(XXXVI) in 10 ml. of water was added 10 ml. of 5% sodium hydroxide. The mixture was shaken vigorously for five minutes and allowed to stand one-half hour. The base was extracted into ether, the ether layer was dried over anhydrous potassium carbonate and then concentrated to 15 ml. When hydrogen bromide was added to the ether solution the hydrobromide was obtained as an oil, which crystallized on standing overnight at 5°. On filtration, 0.60 g. of crude product (83%) was obtained. Recrystallized from ethyl acetate-ethanol, the compound melted at 192.5–193.5°; mixed melting point with an authentic sample of the hydrobromide of 1-isopropyl-2-methylpyrrolidine (XXXVIII)[21] showed no depression.

Cyclic Amines Derived from XXXIX and XL.—The cyclization of 4-bromo-2-methylbutylisopropylamine hydrobromide (XL) was carried out as described above. The amine was extracted into ether and dried; the ether was removed and saturated picric acid in ethanol was added. The picrate was obtained as yellow needles, melting after recrystallization from ethanol at 140–141° (yield 0.64 g., 51%); this was presumably the picrate of 1-isopropyl-3-methylpyrrolidine (XLI).

Cleavage of 5 g. of 4-methoxy-3-methylbutylisopropylamine was carried out by refluxing with 30 ml. of hydriodic acid for three hours. The product separated as a viscous tar. The hydriodic acid was distilled under reduced pressure, and the residue was made basic with 10% sodium hydroxide and shaken for five minutes, extracted into ether and dried over anhydrous potassium carbonate. The amine was distilled, giving 3.0 g. of product, b. p. 150–165°. The picrate prepared from 0.50 g. of this amine (yield 0.60 g., 56%) after recrystallization from ethanol, melted at 140–141°. Mixed melting points with the picrate derived from (XL) showed no depression.

Anal. Calcd. for $C_{14}H_{20}N_4O_7$: C, 47.2; H, 5.7; N, 15.7. Found: C, 47.4, 47.6, 47.2; H, 5.5, 5.4, 5.5; N, 15.8, 15.6.

Cyclic Amines Derived from XLII and XLIII.—To a solution of 1.00 g. of crude 4-bromo-3-ethylbutylisopropylamine hydrobromide (XLII) dissolved in 10 ml. of water was added 10 ml. of a 5% sodium hydroxide solution. The mixture was allowed to stand one-half hour with frequent shaking and the product was extracted into ether and dried over anhydrous potassium carbonate. The same procedure was employed with XLIII. The ether layers were concentrated to 15 ml. and hydrogen bromide was added. Oils separated in both cases which crystallized in fine needles on standing for thirty-six hours. Yields of 0.50 g. and 0.45 g. of crude hydrobromide were obtained from XLIII and XLII, respectively (68% and 62%). Recrystallized from ethyl acetate–ethanol, the hydrobromides, presumably of 1-isopropyl-3-ethyl pyrrolidine (XLIV), melted at 163–165° and showed no depression on mixing.

Anal. Calcd. for $C_9H_{20}BrN$: C, 48.7; H, 9.1; N, 6.3. Found: C, 48.7; H, 9.0; N, 6.3.

Summary

The synthesis of nine isopropylaminoamyl and isopropylaminobutyl ethers, and one bromoamylphthalimide of interest as intermediates for the synthesis of 6-methoxy-8-aminoquinoline antimalarials is described. The reaction of the ethers with hydrobromic acid is discussed, and the relationships of the cyclic derivatives derived from certain of the bromobutylisopropylamines is shown.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

D-Manno-L-*fructo*-octose[1]

BY M. L. WOLFROM AND PASCAL W. COOPER

In continuation of our work on the preparation of the higher ketoses, we report herein the synthesis of a ketoöctose, designated D-manno-L-*fructo*-octose, from D-manno-D-*gala*-heptonic acid through the reaction series $R{-}CO_2H \xrightarrow{PCl_5} R{-}COCl \xrightarrow{CH_2N_2} RCOCHN_2 \xrightarrow[Cu^{++}]{HOAc} RCOCH_2{-}OAc \xrightarrow{Ba(OH)_2} CH_2OH{-}(CHOH)_5{-}CO{-}CH_2OH$, wherein $R = CH_2OAc{-}(CHOAc)_5{-}$. All of the intermediates were obtained in crystalline condition. Although the final octose was not crystallized, it was characterized by its keto acetate and phenylosazone, the latter being first described by Fischer and Passmore.[2] The initial heptonic acid is the one obtainable in preponderant amount on subjecting D-mannose to the cyanohydrin reaction.[2,3] This acid was designated D-α-mannoheptonic acid by Peirce[4] and its complete stereochemical structure was elucidated by him. In the present work, the preparative directions of Hudson and co-workers[5] were followed in obtaining a suitable salt of the heptonic acid.

