Ferric chloride tests with fractions (d) and (e) were negative, with fraction (f) faintly positive, and with fractions (g) and (h), strongly positive. Fraction (g) was shown to consist largely of ethyl γ-acetyl-α,α-dimethylacetoacetate by conversion (by means of concentrated ammonia) into the lactam of 2,2-dimethyl-3-keto-5-amino-4-hexenecarboxylic acid, melting at 139–140°; this is the melting point reported in the literature[18] for this lactam. Fraction (h) presumably consisted entirely of ethyl γ-acetyl-α,α-dimethylacetoacetate.

Summary

1. In the presence of sodium ethoxide and triphenylmethane, ethyl benzoyldimethylacetate is converted completely into ethyl benzoate and ethyl isobutyryl-isobutyrate, the latter being converted into its enolate.

2. In the complete absence of proton donors, ethyl benzoyldimethylacetate is apparently stable toward sodium ethoxide.

3. In the presence of sodium ethoxide, α,α-dimethylacetoacetic ester is converted into γ-acetyl-α,α-dimethylacetoacetic ester and ethyl isobutyrate.

4. These results illustrate the reversibility of the Claisen type of condensation.

5. The mechanisms for these reactions are discussed.

(18) See Conrad and Gast, *Ber.*, **31**, 1342 (1898).

DURHAM, NORTH CAROLINA RECEIVED OCTOBER 30, 1939

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

The Synthesis of Certain Oligosaccharide Acetates in the Mannose Series[1]

BY DELBERT D. REYNOLDS AND WM. LLOYD EVANS

In a recent publication, the authors[2] discussed certain improvements in the well-known Königs and Knorr reaction as it was applied to the synthesis of α- and β-gentiobiose octaacetates. Our present paper contains an account of the first successful use of this reaction in the synthesis of certain acetates in the mannose series of saccharides.

Several epimeric pairs of mono- and disaccharides have been prepared by other workers and the properties of these compounds have been studied carefully. As far as the authors are aware such an epimeric pair in the trisaccharide series has never been reported. Anticipating the interesting problems that would arise from such a synthesis, acetobromogentiobiose was condensed with β-*d*-mannose-1,2,3,4-tetraacetate, a reaction which gave rise to 6-β-gentiobiosido-β-*d*-mannose hendekaacetate. This new hendekaacetate and that of 6-β-gentiobiosido-β-*d*-glucose prepared by Helferich and co-workers[3] make available the first known epimeric pair of trisaccharides. An application of Hudson's isorotation rules has been made to these two compounds.

By another application of the improved Königs and Knorr reaction, 6-β-*d*-glucosido-α-*d*-mannose octaacetate was prepared by the condensation of acetobromoglucose with α-*d*-mannose-1,2,3,4-tetraacetate. This method of preparing this disaccharide is to be preferred to the oxidation of gentiobial by the procedure of Bergmann and Schotte[4] which was utilized previously in this Laboratory[5]; the new method involves fewer steps and gives higher yields.

During the progress of this work it became necessary to prepare ethyl gentiobioside heptaacetate, the synthesis of which is herein described, together with an application of the isorotation rules to its rotation.

Experimental Part

Purification of Reagents.—Chloroform was purified by the method described in an earlier paper.[2] The mannose was prepared according to the method of Levene.[6] Acetobromogentiobiose was prepared from gentiobiose octaacetate by the method of Brauns.[7]

6-Trityl-β-*d*-mannose-1,2,3,4-tetraacetate.—The method of Helferich and Leete[8] was modified in such a way that the yield of 6-trityl-β-*d*-mannose-1,2,3,4-tetraacetate was doubled. One hundred grams of dry mannose and trityl chloride (161 g.) were added to anhydrous pyridine (500 cc.). The mixture was shaken in a thermostat at 50° until solution was complete (four hours). Without cooling, three hundred cc. of acetic anhydride was then

(1) Abstracted from a Thesis presented by Delbert D. Reynolds to the Graduate School of The Ohio State University in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

(2) D. D. Reynolds and W. L. Evans, THIS JOURNAL, **60**, 2559 (1938).

