The extension of the present ideas to the question of the structures of acetals that are obtainable from partially substituted polyhydroxy alcohols, such as the 1,6-dibenzoyl hexitols, is attractive. A survey of the published experimental work in this field indicates that the generalizations may be useful in it, but we postpone detailed discussion until more data are available.

Summary

Attention has been directed to certain correlations between the configurations of D-sorbitol, D-mannitol and dulcitol and the structures of the cyclic methylene acetals which are derived from these hexitols. The structures of the methylene acetals of D-epirhamnitol, adonitol and xylitol have been found to agree with those expected from a consideration of the configurations of these alcohols. The probable structures of the cyclic methylene acetals of the remaining hexitols, namely, allitol, iditol and talitol, are discussed, and it has been found that dimethylene-L-iditol possesses the predicted 2,4:3,5-diacetal structure. The cyclic benzylidene acetals of the sugar alcohols for which definitive structures are known show the same correlation as the methylene acetals.

Proof of the Configurations of the D-Gluco-L-gala-, D-Gluco-L-talo- and D-Gala-L-gulo-octoses

BY RAYMOND M. HANN, ALICE T. MERRILL AND C. S. HUDSON

During the decennium of 1890–1900 Emil Fischer[1] established the configurations of most of the hexoses and pentoses; D-glucose, D-mannose, D-gulose and D-galactose may be mentioned especially, since they are the source materials for the higher carbon sugars that will be discussed in this article. From D-glucose, D-mannose and D-galactose, respectively, he synthesized a group of higher carbon aldoses the full configurations of which were not immediately discernible except in the case of his epimeric pair of D-glucoheptoses; one of these heptoses yielded on reduction an alcohol which was found to be devoid of optical rotation, a fact which established its configuration as *meso* by a conclusive method; the name gluco-gulo-heptitol (or, for special clarity in the present discussion, D-gluco-D-gulo-heptitol) specifies the proved configuration.[2] Since the alcohol possesses *meso* configuration the D-symbols are not required; L-gluco-L-gulo-heptitol is not an enantiomorph, but is the same substance. However, there is no impropriety in using the symbols to indicate the enantiomorphic form of the gluco-heptose from which the alcohol was actually prepared in a given instance. The aldose from which Fischer prepared this *meso* alcohol, the sugar which he named D-α-glucoheptose, must have the configuration (VIII) that is specified by the name D-gluco-D-gulo-heptose. The general method of conclusive proof which he used in this case may be classified as *the proof by way of a meso derivative*. Historically, the method is an extension to more complex substances of the views which had become current concerning the stereoconfiguration of mesotartaric acid. Fischer employed this method in proving the configurations of adonitol,

xylitol and dulcitol, and it has been used to establish the configuration of one of the four possible D-manno-octoses as D-manno-L-manno-octose; the reduction of this sugar yields an alcohol that is devoid of optical activity and must therefore be of *meso* type.[3]

Fischer's second D-glucoheptose (designated β by him) is D-gluco-D-idoheptose (IX), the epimer of D-gluco-D-gulo-heptose, the epimeric relationship being evident from the fact, established by Fischer, that the two aldoheptoses yield the same osazone. This method of conclusive proof of epimeric relationship may be designated *the proof of epimerism by way of osazone identity*. If the configuration of one epimer is known, that of the other may be established by this method.

Looking backward from the vantage ground of today's added knowledge, it can be observed that Fischer would have been fully justified in concluding that his D-galaheptitol (D-gala-L-manno-heptitol) is the enantiomorph of his D-manno-heptitol (D-manno-L-gala-heptitol), a conclusion which would have established at that early date the configurations of the epimeric pairs of D-gala-heptoses and D-mannoheptoses. He proved the identity of natural perseitol with his synthetic D-mannoheptitol, but there is no mention in his articles that the properties which he records for his D-galaheptitol agree closely with those to be expected for the enantiomorph of natural perseitol. The recognition of this relationship and the conclusive verification of it by further experiments are due to Peirce[3]; he established the configurations of D-manno-D-gala-heptose and D-gala-L-manno-heptose by a conclusive method due to Fischer, which may be understood from the observation of the latter that D-sorbitol is the reduc-

(1) Emil Fischer, "Untersuchungen über Kohlenhydrate und Fermente," Julius Springer, Berlin, 1909.

(2) Hudson, THIS JOURNAL, **60**, 1537 (1938).

(3) (a) Peirce, *J. Biol. Chem.*, **23**, 327 (1915); (b) Hann, Maclay, Knauf and Hudson, THIS JOURNAL, **61**, 1268 (1939).

tion product from both D-glucose and L-gulose. This third conclusive method of Fischer's may be designated *the proof by way of an identical active alcohol from two different aldoses*. La Forge[4] used it to establish the configuration of D-gulo-L-gala-heptose and to confirm Peirce's proof for D-gala-L-gluco-heptose.
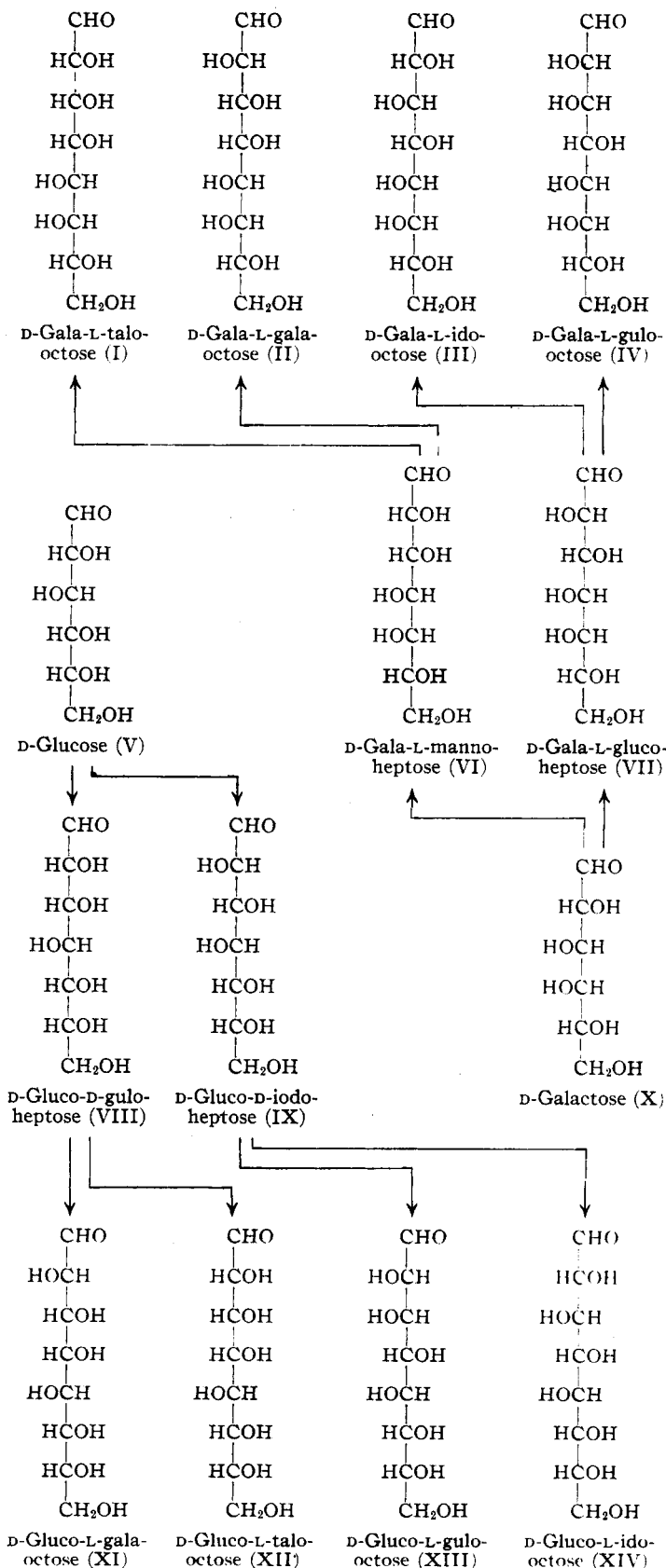
The continuation of such studies in the group of higher carbon sugars is of direct biochemical interest because of the occurrence in nature of two heptitols (perseitol (D-manno-D-gala-heptitol) and volemitol (D-manno-D-talo-heptitol)) and two ketoheptoses (D-mannoheptulose and D-altroheptulose (sedoheptulose)). The determination of the configurations of most synthetic higher carbon sugars and alcohols by the conclusive methods which Fischer introduced is possible in principle but it is a fact that the selection in earlier days of the course of study of diastereo-isomers was dictated by yields, and the chances proved to be disadvantageous for configurational proofs. The outlook changed, however, as a result of the discovery of several independent empirical rules[5] of correlation between optical rotation and configuration, which greatly simplify the study of this higher carbon group; the indications of configuration that these empirical rules give serve as sign posts to direct the experimental work toward the desired goal, namely, that the configurations may be established eventually by Fischer's conclusive methods.