Hudson[6,7] has noted that "the physical and chemical properties (though not the biological) of an aldose and most of its derivatives are conditioned in first measure by the space configurations of carbons one to five inclusive." Dr. Hudson[8] has called our attention to the fact than an extension of this rule to ketoses would involve carbons two to six inclusive and that therefore the two substances, D-gluco-L-*tagato*-octose and D-gala-L-*tagato*-octose, compared in our preceding communication,[1] while having the upper configuration of L-tagatose, differ in the configuration of carbon six. The wide divergence in optical rotation, therein noted, between these two ketoöctoses, is then predictable and is not in disagreement with the general rule. Table I lists the rotations of three ketoöctoses in comparison with the configurationally related ketoheptose and the data indi-

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[1] Paper No. 12 in the series entitled "The Action of Diazomethane upon Acyclic Sugar Derivatives"; previous communication, M. L. Wolfrom and P. W. Cooper, THIS JOURNAL, **71**, 2668 (1949).

[2] E. Fischer and F. Passmore, *Ber.*, **23**, 2226 (1890).

[3] E. Fischer and J. Hirschberger, *ibid.*, **22**, 365 (1889).

[4] G. Peirce, *J. Biol. Chem.*, **23**, 327 (1915).

[5] C. S. Hudson, Olive Hartley and C. B. Purves, THIS JOURNAL, **56**, 1248 (1934).

[6] R. M. Hann, Alice T. Merrill and C. S. Hudson, *ibid.*, **57**, 2100 (1935).

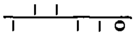
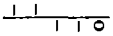
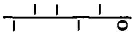
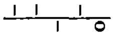
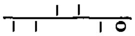
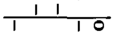
[7] C. S. Hudson, *Advances in Carbohydrate Chem.*, **1**, 26 (1945).

[8] Private communication.

cate close agreement especially when it is borne in mind that the ketoöctoses, being amorphous, are probably not of maximum purity.

TABLE I

COMPARATIVE ROTATIONS OF KETOÖCTOSES AND KETOHEPTOSES OF RELATED CONFIGURATION

Substance	Configuration	Physical state	$[M]_D$[a]	Reference
D-Gala-L-*tagato*-octose		Amorph.	− 4,100°	1
L-Mannoheptulose[b]		Cryst.[b]	− 6,100[b]	9
D-Gala-L-*sorbo*-octose		Amorph.	−10,800	1
L-Glucoheptulose		Cryst.	−14,100	10, 11
D-Manno-L-*fructo*-octose		Amorph.	+15,800	12
D-Galaheptulose		Cryst.	+17,900	13

[a] Measured at 20–25°, $c < 5$, water. Equilibrium values when mutarotation present. [b] Unknown but obtained by reversing the rotatory sign of the known, crystalline enantiomorph.

Experimental

Hexaacetyl-D-manno-D-*gala*-heptonic Acid.—Following the procedure outlined by Hudson, Hartley and Purves,[5] 1 liter of a filtered aqueous solution containing 30.2 g. of sodium cyanide and 69.2 g. of barium chloride was used to dissolve 100 g. of D-mannose and the resultant solution was allowed to stand for twenty-four hours at room temperature. Barium hydroxide octahydrate (175 g.) was dissolved in the solution and after standing overnight at room temperature, the barium D-manno-D-*gala*-heptonate which had crystallized was removed by filtration; yield 39.3 g.

The barium D-manno-D-*gala*-heptonate (39.3 g.) was approximately neutralized with 6 *N* sulfuric acid and the resulting solution then balanced exactly with 0.01 *N* sulfuric acid and 0.01 *N* barium hydroxide. The filtered solution (approximately 1500 ml.) of the free acid was treated, under continuous mechanical stirring, with 9.7 g. of cadmium hydroxide at 50–60° (four hours) and then at room temperature (overnight). The cadmium salt,[14] being of low solubility, was removed by filtration; yield 25.0 g.

