are reported in this

[1] Dains, THIS JOURNAL, **21**, 136 (1899).

[2] Bruce, *ibid.*, **26**, 419 (1904).

[3] McKee, *Am. Chem. J.*, **26**, 209 (1901).

[4] Wheeler and Johnson, *ibid.*, **24**, 189 (1900).

[5] Werner, *J. Chem. Soc.*, **105**, 923 (1914); "The Chemistry of Urea," Longmans, London and New York, **1923**.

[6] Basterfield, *J. Pharmacol.*, **20**, 451 (1923).

[7] Basterfield and Paynter, THIS JOURNAL, **48**, 2176 (1926).

[8] Basterfield, Woods and Wright, *ibid.*, **48**, 2371 (1926).