The two diastereoisomeric acids that are formed in each cyanide synthesis from an aldose are present in unequal proportions and the major product usually possesses properties which render its isolation more practical; the data which have now accumulated support the simple generalization that in the cases of mannose, galactose, glucose and gulose *the isomer which is more readily accessible is the one that carries its hydroxyls on carbon atoms 2 and 4 in trans relationship*.[6] The rule is particu

(4) La Forge, *J. Biol. Chem.*, **41**, 251 (1920); *cf.* Isbell, *J. Research Natl. Bur. Standards*, **19**, 639 (1937).

(5) The lactone rule (Hudson, THIS JOURNAL, **31**, 338 (1910)), the salt-acid rule (Levene, *J. Biol. Chem.*, **23**, 145 (1915), Levene and Meyer, *ibid.*, **26**, 355 (1916)), the phenylhydrazide (Levene, *ibid.*, **23**, 145 (1915), Hudson, THIS JOURNAL, **39**, 462 (1917)), amide (Hudson, *ibid.*, **40**, 813 (1918)) and benzimidazole (Richtmyer and Hudson, *ibid.*, **64**, 1612 (1942)) rules.

(6) Attention was first called to the possibility that this empirical rule applies in the cyanohydrin synthesis from aldoses by Maltby, *J. Chem. Soc.*, 1408 (1923); 1629 (1926); 2769 (1929).

D-Gala-L-talo-octose (I); D-Gala-L-gala-octose (II); D-Gala-L-ido-octose (III); D-Gala-L-gulo-octose (IV); D-Glucose (V); D-Gala-L-manno-heptose (VI); D-Gala-L-gluco-heptose (VII); D-Gluco-D-gulo-heptose (VIII); D-Gluco-D-iodo-heptose (IX); D-Galactose (X); D-Gluco-L-gala-octose (XI); D-Gluco-L-talo-octose (XII); D-Gluco-L-gulo-octose (XIII); D-Gluco-L-ido-octose (XIV)

larly well illustrated in the mannose and galactose series, in which the diastereoisomeric acids that are the more readily accessible ones lead to the following series of sugars: D-arabinose $(R_4R_3L_2)$ → D-mannose $(R_3R_4L_3L_2)^7$ → D-manno-D-gala-heptose $(R_5R_3L_4L_3R_2)$ → D-manno-L-manno-octose $(R_7R_6-L_5L_4R_3R_2)$ and D-lyxose $(R_4L_3L_2)$ → D-galactose $(R_5L_4L_3R_2)$ → D-gala-L-manno-heptose $(R_6L_5L_4-R_3R_2)$ → D-gala-L-gala-octose $(R_7L_6L_5R_4R_3L_2)$. The rule holds as far as is now known in the gulose series, the more accessible path of synthesis being D-xylose $(R_4L_3R_2)$ → D-gulose $(R_5L_4R_3R_2)$ → D-gulo-L-gala-heptose $(R_6L_5R_4R_3L_2)$. The rule also holds in the glucose series; thus D-glucose $(R_5R_4-L_3R_2)$ → D-gluco-D-gulo-heptose $(R_6R_5L_4R_3R_2)$ → D-gluco-L-gala-octose $(R_7R_6L_5R_4R_3L_2)$. Data in the allose, altrose, idose and talose series are either lacking or too limited at present for testing the applicability of the rule in a decisive manner. However, this rule of *trans* configuration enables the investigator in many instances to plan higher carbon syntheses with considerable assurance, as will now be illustrated from the present research.

An apparently trustworthy indication of the full configuration of one of the D-gluco-octoses (Fischer's D-α-gluco-octose; D-gluco-L-gala-octose (XI)) came through the lactone rule[8]; further evidence supporting this configuration was gradually attained through application of the phenylhydrazide,[9] amide[9] and benzimidazole rules.[5] The octitol from the reduction of (XI) is readily prepared because it lies in the main path of synthesis from D-glucose; Fischer discovered it (m. p. 141°, $[\alpha]_D$ +2.0°) and Philippe[10] prepared it again (m. p. 156–158°, $[\alpha]_D$ +1.9°). If its configuration has been correctly indicated by the rules of rotation the substance must be identical with one of the four possible D-galaoctitols (the alcohols from the reductions of (I), (II), (III) and (IV)), namely, D-gala-L-gulo-octitol. No other gluco-octitol structure can be identical with a gala-octitol structure. How could the synthesis of this particular gala-octitol be planned? Evidently it lies off the main course of synthesis because it is known from Fischer's work that this course leads to a gala-octitol (m. p. 230°) that is not identical with the gluco-octitol from (XI); Fischer's gala-octitol is now believed on strong evidence to be the gala-octitol from (II).[11] The desired gala-octitol cannot be in the series above (VI) but should be in that above (VII); although the preparation of (VII) from galactose (X) is laborious because of the small yield, the synthesis

of (IV) from (VII) would be expected by the *trans* addition rule to give a good yield. Also, the direction of rotation of the phenylhydrazide in the (IV) group should be negative and that of the phenylhydrazide in the (III) group positive, which could serve as an indication that the correct path is being followed in the succeeding steps to the lactone, the octose (IV) and the desired gala-octitol. It was found in practice that this plan succeeded smoothly; although the preparation of a good supply of D-gala-L-gluco-heptose (VII) from D-galactose consumed much time, the addition of hydrocyanic acid to (VII) led to a 30% yield of an easily isolated levorotatory octonic phenylhydrazide, from which the crystalline lactone was obtained in 80% yield. The pure crystalline octose was made by the reduction of this lactone with sodium amalgam, the yield being 57%. The reduction of the octose by hydrogen and Raney nickel produced the pure octitol in nearly quantitative yield; this gala-octitol was found to be identical with the gluco-octitol that has been mentioned, which is conclusive proof of the configurations of (IV) and (XI). This octitol is easily identified; it crystallizes readily as prisms of m. p. 153–154° and shows $[\alpha]^{20}D$ +2.4° in water; its octaacetate has m. p. 88–89° and $[\alpha]^{20}D$ +20.6° in chloroform (the sample from the glucose series rotated +20.7°, that from the galactose series +20.5°). Mixtures of samples from the two series showed no depression of the recorded sharp melting point. Optical measurements by Mr. George L. Keenan also showed identity for the samples.