Cadmium D-manno-D-*gala*-heptonate (19.8 g.) was acetylated according to the general procedure of Ladenburg, Tishler, Wellman and Babson[15]; yield 25.8 g., m. p. 202–204°, $[\alpha]^{27}D$ + 2° (*c* 4.9, U.S.P. $CHCl_3$). Pure hexaacetyl-D-manno-D-*gala*-heptonic acid was obtained on two recrystallizations from chloroform–petroleum ether; m. p. 206–208° (cor.), $[\alpha]^{27}D$ + 3.5° (*c* 4.2, U.S.P. $CHCl_3$).

Anal. Calcd. for $C_7H_8O_8(CH_3CO)_6$: C, 47.70; H, 5.47; sapn. value (7 equivs.), 14.63 ml. 0.1 *N* NaOH per 100 mg. Found: C, 47.41; H, 5.38; sapn. value, 14.71 ml.

Hexaacetyl-D-manno-D-*gala*-heptonyl Chloride.—Hexaacetyl-D-manno-D-*gala*-heptonic acid (2.0 g.), suspended in 15 ml. of anhydrous ether, was treated with 0.98 g. of phosphorus pentachloride and the mixture was shaken mechanically for two hours. The resulting clear solution was diluted with 50 ml. of petroleum ether and crystallization resulted on standing overnight in the ice-box; yield 1.4 g., m. p. 106–108° (cor.), $[\alpha]^{27}D$ −3.7° (*c* 4.2, abs. $CHCl_3$). Several recrystallizations from anhydrous ether failed to alter these constants. It was readily soluble in acetone and chloroform, moderately so in ether, and was insoluble in water and petroleum ether.

Anal. Calcd. for $C_7H_7O_7Cl(CH_3CO)_6$: C, 45.93; H, 5.27; Cl, 7.13; sapn. value (8 equivs.), 16.11 ml. 0.1 *N* NaOH per 100 mg. Found: C, 45.70; H, 5.12; Cl, 7.06; sapn. value, 15.92 ml.

1-Diazo-1-desoxy-*keto*-D-manno-L-*fructo*-octose Hexaacetate.—A solution of hexaacetyl-D-manno-D-*gala*-heptonyl chloride (4.8 g.) in dry ether (50 ml.) was poured slowly with stirring into 112 ml. of anhydrous ether containing 1.26 g. of diazomethane. There was a vigorous evolution of nitrogen gas during the addition and subsequent precipitation of the product. The mixture was allowed to stand at 0° for four hours and was then permitted to warm gradually to room temperature. The crude material was isolated by distillation of the ether at atmospheric pressure; yield 4.3 g., m. p. 124–128° (cor.), $[\alpha]^{26}D$ + 37.5° (*c* 5.1, U.S.P. $CHCl_3$). Further recrystallization from benzene–petroleum ether failed to produce pure material.

The product (2 g.) was dissolved in 60 ml. of benzene and placed on a chromatographic column (250 mm. long × 50 mm. diam.[16]) containing 200 g. of Magnesol–Celite[17] (5:1 by wt.) and developed with 1500 ml. of benzene-ethanol (100:1 by vol.). The main zone[17] containing the diazomethyl ketone was near the middle of the column. After elution from the cut zone by 500 ml. of acetone, 1.1 g. of material was obtained on recrystallization from benzene-petroleum ether; m. p. 126–128° (uncor.), $[\alpha]^{26}D$ + 45.6° (*c* 4.0, U.S.P. $CHCl_3$). The material was further purified by one more chromatographic treatment effected in the same manner; yield 0.8 g., m. p. 128–130° (cor.), $[\alpha]^{26}D$ + 50° (*c* 4.0, U.S.P. $CHCl_3$).

This diazomethyl ketone formed greenish-yellow needles. It was soluble in acetone, benzene and chloroform, moderately so in warm alcohol and warm ether, and was insoluble in water and petroleum ether. It reduced Fehling solution and evolved nitrogen when treated with acids.

Anal. Calcd. for $C_{20}H_{26}O_{13}N_2$: C, 47.81; H, 5.22; N, 5.57. Found: C, 48.03; H, 5.15; N, 5.81.