(3) B. Helferich and R. Gootz, *Ber.*, **64**, 109 (1931); B. Helferich and W. Schaefer, *Ann.*, **450**, 236 (1926).

(4) M. Bergmann and H. Schotte, *Ber.* **54**, 440 (1921).

(5) H. J. Dauben and W. L. Evans, THIS JOURNAL, **60**, 886 (1938).

(6) P. A. Levene, *J. Biol. Chem.*, **108**, 419 (1935).

(7) D. H. Brauns, THIS JOURNAL, **49**, 3170 (1927).

(8) B. Helferich and J. Leete, *Ber.*, **62**, 1552 (1929).

added in one portion. After standing at room temperature for about eighteen hours, the reaction mixture was poured slowly into seven liters of mechanically stirred ice water. The reaction product separated as a white amorphous solid. The water was changed twice in order to remove the pyridine. The crude product was separated by filtration, washed well with cold water and dried in the open air. It was then dissolved in hot 95% ethanol, decolorized with Carboraffin and the β-isomer allowed to crystallize. It was recrystallized from the same solvent; yield 150 g.; m. p. 204–206° (corr.).

β - *d* - Mannose - 1,2,3,4 - tetraacetate.—β - *d* - Mannose-1,2,3,4-tetraacetate was prepared according to the directions of Helferich and Leete[8] except for the method of crystallization.

Forty-six grams of 6-trityl-β-*d*-mannose-1,2,3,4-tetraacetate was dissolved in glacial acetic acid (200 cc.) by warming on a water-bath. The solution was cooled to 10°. Acetic acid (18 cc.) saturated with hydrogen bromide at 0° was added and the solution shaken for about forty-five seconds. The trityl bromide was removed at once by filtration and the filtrate poured into one liter of cold water. The tetraacetate was extracted with chloroform (250 cc.). The chloroform layer was washed twice with ice water and then dried over anhydrous sodium sulfate. After filtration, the chloroform was partially removed by a stream of dry air. The last traces were removed under reduced pressure. Anhydrous ether (100 cc.) was added and the sirup rubbed with a glass rod. Crystallization took place instantaneously. The product was purified by dissolving it in a minimum amount of U. S. P. chloroform and then adding anhydrous ether until crystallization began; yield 19.3 g.; m. p. 135.5–136.5° (corr.).

6-β-Gentiobiosido-β-*d*-mannose Hendekaacetate.—Sixteen grams (1.2 mol) of β-*d*-mannose-1,2,3,4-tetraacetate, silver oxide (26 g.), Drierite (100 g.) preheated at 240° for two hours, and dry, alcohol-free chloroform (150 cc.) were placed in a 500 cc. three-necked, round-bottomed flask equipped with a mercury-sealed mechanical stirrer, a calcium chloride drying tube and a dropping funnel. The flask was wrapped in black paper. The contents of the flask were stirred for about one hour to ensure the complete absence of water. Iodine (5 g.) was then added to the reaction mixture. Acetobromogentiobiose[7] (26.6 g., 1 mol) was dissolved in dry, alcohol-free chloroform (100 cc.) and then added through the dropping funnel to the reaction mixture over a course of about one hour. The stirring was then continued for an additional twenty-four hours. The reaction mixture was filtered through a layer of "Filter-Cel" and the residue washed well with U. S. P. chloroform. The filtrate was blown down by a stream of dry air and finally concentrated to a sirup under reduced pressure. The sirup was then dissolved in 95% ethanol. Crystallization began after a short time at room temperature. After standing in the refrigerator overnight, the crystals were filtered and dried; yield 27 g. (73.4%), m. p. 116–118° (corr.); after six recrystallizations, m. p. 122–123° (corr.) and $[\alpha]^{25}D$ −21.02° (*c*, 3.92; *l*, 2; $CHCl_3$).