The phenylosazone of D-gluco-L-talo-octose proved to be identical with that of D-gluco-L-gala-octose, which is conclusive proof of the epimeric relationship of these aldoses.

Similar Sugars.—Attention has been called at various times to the similarity of the properties of higher carbon sugars to those of a corresponding hexose which possesses like configuration for carbon atoms 2, 3, 4 and 5.[12] The relationship is not restricted to cyclic forms of the sugars, glycosides and lactones, but applies also to the aldonic amides, phenylhydrazides and benzimidazoles. In Tables I, II and III such similarities are shown from data on the octoses that are the subject of this article. In naming the α- and β-forms of such a sugar as D-gluco-L-gala-octose the known crystalline form could logically be named β,D-gluco-L-gala-octose and some years ago we used this plan; on the other hand, it can also be named logically D-gluco-α,L-gala-octose, a designation which seems preferable because it aids the recognition that the form is similar to α,L-galactose.

(7) This is an abbreviation of the D-mannose configuration

$$CH_2OH-\overset{H}{\underset{OH}{C}}-\overset{H}{\underset{OH}{C}}-\overset{OH}{\underset{H}{C}}-\overset{OH}{\underset{H}{C}}-CHO,$$ which is self-explanatory; it

is seen that the OH on carbon 2 is *trans* with respect to that on carbon 4 (L₃ and R₄).

(8) Hudson, THIS JOURNAL, **39**, 463 (1917); *cf.* Anderson, *ibid.*, **33**, 1510 (1911), who inferred the configuration from the rotation of the octose.

(9) Hockett and Hudson, *ibid.*, **60**, 622 (1938).

(10) Philippe, *Ann. chim. phys.*, **26**, 356 (1912).

(11) Maclay, Hann and Hudson, THIS JOURNAL, **60**, 1035 (1938).

(12) References to articles from this Laboratory are: *ibid.*, **52**, 1695 (1930), **57**, 2100 (1935), **59**, 548 (1937), **60**, 1035, 1537 (1938), **64**, 247 (1942). See also Isbell, *J. Research Natl. Bur. Standards*, **18**, 505 (1937). An early foreshadowing of this general relationship is noticeable in Fischer's comparison of the methyl xylosides with the methyl glucosides, *Ber.*, **28**, 1145, 1429 (1895).

TABLE I

COMPARISON OF ROTATIONS OF SUBSTANCES IN THE D-GALACTOSE AND D-GLUCO-L-GALA-OCTOSE SERIES

Solvent, water (W), chloroform (C), or N hydrochloric acid (N HCl)

			D-Galactose Series $[\alpha]_D$	$[M]_D$			D-Gluco-l-gala-octose Series $[\alpha]_D$	$[M]_D$
Sugar (W)	initial	(αD)	$+150.7^a$	$+27,100$	(αL)		$- 87$	$-24,000$
	equilibrium		$+ 80.2$	$+ 9,510$			$- 44.6$	$-12,300$
	initial	(βD)	$+ 52.8$	$+14,400$	(βL)		unknown	......
Aldonic acid amide (W)			$+ 30.2^b$	$+ 5,890$			$- 24.4^i$	$- 6,230$
Aldonic acid phenylhydrazide (W)			$+ 11.0^c$	$+ 3,150$			$- 17.8^i$	$- 6,160$
γ-Lactone (W)			$- 77.6^d$	$-13,800$			$+ 53.7^i$	$+12,800$
Benzimidazole (N HCl)			$+ 45.1^e$	$+12,100$			$- 44.7$	$-14,700$
Sugar acetate (C)		(αD)	$+106.7^f$	$+41,600$	(αL)		$- 75.1$	$-40,100$
		(βD)	$+ 25.0^f$	$+ 9,760$	(βL)		0	0
Methyl glucoside (W)		(αD)	$+196.1^g$	$+38,100$	(αL)		-138.0	$-35,100$
Methyl glucoside acetate (C)		(αD)	$+133.0^g$	$+48,200$	(αL)		$- 99.0$	$-50,100$
Benzyl mercaptal (W)			$- 26.4^h$	$-10,800$			$+ 15.8$	$+ 7,440$

^{a} Isbell and Pigman, *J. Research Natl. Bur. Standards*, **18**, 158 (1937). ^{b} Hudson and Komatsu, THIS JOURNAL, **41**, 1141 (1919). ^{c} Nef, *Ann.*, **403**, 296 (1914). ^{d} Ruff and Franz, *Ber.*, **35**, 948 (1902). ^{e} Richtmyer and Hudson, THIS JOURNAL, **64**, 1613 (1942). ^{f} Hudson and Parker, *ibid.*, **37**, 1589 (1915). ^{g} Dale and Hudson, *ibid.*, **52**, 2534 (1930). ^{h} Pacsu and Ticharich, *Ber.*, **62**, 3104 (1929). ^{i} Hockett and Hudson, THIS JOURNAL, **60**, 622 (1938).

TABLE II

COMPARISON OF ROTATIONS OF SUBSTANCES IN THE D-TALOSE AND D-GLUCO-L-TALO-OCTOSE SERIES

Solvent, water (W), chloroform (C), or N hydrochloric acid (N HCl)

			D-Talose Series $[\alpha]_D$	$[M]_D$		D-Gluco-l-talo-octose Series $[\alpha]_D$	$[M]_D$
Sugar (W)	initial	(αD)	$+68.0^a$	$+12,200$	(αL)	-32^f	$-7,690$
	equilibrium		$+21.0^a$	$+ 3,780$		$- 6.5^f$	$-1,560$
	initial	(βD)	$+13.2^a$	$+ 2,380$	(βL)	unknown	.....
γ-Lactone (W)			-34.7^b	$- 6,180$		$+24.6^g$	$+5,860$
Amide (W)			-13.1^c	$- 2,560$		$+12.1^g$	$+3,090$
Phenylhydrazide (W)			-25.4^d	$- 7,270$		$+25.9^g$	$+8,970$
Benzimidazole (N HCl)			-23.0^e	$- 6,170$		$+18.6^f$	$+6,110$

^{a} Pigman and Isbell, *J. Research Natl. Bur. Standards*, **19**, 192 (1937). ^{b} Cretcher and Renfrew, THIS JOURNAL, **54**, 1590 (1932). ^{c} Renfrew and Cretcher, *ibid.*, **54**, 4402 (1932). ^{d} Hedenburg and Cretcher, *ibid.*, **49**, 478 (1927). ^{e} Haskins and Hudson, *ibid.*, **61**, 1267 (1939). ^{f} Merrill, Hann and Hudson, *ibid.*, **65**, 994 (1943). ^{g} Hockett and Hudson, *ibid.*, **60**, 622 (1938).