***keto*-D-Manno-L-*fructo*-octose Heptaacetate.**—A solution of 1-diazo-1-desoxy-*keto*-D-manno-L-*fructo*-octose hexaacetate (5.0 g.) in 50 ml. of glacial acetic acid containing a trace of cupric acetate (75 mg.) was heated to reflux. As soon as the violent reaction had subsided, the solution was evaporated under reduced pressure at 50° to about 10 ml. The solution was then diluted with 75 ml. of chloroform, washed three times with water, dried with anhydrous sodium sulfate and evaporated under reduced pressure to a sirup. Since Wolfrom and Thompson[18] had shown that considerable deacetylation takes place in this general procedure, the sirup was reacetylated by treatment with 50 ml. of acetic anhydride containing 0.5 g. of zinc chloride. After standing overnight at room temperature the acetic anhydride was hydrolyzed with 200 g. of ice and water. The acetate was extracted with chloroform, the chloroform solution washed with water, dried and evaporated under reduced pressure to a sirup. The sirup failed to crystallize.

The sirup (2 g.) was dissolved in 60 ml. of benzene and placed on a chromatographic column (250 mm. long × 55 mm. diam.[16]) containing 200 g. of Magnesol–Celite[17] (5:1 by wt.) and developed with 1500 ml. of benzene-ethanol (100:1 by vol.). The contents of the principal zone,[17] near the bottom, after elution with 600 ml. of acetone, failed to crystallize. On repetition of this chroma-

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(9) F. B. LaForge, *J. Biol. Chem.*, **28**, 511 (1917).

(10) G. Bertrand and G. Nitzberg, *Compt. rend.*, **186**, 925 (1928).

(11) W. C. Austin, THIS JOURNAL, **52**, 2106 (1930).

(12) Present communication.

(13) M. L. Wolfrom, R. L. Brown and E. F. Evans, THIS JOURNAL, **65**, 1021 (1943).

(14) G. Hartmann, *Ann.*, **272**, 190 (1893).

(15) K. Ladenburg, M. Tishler, J. W. Wellman and R. D. Babson, THIS JOURNAL, **66**, 1217 (1944).

(16) Adsorbent dimensions.

(17) W. H. McNeely, W. W. Binkley and M. L. Wolfrom, THIS JOURNAL, **67**, 527 (1945).

(18) M. L. Wolfrom and A. Thompson, *ibid.*, **68**, 1453 (1946).

tographic procedure, the product finally crystallized. Pure material was obtained on one recrystallization from acetone and petroleum ether; yield 0.5 g., m. p. 86–88° (cor.), $[\alpha]^{25}\text{D}$ $-14.9°$ (c 4.3, U.S.P. $CHCl_3$). The compound reduced hot Fehling solution, gave the Pacsu[19] *keto*-acetate test, and exhibited an absorption band with a maximum at 2840 Å.; log $\epsilon_{\text{max.}}$[20] = 1.79 (0.0070 M in U.S.P. chloroform, 1 cm. cell, Beckman quartz spectrophotometer, model DU).

Anal. Calcd. for $C_{22}H_{30}O_{15}$: C, 49.43; H, 5.65. Found: C, 49.47; H, 5.94.

D-Manno-L-*fructo*-octose and its Phenylosazone.—Four grams of *keto*-D-manno-L-*fructo*-octose heptaacetate was deacetylated with barium hydroxide as described for *keto*-D-psicose pentaacetate[21] and the resultant colorless, amorphous solid was isolated in the same manner; yield 1.8 g. of amorphous material, $[\alpha]^{26}\text{D}$ $+66.4°$ (c 3.2, H_2O, no mutarotation). The substance was water-soluble, possessed a sweet taste, and reduced hot Fehling solution; it was not fermentable by bakers' yeast.

Anal. Calcd. for $C_8H_{16}O_8$: C, 40.00; H, 6.72. Found: C, 39.99; H, 6.76.

The crystalline phenylosazone of this octose was prepared; m. p. 222–223° (dec., cor.), in agreement with the value of 223° (dec.) reported by Fischer and Passmore.[2]

Anal. Calcd. for $C_{20}H_{26}O_6N_4$: C, 57.40; H, 6.26; N, 13.39. Found: C, 57.29; H, 5.96; N, 13.61.

Summary

1. D-Manno-D-*gala*-heptonic acid has been converted to the amorphous D-manno-L-*fructo*-octose, characterized by its crystalline *keto*-acetate and phenylosazone.

2. Crystalline hexaacetyl-D-manno-D-*gala*-heptonic acid, its acid chloride, and 1-diazo-1-desoxy-*keto*-D-manno-L-*fructo*-octose hexaacetate are described.