Anal. Calcd. for $C_{18}H_{21}O_{18}(COCH_3)_{11}$: (a) acetyl, 11.39 cc. of 0.1 *N* sodium hydroxide per 100 mg. sample; C, 49.66; H, 5.63; mol. wt., 966. Found: (b) acetyl, 11.41 and 11.42; C, 48.55; H, 5.62; mol. wt., by Rast method, 935 and 1000.

Ethyl Gentiobioside Heptaacetate.—The preparation of 6-β-gentiobiosido-β-*d*-mannose hendekaacetate was repeated several times. In one instance crystalline ethyl gentiobioside heptaacetate was isolated as a result of insufficiently purified chloroform. Ethyl gentiobioside heptaacetate has not been recorded in the literature. For identification and characterization, it has been prepared by the method described for 6-β-gentiobiosido-β-*d*-mannose hendekaacetate. A mixture of absolute ethanol (100 cc.), silver oxide (10 g.), Drierite (50 g.) and dry chloroform (75 cc.) was stirred for one hour. One gram of iodine was added. Acetobromogentiobiose (15 g.) was dissolved in dry chloroform (25 cc.) and then added to the reaction mixture over a period of about one hour. After stirring for twenty-four hours, the reaction mixture was treated as previously described for 6-β-gentiobiosido-β-*d*-mannose hendekaacetate. Crystallization began as soon as the chloroform was removed. The product was filtered and recrystallized from 95% ethanol; yield 11.7 g. (82%) m. p. 158–159° (corr.); $[\alpha]^{25}D$ −23.06° (*c*, 4.12; *l*, 2; $CHCl_3$).

Anal. Calcd for $C_{14}H_{19}O_{11}(COCH_3)_7$; acetyl, 10.54 cc. of 0.1 *N* sodium hydroxide per 100 mg. of sample. Found: acetyl, 10.51 cc.

6-Trityl-α-*d*-mannose-1,2,3,4-tetraacetate.—A mixture of dry mannose (20 g.), trityl chloride (32.2 g.) and anhydrous pyridine (100 cc.) was shaken mechanically at room temperature. Solution was effected within four hours. The solution was placed in the refrigerator at 0° for fifteen hours and then poured slowly into two liters of mechanically stirred ice water. This water was changed three times. The granular precipitate was then filtered and dried, after which it was dissolved in pyridine and placed in the refrigerator for twelve hours. It was then kept at a temperature of 0–5° while 60 cc. of acetic anhydride was added and then placed in the refrigerator overnight. Ice water was added to turbidity and the solution poured slowly into three liters of mechanically stirred ice water. The water was changed twice. The dried precipitate (48 g.) was taken up in absolute ethanol (300 cc.), decolorized with Carboraffin and filtered. Crystallization began when the solution was blown down by a stream of dry air; yield 15 g. After one recrystallization $[\alpha]D$ +73.5° ($CHCl_3$); m. p. 123–124° (corr.).

6-β-*d*-Glucosido-α-*d*-mannose Octaacetate.—6-Trityl-α-*d*-mannose-1,2,3,4-tetraacetate (34 g.) was dissolved in glacial acetic acid (100 cc.). After cooling to 10° a saturated solution of hydrogen bromide in glacial acetic acid (18 cc.) was added. The solution was shaken for about one minute, filtered and the filtrate poured into one liter of water (25°). This water was stirred for one hour, in order to dissolve the α-*d*-mannose-1,2,3,4-tetraacetate and then filtered. The filtrate was extracted with U. S. P. chloroform (500 cc.), the chloroform portion washed three times with three 400-cc. portions of ice water, dried over anhydrous sodium sulfate and blown down to a sirup. This sirup was finally concentrated under reduced pressure and taken up in anhydrous alcohol-free chloroform.