TABLE III

COMPARISON OF ROTATIONS OF SUBSTANCES IN THE D-GULOSE, D-GULCO-D-GULO-HEPTOSE AND D-GALA-L-GULO-OCTOSE SERIES

			D-Gulose Series $[\alpha]_D^a$	$[M]_D$		D-Gluco-d-gulo-heptose Series $[\alpha]_D^a$	$[M]_D$		D-Gala-l-gulo-octose Series $[\alpha]_D^a$	$[M]_D$
Sugar	initial	(αD)	$+61.6^b$	$+11,100$	(αD)	unknown	......	(αL)	unknown	.....
	equilibrium		-26.4^b	$- 4,760$		-20.2^g	$- 4,240$		$+19.3$	$+ 4,640$
	initial	(βD)	unknown	......	(βD)	-28.7^g	$- 6,030$	(βL)	$+24.9$	$+ 5,980$
Aldonic acid amide			$+15.2^c$	$+ 2,970$		$+10.6^e$	$+ 2,390$		$- 5.8$	$- 1,480$
Aldonic acid phenylhydrazide			$+13.7^d$	$+ 3,900$		$+ 9.3^h$	$+ 2,940$		-10.3	$- 3,570$
γ-Lactone			-57.1^e	$-10,200$		-55.3^i	$-11,510$		$+48.0$	$+11,400$
Benzimidazole			$+16.7^f$	$+ 4,480$		$+14.3^f$	$+ 4,250$		-11.2	$- 3,680$

^{a} The specific rotations of all of the compounds except the benzimidazoles were measured in aqueous solution. The rotations of the benzimidazoles were determined in N hydrochloric acid. ^{b} Isbell, *J. Research Natl. Bur. Standards*, **5**, 744 (1930). The measurement was made on a sugar solution prepared by the action of silver oxalate on α-gulose calcium chloride monohydrate. ^{c} Hudson and Komatsu, THIS JOURNAL, **41**, 1146 (1919). ^{d} Nef, *Ann.*, **403**, 271 (1914). ^{e} Nef, *ibid.*, **403**, 269 (1914). ^{f} Haskins and Hudson, THIS JOURNAL, **61**, 1267 (1939). ^{g} Isbell, *J. Research Natl. Bur. Standards*, **18**, 520 (1937). ^{h} Hudson, THIS JOURNAL, **39**, 467 (1917). ^{i} Kiliani, *Ber.*, **19**, 770 (1886).

A Simple Proof of the Configurations of Glucose and Galactose

The newly established fact that D-gluco-l-gala-octose and D-gala-l-gulo-octose yield the same active octitol, combined with the well-known facts that gala-hexitol (dulcitol) and gluco-gulo-heptitol are devoid of optical activity (*meso*), furnishes a new and very simple proof of the con-figurations in the glucose and galactose series; extensions from it to prove the configurations of many other simple monoses will be obvious. Writing the skeleton diagram for an octitol as in A, following Fischer's fundamental convention in projecting the tetrahedra so that the lower edges (broken lines) lie in the plane of the paper, and numbering the carbon atoms as for a gluco-

(A)
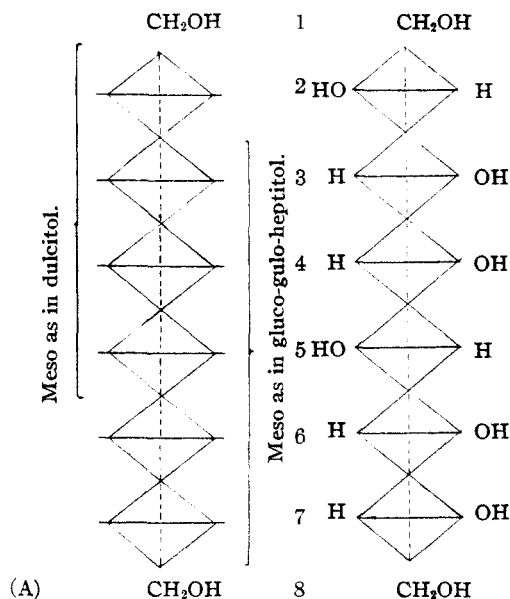
octitol derivative, it will be noted that for D-gluco-L-gala-octitol the portions of the diagram included by carbon atoms 2 to 5 and 3 to 7 represent the *meso* structures of gala-hexitol (dulcitol) and gluco-gulo-heptitol, respectively. The proof of configuration of D-glucose and D-galactose is then the following:

Step 1. By convention for D-glucose, OH is on the right of C_7.

Step 2. By the gluco-gulo-heptitol *meso* relationship, OH is on the right of C_3.

Step 3. By the dulcitol *meso* relationship, OH is on the right of C_4.

Step 4. By the gluco-gulo-heptitol *meso* relationship, OH is on the right of C_6.

Step 5. By the dulcitol *meso* relationship, the OH on C_2 must be on the same side as the OH on C_5; by the fact that the octitol is optically active, it cannot be of *meso* configuration and therefore the hydroxyls on C_2 and C_5 are both on the left side.

We are indebted to Mr. George L. Keenan of the Food and Drug Administration of the Federal Security Agency for the determination of the optical crystallographic properties of D-gluco-L-gala-octitol and its octaacetate, and to Dr. A. T. Ness of this Institute for performing the microchemical analyses, and to Mr. Harry W. Diehl for preparing many kilograms of galactose.

Experimental

I. Compounds of the D-Gluco-L-gala-octose Series

D-Gluco-L-gala- and D-Gluco-L-talo-octonic Acid Derivatives from D-Gluco-D-gulo-heptose.—Six hundred grams of D-gluco-D-gulo-heptose was converted to a mixture of the epimeric gluco-octonic acids as described by Hockett and Hudson.[9] Following the removal of calcium and sulfate ions the acid solution was concentrated *in vacuo* to a volume of 1500 cc. and cooled to 5° for forty-eight hours to allow the crystallization of D-gluco-L-talo-octonic lactone. The lactone, which weighed 122 g. (16%) and rotated

$[\alpha]^{20}D +25.2°$[18] in aqueous solution in agreement with the recorded value of $+24.6°$, was separated by filtration and the filtrate was diluted with 3 liters of water and neutralized to phenolphthalein with warm 10% aqueous barium hydroxide; the barium salt which crystallized upon cooling the solution weighed 304 g. and an additional 114 g. was obtained from the mother liquor by concentrating it to 750 cc.; the salt was recrystallized from 15 parts of boiling water and formed very small plates which showed $[\alpha]^{20}D -0.8°$ in aqueous solution (c, 2.0). An analysis for barium showed 21.28% in agreement with the calculated value, 21.21%, for anhydrous barium gluco-octonate. The filtrate from which the barium D-gluco-L-gala-octonate had been separated was further reduced in volume to 400 cc. and it deposited 245 g. of barium D-gluco-L-talo-octonate as microcrystalline irregularly shaped granules; this salt, after recrystallization from 2 parts of boiling water, showed $[\alpha]^{20}D -1.0°$ in aqueous solution (c, 4.0) and a barium content of 21.27%. The yields of crystalline products represent a conversion of 271 g. (45%) of the D-gluco-D-gulo-heptose to barium D-gluco-L-gala-octonate and 258 g. (43%) to D-gluco-L-talo-octonic acid compounds.