3. Paralleling the higher aldoses,[6,7] ketoheptoses and ketoöctoses of like configurations in carbons two to six, inclusive, have similar optical rotations.

COLUMBUS, OHIO RECEIVED AUGUST 3, 1949

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[19] E. Pacsu and F. V. Rich, THIS JOURNAL, **55**, 3018 (1933); F. B. Cramer and E. Pacsu, *ibid.*, **59**, 1467 (1937).

[20] $\epsilon_{\text{max.}} = E_{\text{max.}} \times \text{mol. wt.}/(C \times D)$; C = g./l., D = cell thickness in cm.

[21] M. L. Wolfrom, A. Thompson and E. F. Evans, THIS JOURNAL, **67**, 1793 (1945).

[CONTRIBUTION FROM THE PULP MILLS RESEARCH PROJECT AND THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF WASHINGTON]

Functional Derivatives of Lignin Sulfonic Acid

BY D. M. RITTER, E. D. OLLEMAN, D. E. PENNINGTON AND K. A. WRIGHT

Methods based upon isolation of quinolinium salts[1] or upon dialysis[2,3] have been found to yield lignin sulfonates of considerable chemical homogeneity. With such material available it appeared desirable to repeat and extend previous work[4] on methylated and acetylated lignin sulfonates. A summary of the derivatives prepared and their composition is given in Table I.

Exhaustive diazomethane methylation of lignin sulfonate ion (I) yielded a product (II), for which the name "hemimethoxy" lignin sulfonate ion is suggested. Through methylation of either (I) or (II) with dimethyl sulfate gave the "permethoxy" lignin sulfonate ion (III). The methoxyl and sulfur contents of (II) and (III) agreed with data obtained by Hibbert and his coworkers[4e] for products obtained in the same two ways and the product made by Freudenberg[4d] was also apparently identical.

The water-soluble product obtained by cautious acetylation with sodium acetate as a catalyst was called the "peracetoxy" derivative. The composition of the "peracetoxy" lignin sulfonate corresponded closely to that expected from lignin sulfonates with the hydroxyl group contents reported by Freudenberg, Lautsch and Piazolo.[5] Acetylation of the "hemimethoxy" lignin sulfonate was accomplished with the sodium acetate catalyst, but with several catalysts listed in Table II, acetylation of the "permethoxy" derivative proceeded only to the degree that methoxyl groups were displaced.

In reactions somewhat analogous to those between ammonium salts of strong acids and diazomethane,[6] the methyl esters (VI), (VII) and (VIII) were prepared from "hemimethoxy," "permethoxy" and "peracetoxy" lignin sulfonic acids (II), (III) and (IV), respectively. In each case the reaction occurred between the solid acid suspended in solutions of diazomethane in solvents for the esters. Esterification of the permethoxy and peracetoxy lignin sulfonic acids was accompanied by some desulfonation, and in the latter case some replacement of acetoxy groups by methoxy groups occurred.

It is well established that there are two steps in the methylation of lignin sulfonates.[4e] On the basis of synthesis the final product obtained with diazomethane, hemimethoxy lignin sulfonate ion (II), is a distinct chemical individual and not merely an intermediate to the permethoxy lignin

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[1] Olleman, Pennington and Ritter, *J. Coll. Science*, **3**, 185 (1948).

[2] Peniston and McCarthy, THIS JOURNAL, **70**, 1327 (1948).

[3] Markham, Peniston and McCarthy, *ibid.*, **71**, 3599 (1949).

[4] (a) Klason, *Ber.*, **53**, 1864 (1920); (b) Heuser and Samuelsen, *Cellulosechem.*, **3**, 78 (1922); (c) Hägglund and Carlsson, *Biochem. Z.*, **257**, 467 (1933); (d) Freudenberg and Sohns, *Ber.*, **66B**, 262 (1933); (e) King, Brauns and Hibbert, *Can. J. Research*, **13B**, 88 (1935); (f) Tomlinson and Hibbert, THIS JOURNAL, **58**, 340 (1936); (g) Erdtman, *Svensk Papperstidning*. **45**, 392 (1942).

[5] Freudenberg, Lautsch and Piazolo, *Cellulosechem.*, **22**, 97 (1944).

[6] Eistert, "Newer Methods of Preparative Organic Chemistry," Interscience Publishers, New York, N. Y., 1948, pp. 520, 521.