To this chloroform solution were added Drierite (15 g.), and silver oxide (8 g.). After stirring for one-half hour,

iodine (0.5 g.) was added and then acetobromoglucose (8 g.), dissolved in anhydrous alcohol-free chloroform (35 cc.), was added over a course of one hour. The apparatus used was the same as that for the preparation of 6-β-gentiobiosido-β-*d*-mannose hendekaacetate. The reaction mixture was stirred for a total of twenty-four hours, filtered and concentrated to a sirup. This sirup was dissolved in 95% ethanol (50 cc.) and placed in the refrigerator. Crystallization began immediately; yield 6 g. (45.5%); after one recrystallization $[\alpha]_D$ +26.01° (*c*, 2.96; *l*, 2; $CHCl_3$), the same value as that recorded by Dauben and Evans.[5]

Discussion

The isorotation rules of Hudson[9] afford a means of arriving at the approximate rotation of the trisaccharide acetate. If it is assumed that the epimeric difference of the molecular rotation between 6-β-gentiobiosido-β-*d*-glucose hendekaacetate and 6-β-gentiobiosido-β-*d*-mannose hendekaacetate has the same value as that between β-*d*-glucose pentaacetate and β-*d*-mannose pentaacetate under the experimental conditions indicated by the symbol, $[\alpha]^{25}D$, then by the relation

$$[\alpha_A]M_A{}^{10} - [\alpha_B]M_B = [\alpha_{A'}]M_{A'} - [\alpha_{B'}]M_{B'}$$

it is possible to calculate the approximate rotation of 6-β-gentiobiosido-β-*d*-mannose hendekaacetate (B) from the known values of the molecular rotations of 6-β-gentiobiosido-β-*d*-glucose hendekaacetate (A),[3] β-*d*-glucose pentaacetate (A)[11] and β-*d*-mannose pentaacetate (B)[11] all measurements referring to chloroform solutions. Thus

$$\begin{aligned}[\alpha_B]M_B &= [\alpha_A]M_A - [\alpha_{A'}]M_{A'} + [\alpha_{B'}]M_{B'}\\ &= (-7728) - (1482) + (-9828)\\ &= -19{,}038\\ \therefore [\alpha_B] &= -19.7° \text{ (The observed value is } -21.0°.)\end{aligned}$$

Hudson[12] and Isbell[13] have shown previously that the values for the epimeric difference in the α-derivatives of the mannose series are entirely different from those of the β-derivatives. This is illustrated for the acetates in Table I.

Haworth and Hirst[14] have pointed out that the values of "the epimeric differences required by Hudson's scheme are not found in 4-glucosidomannose octaacetate and cellobiose octaacetate." However, it may be observed from Table I, as was shown by Dauben and Evans,[5] that the epimeric differences of α-gentiobiose octaacetate and 6-β-*d*-glucosido-α-*d*-mannose octaacetate agree very well with that of α-*d*-glucose pentaacetate and α-*d*-mannose pentaacetate. Further observation shows that the epimeric difference for 6-β-gentiobiosido-β-*d*-glucose hendekaacetate and the newly synthesized 6-β-gentiobiosido-β-*d*-mannose hendekaacetate agree in a satisfactory way with that of β-*d*-glucose pentaacetate and β-*d*-mannose pentaacetate. It thus appears that the epimeric relationships hold for the 6-linked sugar acetates, although they fail for the 4-linked acetates. Since the epimeric difference is twice the rotational value of carbon 2, the farther the glucosido portion is removed from carbon 2 the less influence it seems to have on the value of the epimeric difference.