D-Gluco-L-gala-octonic Acid Lactone.—The lactone was obtained from the barium salt by the directions of Hockett and Hudson and it agreed in m. p. (151–152°) and rotation, $[\alpha]^{20}D +53.7°$, with their recorded values.

Methyl D-Gluco-L-gala-octonate.—This ester was occasionally obtained in admixture with the lactone when methyl alcohol was employed for the recrystallization of the latter substance. It was more soluble in water than the lactone and a separation could be effected by stirring the mixed crystals with 2 parts of cold water for five minutes, filtering off the lactone, and adding 4 parts of ethyl alcohol to the filtrate to precipitate the ester. The compound crystallized in plates, which rotated $[\alpha]^{20}D +8.3°$ in aqueous solution (c, 2.2) and melted with decomposition at 162°

Anal. Calcd. for $C_9H_{18}O_9$: C, 40.00; H, 6.81; neutralization equivalent, 270. Found: C, 40.00; H, 6.71; neutralization equivalent, 270.

D-Gluco-α-L-gala-octose Dihydrate.—A solution of 50 g. of D-gluco-L-gala-octonic lactone in 200 cc. of water was reduced in the usual manner with 2000 g. of 2.5% sodium amalgam. The reduced solution was filtered to remove the separated sodium sulfate and the filtrate was concentrated *in vacuo* to a volume of 500 cc. and poured while still warm into 1200 cc. of warm 85% alcohol. The sodium salt of D-gluco-L-gala-octonic acid which crystallized was removed by filtration and the filtrate was concentrated *in vacuo* to a volume of 125 cc. and allowed to stand at 20° for several days to complete the crystallization of the sugar. The yield was 38 g. (65%). The dihydrate was recrystallized from 2 parts of water and it formed fine needles which melted at 96–97° and exhibited an equilibrium $[\alpha]^{20}D$ value of $-44.6°$ (c, 2.0) in water, which corresponds to the value $-51.3°$ on the basis of anhydrous octose. Philippe[10] reported a melting point of 98° and rotations of $-43.2°$ and $-44.2°$. Fischer[14] recorded a melting point of 93° and a rotation of $-43.9°$. The compound is only slowly soluble in water at 20° (see section on the solubility relationships of the mono and dihydrates) and hence the early stages of its mutarotation could not be determined. The mutarotation coefficient is not unimolecular and shows the decreasing values characteristic of sugars of the α-galactose structure. The dihydrate seems to be the stable pyranose form and collateral evidence from solubility considerations and rotational relationships with respect to the monohydrate support this conclusion. The course of a characteristic mutarotation is summarized in Table IV.

Anal. Calcd. for $C_8H_{16}O_8 \cdot 2H_2O$: C, 34.78; H, 7.30; H_2O, 13.04. Found: C, 34.67; H, 7.35; H_2O, 13.01.

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(13) All of the crystalline compounds described in the experimental part were recrystallized to constant melting point and specific rotation $[\alpha]^{20}D$; *c* is the concentration in grams in 100 cc. of solution; the tube length was 4 dm.

(14) Fischer, *Ann.*, **270**, 96 (1892).

TABLE IV

MUTAROTATION OF D-GLUCO-α-L-GALA-OCTOSE DIHYDRATE IN WATER

Concentration, 0.5000 g. in 25 cc. solution; tube length, 4 dm.; $T = 20 \pm 05°$.

Time after making solution, min.	$[\alpha]^{20}D$ of dihydrate .	$k_1 + k_2$
10	−77.5	...
11	−76.2	0.018
12	−75.5	.013
13	−74.9	.012
14	−74.0	.012
15	−73.2	.012
20	−70.2	.011
25	−67.1	.011
30	−64.9	.010
45	−63.4	.009
60	−56.5	.009
75	−54.1	.008
90	−51.9	.008
105	−50.6	.008
120	−49.3	.008
24 hrs. (final)	−44.6	...

The final value on the basis of anhydrous octose is −44.6° × 276/240 = −51.3°.

D-Gluco-L-gala-octose Monohydrate.—The monohydrate was readily obtained by recrystallization of the dihydrate from 15 parts of absolute methyl alcohol. The compound crystallized in fine needles which melted at 92° and exhibited an equilibrium rotation $[\alpha]^{20}D$ −46.7° (c, 2.0) in water. In contrast to the dihydrate the monohydrate is readily soluble in water. Its rate of mutarotation is initially very rapid, but at the end of ten minutes it approaches that of the dihydrate. This behavior suggests that the monohydrate is a furanose form and that the rapid initial change is due in part to its conversion to pyranose. The course of a typical mutarotation is summarized in Table V.

TABLE V

MUTAROTATION OF D-GLUCO-α-L-GALA-OCTOSE MONOHYDRATE IN WATER

Concentration, 0.5003 g. in 25 cc. solution; tube length, 4 dm.; $T = 20 \pm 0.5°$.

Time after making solution, min.	$[\alpha]^{20}D$ of monohydrate	$k_1 + k_2$
3	−63.0	...
4	−62.0	0.027
5	−61.0	.028
6	−60.4	.025
7	−60.1	.021
8	−59.7	.019
9	−59.3	.018
10	−58.9	.018
11	−58.6	.017
13	−58.2	.015
15	−57.5	.015
20	−55.8	.015
25	−55.0	.013
30	−54.1	.009
45	−52.9	.010
60	−51.4	.009
75	−50.4	.009
24 hrs. (final)	−46.7	...

The final value on the basis of anhydrous octose is −46.7° × 258/240 = −50.2°.

Anal. Calcd. for $C_8H_{16}O_8 \cdot H_2O$: C, 37.21; H, 7.03; H_2O, 6.98. Found: C, 37.29; H, 6.92; H_2O, 7.14.

Solubility Relationships of the Mono- and Dihydrates.—(1) A sample of 3.0 g. of the dihydrate was suspended in 30 cc. of water and shaken at 20° for a week. The undissolved material was then filtered off and the concentration of dissolved sugar (expressed as dihydrate) was determined polarimetrically and found to be 1.7106 g. or 5.7%. (2) A sample of 0.5 g. of the monohydrate dissolved completely in 5 cc. of water at 20° to give a 10% solution in less than one minute and on standing a further two minutes glistening needles of the dihydrate separated, increasing gradually in amount on standing. A similar experiment containing one drop of ammonia showed a marked increase in the rate of crystallization of the dihydrate.

Heptaacetyl-D-gluco-α-L-gala-octose.—A suspension of 10 g. of D-gluco-L-gala-octose dihydrate in a mixture of 50 cc. of pyridine and 50 cc. of acetic anhydride cleared after a week at 20°. The solution was poured upon crushed ice and the crystalline product (18.5 g., 96%) was removed by filtration. The crude product showed $[\alpha]^{20}D$ −33° in chloroform and it was apparently a mixture. After several recrystallizations from 4 parts of absolute alcohol the pure α-L-form was obtained in plates which melted at 138° and rotated $[\alpha]^{20}D$ −75.1° (c, 2.0) in chloroform. The compound is soluble in ether, acetone, benzene, carbon tetrachloride and ethyl acetate and insoluble in cold water. The yield of the pure α-form was 7.0 g. (36%). A solution of 0.2091 g. of the substance in 25 cc. of the 2% sulfuric acid acetylating mixture which has been shown[16] to bring about an α-β shift in other sugar acetates showed an initial $[\alpha]^{20}D$ value of −81°, which gradually changed to −66° in seven hours at 20°.