TABLE I

EPIMERIC DIFFERENCES OF MOLECULAR ROTATION IN THE GLUCOSE AND MANNOSE SERIES

Sugar acetates	$[\alpha]_D$	Mol. epimeric diff.
α-Glucose pentaacetate	+101.6°	+18,200
α-Mannose pentaacetate	+ 55.0°	
α-Gentiobiose octaacetate	+ 52.4°	+17,900
α-6-Glucosidomannose octaacetate	+ 26.0°	
α-Cellobiose octaacetate	+ 42.0	+ 3,260
α-4-Glucosidomannose octaacetate	+ 36.2	
β-Glucose pentaacetate	+ 3.8	+11,300
β-Mannose pentaacetate	− 25.2	
β-Gentiobiosido-β-*d*-glucose hendekaacetate	− 8.0	+12,600
β-Gentiobiosido-β-*d*-mannose hendekaacetate	− 21.0	
β-Cellobiose octaacetate	− 14.6	− 1,940
β-4-Glucosidomannose octaacetate	− 13.0	

Table I, as was shown by Dauben and Evans,[5] that the epimeric differences of α-gentiobiose octaacetate and 6-β-*d*-glucosido-α-*d*-mannose octaacetate agree very well with that of α-*d*-glucose pentaacetate and α-*d*-mannose pentaacetate. Further observation shows that the epimeric difference for 6-β-gentiobiosido-β-*d*-glucose hendekaacetate and the newly synthesized 6-β-gentiobiosido-β-*d*-mannose hendekaacetate agree in a satisfactory way with that of β-*d*-glucose pentaacetate and β-*d*-mannose pentaacetate. It thus appears that the epimeric relationships hold for the 6-linked sugar acetates, although they fail for the 4-linked acetates. Since the epimeric difference is twice the rotational value of carbon 2, the farther the glucosido portion is removed from carbon 2 the less influence it seems to have on the value of the epimeric difference.

The rotation of the new β-ethyl gentiobioside heptaacetate may be calculated from the known values for

β-methylgentiobioside heptaacetate[15] ($[M]_D$ = (−18.9)-(650) = −12.300)

β-methylglucoside tetraacetate[16] ($[M]_D$ = (−18.3)(362) = −6600)

β-ethylglucoside tetraacetate[17] ($[M]_D$ = (−22.7)(374) = −8535)

The isorotation rules give the augmentation of the molecular rotation from the methyl to the ethyl compound as 8535−6600 = 1935; hence

(9) C. S. Hudson, "Rapports sur les Hydrates de Carbone, Dixième Conférence de l'Union Internationale de Chimie," 1930, p. 59.

(10) *M* = Molecular weight.
$[\alpha_A]M_A$ = Molecular rotation of 6-β-gentiobiosido-β-*d*-glucose hendekaacetate.
$[\alpha_B]M_B$ = Molecular rotation of 6-β-gentiobiosido-β-*d*-mannose hendekaacetate.
$[\alpha_{A'}]M_{A'}$ = Molecular rotation of β-*d*-glucose pentaacetate.
$[\alpha_{B'}]M_{B'}$ = Molecular rotation of β-*d*-mannose pentaacetate.

(11) Hudson, "Scientific Papers of the Bureau of Standards," No. 533.

(12) Hudson, THIS JOURNAL, **48**, 1424, 1434 (1926).

(13) Isbell, *Bur. Standards J. Research*, **5**, 1179 (1930).

(14) W. Haworth and E. Hirst, *J. Chem. Soc.*, 2631 (1930).

(15) Hudson and Johnson, THIS JOURNAL, **39**, 1272 (1917).

(16) Hudson and Dale, *ibid.*, **37**, 1264 (1915).

(17) Ferguson, *ibid.*, **54**, 4086 (1932).

the $[\alpha]D$ value for β-ethylgentiobioside heptaacetate is calculated to be $(-12{,}300-1935)/664 = -21.4°$, which agrees satisfactorily with the observed value, $-23.1°$.

Acknowledgment.—The authors wish to acknowledge the assistance given by William G. Dauben and Harold D. McDowell during the progress of this work.