Anal. Calcd. for $C_{22}H_{30}O_{15}$: C, 49.44; H, 5.66; CH_3CO, 56.4. Found: C, 49.48; H, 5.59; CH_3CO, 56.2.

Heptaacetyl-D-gluco-β-L-gala-octose.—The mother liquor from the absolute alcohol recrystallization of the mixture of heptaacetates was concentrated *in vacuo* to a dry sirup; the sirup was extracted with warm water, in which it was partially soluble, and after standing at room temperature for several days the extract deposited crystals of the impure β-L-acetate. The compound was recrystallized from 100 parts of water, and the pure substance formed prisms which melted at 92–93°; it was readily soluble in methyl and ethyl alcohols, ether, acetone and warm water and relatively insoluble in cold water; it did not exhibit detectable rotation in chloroform solution (c, 0.8). A solution of 0.2579 g. of the compound in 25 cc. of the 2% acid acetylating mixture mentioned previously did not exhibit a rotation immediately upon solution, but within three minutes it showed $[\alpha]^{20}D$ −2° and mutarotation to a constant value −64° in six hours. From an experiment in which 5.0 g. of the α-L-heptaacetate (−75.1° was treated with the mixture, a recovery of 1.3 g. (26%) of the β-heptaacetate was accomplished. The two forms of the acetate are evidently converted to the same equilibrium mixture (based on the specific rotations in chloroform approximately 81% of alpha and 19% of beta form would be expected) by the acetylation solution, a behavior which is analogous to that of the galactopyranose pentaacetates.[16]

Anal. Calcd. for $C_{22}H_{30}O_{15}$: C, 49.44; H, 5.66; CH_3CO, 56.4. Found: C, 49.35; H, 5.51; CH_3CO, 56.1.

Methyl D-Gluco-α-L-gala-octoside.—Ten grams of the octose dihydrate was refluxed for two hours with 100 cc. of methyl alcohol containing 1.5% of dry hydrochloric acid; the solution, which was devoid of reducing power, was treated with 15 g. of dry silver carbonate and the halogen-free filtrate was concentrated to a sirup, which gradually crystallized on standing. The yield of product was 5.3 g. (58%). The glycoside was recrystallized from 2 parts of methyl alcohol or 10 parts of ethyl alcohol and was obtained in the form of aggregates of microcrystalline plates:

(15) Montgomery and Hudson, THIS JOURNAL, **56**, 2463 (1934).

(16) Hudson and Parker, *ibid.*, **37**, 1589 (1915).

it melted at 156–157° and exhibited a specific rotation of −138.0° (c, 1.7) in water; it is soluble in water, dioxane and pyridine and insoluble in ether and chloroform.

Anal. Calcd. for $C_9H_{18}O_8$: C, 42.52; H, 7.14; OCH_3, 12.21. Found: C, 42.41; H, 7.10; OCH_3, 12.10.

Methyl D-Gluco-α-L-gala-octoside Hexaacetate.—A solution of 1.9 g. of methyl D-gluco-α-L-gala-octoside in a mixture of 25 cc. of pyridine and 25 cc. of acetic anhydride was allowed to stand at room temperature overnight and then poured upon crushed ice. The reaction mixture was extracted with carbon tetrachloride in the usual manner and the extract, after drying over anhydrous sodium sulfate, was concentrated *in vacuo* to a dry sirup (3.6 g., 95%). The sirup was dissolved in 12 cc. of alcohol and crystallization of the hexaacetate was accomplished by the gradual addition of 7 cc. of water. The yield was 3.2 g. (84%). The compound was recrystallized from 4 parts of 50% ethyl alcohol or one part of absolute isopropyl alcohol and formed prisms which melted at 86–87° and had a specific rotation $[\alpha]^{20}D$ −99.0° in chloroform (c, 0.81); it is also soluble in acetone, ether and ethyl acetate and insoluble in water.

Anal. Calcd. for $C_{21}H_{30}O_{14}$: C, 49.80; H, 5.97; OCH_3, 6.13; CH_3CO, 51.0. Found: C, 49.77; H, 5.95; OCH_3, 6.07; CH_3CO, 50.9.

D-Gluco-L-gala-octose Dibenzyl Mercaptal.—Two cubic centimeters of benzyl mercaptan was added to a solution of 1 g. of D-gluco-L-gala-octose dihydrate in 2 cc. of concentrated hydrochloric acid and the reaction mixture was agitated vigorously for one hour, when crystallization commenced and the mixture gradually set up to a solid mass. The magma was thinned with 5 cc. of alcohol and the mercaptal was separated by filtration; the yield was 0.8 g. (47%). The substance was recrystallized from 50 parts of alcohol as fine needles which melted at 157° and exhibited a specific rotation $[\alpha]^{20}D$ +15.8° in pyridine (c, 0.8).

Anal. Calcd. for $C_{22}H_{30}O_7S_2$: C, 56.15; H, 6.43; S, 13.62. Found: C, 56.35; H, 6.54; S, 13.50.

D-Gluco-L-gala-octitol.—A solution of 15 g. of D-gluco-L-gala-octose dihydrate in 70 cc. of water was rocked in a bomb for six hours with 3 g. of Raney nickel at 98° under a hydrogen pressure of 166 atmospheres. The catalyst was separated by filtration and the filtrate, upon concentration *in vacuo*, deposited the crystalline sugar alcohol in nearly quantitative yield. The D-gluco-L-gala-octitol was recrystallized by solution in 2 parts of water and the addition of 4 parts of alcohol; it crystallized in the form of small prisms, which melted at 153–154° and showed a specific rotation $[\alpha]^{20}D$ +2.4° in aqueous solution (c, 4.0). Fischer reported a melting point of 141° and a specific rotation $[\alpha]^{20}D$ +2.0° for the octitol which he prepared by sodium amalgam reduction of his α-gluco-octose; Philippe recorded a melting point of 156–158° and a specific rotation $[\alpha]^{15}D$ +1.9° in water. A microanalytical examination of the compound by Mr. George L. Keenan showed that the finely powdered substance consists of irregular fragments which do not extinguish sharply with crossed nicols (parallel polarized light); in convergent polarized light (crossed nicols) partial biaxial interference figures occur occasionally; the refractive indices are n_α = 1.532, n_β = 1.537 and n_γ = 1.556, all ±0.002. The substance is identical microscopically with the D-gala-L-gulo-octitol which is described in a later section of this communication.

Anal. Calcd. for $C_8H_{18}O_8$: C, 39.66; H, 7.49. Found: C, 39.64; H, 7.43.

Octaacetyl-D-gluco-L-gala-octitol.—A mixture of 2.7 g. of D-gluco-L-gala-octitol, 0.7 g. of fused sodium acetate and 12 cc. of acetic anhydride was heated gently in a 125-cc. Erlenmeyer flask under reflux to incipient reaction and the source of heat was removed; the acetylation proceeded exothermically and sufficient heat was generated to boil the anhydride. After the original reaction had subsided the mixture was refluxed for fifteen minutes, cooled to room temperature, and poured over crushed ice. The sirup which separated resisted crystallization, but was finally

obtained in crystalline condition by allowing a solution of the sirup in about 10 parts of absolute alcohol to stand for two months. The yield was 2.3 g. (36%). The octaacetate deposited from its solution in 3 parts of alcohol as clusters of elongated rod-like prisms; it melted at 88–89° and rotated $[\alpha]^{20}D$ +20.7° in chloroform (c, 3.8). An examination of the substance by Mr. Keenan shows that, when powdered for examination by the immersion method, it breaks up into irregular fragments that do not extinguish sharply with crossed nicols; they show biaxial interference figures in convergent polarized light (crossed nicols), the optic sign being negative. The refractive indices are n_α = 1.454, n_β = 1.502 and n_γ = 1.512, all ±0.002. The compound is identical microscopically with octaacetyl D-gala-L-gulo-octitol.

Anal. Calcd. for $C_{24}H_{34}O_{16}$: C, 49.82; H, 5.92; CH_3CO, 59.5. Found: C, 49.90; H, 6.12; CH_3CO, 59.6.

II. Compounds of the D-Gluco-L-talo-octose Series

2-[D-Gluco-L-talo-heptahydroxyheptyl]-benzimidazole. —One gram of D-gluco-L-talo-octonic lactone was converted to the potassium salt and condensed with o-phenylenediamine by the method of Moore and Link.[17] The benzimidazole was very soluble in water and was purified by recrystallization from alcohol, from which it deposited as needles melting at 191–192° and rotating $[\alpha]^{20}D$ +18.6° in 1 N hydrochloric acid (c, 0.8). The yield of purified base was 0.8 g. (58%). As previously mentioned, the observed positive rotation of the substance is in agreement with the benzimidazole rule.

Anal. Calcd. for $C_{14}H_{20}O_7N_2$: C, 51.21; H, 6.14; N, 8.53. Found: C, 51.19; H, 6.14; N, 8.64.

A preparation, using the procedure described by Haskins and Hudson,[18] in the absence of hydrochloric acid, gave a mixture of the benzimidazole (39%) and di-[D-gluco-L-talo-octonyl]-o-phenylenediamine (40%). The latter compound is less soluble than the benzimidazole in 80% alcohol and by fractional recrystallization of the mixture from this solvent it was obtained in the form of needles melting at 149° and rotating $[\alpha]^{20}D$ +11.7° in aqueous solution (c, 1.0).

Anal. Calcd. for $C_{22}H_{36}O_{16}N_2$: C, 45.20; H, 6.21; N, 4.79. Found: C, 45.13; H, 6.31; N, 4.98.

D-Gluco-α-L-talo-octose.—A solution of 40 g. of D-gluco-L-talo-octonic lactone in 400 cc. of water was reduced in the usual manner with 2000 g. of 2.5% sodium amalgam. The solution was concentrated to 500 cc., poured into 950 cc. of warm 80% alcohol and the precipitated sodium sulfate separated by filtration. The filtrate was added to that obtained from a second similar reduction and the combined solution was concentrated to 300 cc. and poured into 400 cc. of warm methyl alcohol. The precipitated sodium D-gluco-L-talo-octonate was separated by filtration and the filtrate was concentrated *in vacuo* to a thin sirup and poured into 500 cc. of hot methyl alcohol to complete the precipitation of the sodium salts. The filtrate was again concentrated *in vacuo* to a sirup, which was dissolved in 100 cc. of hot methyl alcohol; the thick sirup which deposited from this solution as it cooled gradually crystallized. The product weighed 22.4 g. and showed an equilibrium $[\alpha]^{20}D$ value −5.3° in water. An additional 18.3 g. of octose showing a somewhat lower equilibrium value (−4.8°) was obtained from the mother liquor and hot methyl alcohol extracts of the sodium octonate fractions, bringing the total yield of non-recrystallized octose to 40.7 g. (50%). The compound was recrystallized from 10 parts of boiling methyl alcohol as glistening prisms which melted at 117–118°. The course of its mutarotation (Table VI) is not unimolecular. The final specific rotation of the sugar is −6.5° and the initial rotation is approximately −32°. A 2% aqueous solution of the octose was not fermented by either bakers' or brewers'

(17) Moore and Link, *J. Biol. Chem.*, **133**, 300 (1940); *J. Org. Chem.*, **5**, 637 (1940).

(18) Haskins and Hudson, THIS JOURNAL, **61**, 1267 (1939).

yeast during a test period of twenty-four hours at 37°, conditions which caused rapid fermentation of a 2% aqueous D-glucose solution.

Anal. Calcd. for $C_8H_{16}O_8$: C, 40.00; H, 6.71. Found: C, 40.12; H, 6.80; iodometric titration, 0.0808 g. consumed 6.86 cc. 0.1 N iodine equivalent to 0.0824 g. of octose.

TABLE VI

Mutarotation of D-Gluco-α-L-talo-octose in Water

Concentration, 0.4042 g. in 25 cc. solution; tube length, 4 dm.; $T = 20 \pm 0.5°$

Time, minutes	$[\alpha]^{20}D$	$k_1 + k_2$
2.3	−26.2	...
3.0	−23.6	0.087
4.0	−20.9	.080
4.5	−19.8	.077
6.5	−16.0	.075
9.0	−12.8	.073
10.0	−11.8	.073
15.0	− 9.8	.068
20.0	− 8.0	.062
30.0	− 7.5	.053
60.0	− 6.5	...
24 hrs.	− 6.5	...

Phenylosazone from D-Gluco-L-talo-octose.—This compound was prepared in the usual manner by heating an aqueous solution of the sugar with a few drops of acetic acid and an excess of phenylhydrazine. The osazone crystallized from its alcoholic solution in the form of needles which decomposed at 216–217° upon heating in a capillary tube; a pyridine solution of the osazone (c, 1.0) showed mutarotation changing from initial value $[\alpha]^{20}D$ −87° to a value of −53° in four days. The phenylosazone prepared from D-gluco-L-gala-octose (Fischer's α-gluco-octose) decomposed at 216–217° (Fischer[19] reported a decomposition point of 210–212°) and its pyridine solution exhibited mutarotation from $[\alpha]^{20}D$ −87° to −51° in four days. A mixed melting point determination, using phenylosazone from the two sources, also decomposed at 216–217°. The osazones are therefore identical and D-gluco-L-gala- and D-gluco-L-talo-octoses are epimers.

Anal. Calcd. for $C_{20}H_{26}O_6N_4$: C, 57.40; H, 6.26. Found: C, 57.36; H, 6.19.

Phenyl-D-gluco-L-gala-octosazone Hexaacetate.—A solution of 0.5 g. of phenyl-D-gluco-L-gala-octosazone in a mixture of 5 cc. of pyridine and 5 cc. of acetic anhydride was allowed to stand at room temperature for forty-eight hours and then poured upon crushed ice. The precipitated acetate (0.8 g., quantitative) could not be crystallized from a variety of organic solvents, but by solution in pyridine and the addition of water it was obtained in the form of a yellow powder which melted at 95° and rotated $[\alpha]^{20}D$ +78.0° in chloroform (c, 0.8). A repetition of the precipitation procedure did not change these constants and an analysis of the purified product agreed with the values for a hexaacetate.

Anal. Calcd. for $C_{32}H_{38}O_{12}N_4$: C, 57.30; H, 5.71; CH_3CO, 38.5. Found: C, 57.27; H, 5.59; CH_3CO, 38.4.