Summary

1. A new crystalline 6-β-gentiobiosido-β-*d*-mannose hendekaacetate has been synthesized by the improved Königs and Knorr reaction and its physical properties determined. This is the first time that a crystalline 6-linked oligosaccharide acetate containing mannose has been synthesized by this method.

2. The epimeric difference relationships of the new 6-β-gentiobiosido-β-*d*-mannose hendekaacetate and the known 6-β-gentiobiosido-β-*d*-glucose hendekaacetate have been correlated with others of the mannose series. The specific rotation as calculated by Hudson's rules is $-19.7°$. The observed specific rotation is $[\alpha]^{25}D$ $-21.0°$. It has been pointed out that the values of the epimeric differences as required by Hudson's scheme seem to hold for 6-linked sugars although they do not hold for 4-linked sugars.

3. The known 6-β-*d*-glucosido-α-*d*-mannose octaacetate has been made more available by the improved Königs and Knorr reaction. Its preparation represents the second synthesis of a crystalline 6-linked oligosaccharide acetate containing a mannose unit.

4. Ethylgentiobioside heptaacetate has been synthesized and its physical properties determined, m. p. 158–159° (corr.); $[\alpha]^{25}D$ $-23.1°$. This rotation agrees with that which is calculated $(-21.4°)$ from Hudson's rules.

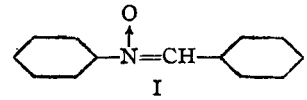
COLUMBUS, OHIO RECEIVED OCTOBER 11, 1939

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

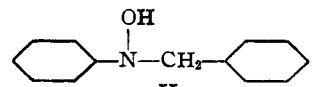
Secondary Amines from Nitro Compounds

BY WILLIAM S. EMERSON AND H. W. MOHRMAN

Since most aromatic primary amines are prepared by the reduction of nitro compounds, it seemed possible that the procedure for reductive alkylation of these amines[1] could be adapted to apply directly to the original nitro compounds. Vavon and Crajcinovic,[2] reduced a mixture of nitrobenzene and benzaldehyde with hydrogen and platinum. By suitably interrupting the reduction they obtained the nitrone I or the alkylarylhydroxylamine II.



I



II

They postulated the course of the reaction as (1) reduction of the nitrobenzene to phenylhydroxylamine, (2) condensation of the phenylhydroxylamine with the benzaldehyde to give the nitrone I and (3) reduction of the nitrone to the substituted hydroxylamine II.

In order to obtain secondary amines it, therefore, appeared necessary to determine satisfactory conditions for the reduction of the hydroxylamine II. From the work of Major[3] it seemed likely that hydrogen and a catalyst would be suitable. He reduced *p*-nitrophenol with hydrogen and platinum in acetone solution to obtain good yields of *p*-hydroxy-N-isopropylaniline. Later he extended the reaction to obtain N,N′-diisopropyl-*p*-phenylenediamine in good yield from *p*-nitroaniline, but states he was unable to obtain alkylation with nitrobenzene and acetone or with *p*-nitrophenol and formaldehyde or acetaldehyde. Benzaldehyde, however, gave *p*-hydroxydibenzylaniline with *p*-nitrophenol. For these reactions Major postulated the same mechanism as that proposed by Vavon and Crajcinovic.

We have found that when an alcoholic solution of an aromatic nitro compound and an aldehyde is reduced with hydrogen and Raney nickel in the presence of sodium acetate as a condensing agent, the corresponding secondary amine is formed in good yield. The reaction is apparently general

(1) Emerson and Walters, THIS JOURNAL, **60**, 2023 (1938); Emerson and Robb, *ibid.*, **61**, 3145 (1939).

(2) Vavon and Crajcinovic, *Compt. rend.*, **187**, 420 (1928).

(3) Major, THIS JOURNAL, **53**, 1901, 2803, 4373 (1931); *Chem. Abs.*, **29**, 178 (1935) (U. S. Patent 1,978,433).