D-Gluco-L-talo-ocitol.—To a solution of 5.0 g. of D-gluco-L-talo-octose in 75 cc. of water, 3 g. of Raney nickel was added and the sugar was reduced at 98° for six hours under a hydrogen pressure of 133 atmospheres. The catalyst was separated by filtration and the filtrate, upon concentration *in vacuo* to dryness, deposited the crystalline octitol. The yield was quantitative. The compound crystallized from its solution in 8 parts of 50% alcohol as prisms which melted at 161–162° and rotated $[\alpha]^{20}D$ −0.8° in aqueous solution (c, 4.12).

(19) Fischer. *Ann.*, **270**, 98 (1892).

Anal.[20] Calcd. for $C_8H_{18}O_8$: C, 39.67; H, 7.49. Found: C, 39.60; H, 7.62.

Octaacetyl-D-gluco-L-talo-octitol.—A mixture of 5.0 g. of the octitol, 1.25 g. of fused sodium acetate and 25 cc. of acetic anhydride was heated gently and, following a vigorous exothermic reaction, refluxed for fifteen minutes. The reaction mixture was cooled, poured upon crushed ice and the octaacetate readily crystallized. The yield was 10.2 g. (86%). On recrystallization from 4 parts of alcohol the octaacetate formed prisms melting at 101–102° and rotating $[\alpha]^{20}D$ +17.4° in chloroform (c, 2.8); it is soluble in ethyl acetate, acetone and ether and nearly insoluble in water.

Anal. Calcd. for $C_{24}H_{34}O_{16}$: C, 49.82; H, 5.92; CH_3CO, 59.5. Found: C, 49.76; H, 5.97; CH_3CO, 59.2.

III. Compounds of the D-Gala-L-gulo-octose Series

D-Gala-L-gulo- and D-Gala-L-ido-octonic Phenylhydrazides from D-Gala-L-gluco-heptose.—To an ice-cold solution of 100 g. of D-gala-L-gluco-heptose[21] in 200 cc. of water was added 0.5 cc. of concentrated ammonium hydroxide and 30 cc. of liquid hydrocyanic acid and the reaction mixture was allowed to stand at 5° for one week; the pale yellow solution was diluted with 1000 cc. of water, heated at 50–60° for six hours to change any remaining cyanohydrin to amide and then boiled with 140 g. of barium hydroxide octahydrate (keeping the volume constant by addition of hot water) until ammonia was no longer evolved; the barium was balanced out as barium sulfate by the addition of 6.5 N sulfuric acid and the barium sulfate was removed by filtration. The filtrate, which was essentially a solution of the epimeric D-gala-L-gulo- and D-gala-L-ido-octonic acids was concentrated to a volume of 250 cc. and heated on the steam-bath for three hours with 76 cc. (1.6 molecular equivalents) of phenylhydrazine and 48 cc. of acetic acid; as the solution cooled it deposited 57.3 g. of a crystalline precipitate, which was mainly the sparingly soluble D-gala-L-gulo-octonic acid phenylhydrazide; a second crop (15.0 g.) of less pure material precipitated from the filtrate upon diluting it with 250 cc. of alcohol, and a third crop (13.5 g.), which contained some D-gala-L-ido-octonic acid phenylhydrazide, was obtained by concentration of the filtrate. These three fractions, upon recrystallization from 30 parts of boiling water gave 50.1 g. (30%) of pure D-gala-L-gulo-octonic acid phenylhydrazide in the form of glistening thin plates which melted with decomposition at 214–215° and rotated $[\alpha]^{15}D$ −10.3° in water (c, 1.0). The compound is nearly insoluble in alcohol, acetone and chloroform, but dissolves in warm acetic acid and pyridine.

Anal. Calcd. for $C_{14}H_{22}O_8N_2$: C, 48.55; H, 6.40; N, 8.09. Found: C, 48.59; H, 6.48; N, 8.13.

The solution from which the D-gala-L-gulo-octonic acid phenylhydrazide had been crystallized as completely as possible was concentrated *in vacuo* to a thick sirup, which was dried at the vacuum pump for two hours at 80°, and then dissolved in 200 cc. of warm methyl alcohol; after several days, the thick mat of crystals (52 g., 32%) which had formed was broken up and recrystallized from 5 parts of hot water. An analysis indicated that the product was a monohydrate of an octonic acid phenylhydrazide; its specific rotation $[\alpha]^{20}D$ +15.4° in water agreed in sign and was comparable in magnitude with that calculated, namely +10.2°, by the phenylhydrazide rule for D-gala-L-ido-octonic acid phenylhydrazide. The melting point varied with the rate of heating; when the bath was heated at a rate of 1° in three minutes it melted at 162–163° with decomposition, at a rate of 2° in one minute

(20) These data are from the work of Dr. W. Dayton Maclay, who prepared the octitol and its acetate before the sugar was known in crystalline condition. He used a solution of the sugar which resulted from the reduction of pure D-gluco-L-talo-octonic lactone by sodium amalgam and its sugar content was estimated by iodometric titration. Recently we have re-prepared this alcohol by Raney hydrogen reduction of a solution of the pure crystalline octose.

(21) Hann and Hudson, This Journal, **59**, 550 (1937).

the melting point was 165–166°; the substance is soluble in warm methyl and ethyl alcohols, pyridine and acetic acid and practically insoluble in acetone, chloroform and benzene.

Anal. Calcd. for $C_{14}H_{22}O_8N_2 \cdot H_2O$: C, 46.15; H, 6.64; N, 7.69; H_2O, 4.94. Found: C, 46.19; H, 6.79; N, 7.61; H_2O, 5.45.

D-Gala-L-gulo-octonic Acid Lactone.—The lactone was prepared from the phenylhydrazide by the copper sulfate oxidation procedure previously described.[22] A solution of 40.0 g. of D-gala-L-gulo-octonic acid phenylhydrazide and 69.1 g. (2.2 molecular equivalents) of copper sulfate pentahydrate in 1000 cc. of water was boiled under reflux for five hours; copper ions were removed as sulfide and the sulfuric acid as barium sulfate. The filtrate was concentrated to a small volume and evaporated on the steam-bath to a sirupy partly crystalline mass, which was then kept in an oven at 50° until the weight became nearly constant. The yield of crystalline solid was 24.5 g. (89%) and the product was recrystallized from 20 parts of boiling alcohol with a recovery of 80% of pure D-gala-L-gulo-octonic acid lactone. The lactone crystallized in the form of prisms which melted at 131–133°; in aqueous solution (*c*, 1.2) it showed mutarotation from an initial $[\alpha]^{20}D$ +48.0° to an equilibrium value of +44.4° in five hours; it is soluble in water and warm methyl and ethyl alcohols and practically insoluble in acetic acid, chloroform and benzene.

Anal. Calcd. for $C_8H_{14}O_8$: C, 40.34; H, 5.92; neutralization equivalent, 238.2. Found: C, 40.35; H, 6.01; neutralization equivalent, 239.1.

D-Gala-L-gulo-octonic Acid Amide.—A solution of 1.0 g. of D-gala-L-gulo-octonic acid lactone in 10 cc. of liquid ammonia was allowed to evaporate to dryness under anhydrous conditions and the dry residue was kept in a desiccator beside small beakers containing sulfuric acid and solid sodium hydroxide until it was free of ammonia; the finely powdered. solid, upon recrystallization from 500 parts of boiling ethyl alcohol, formed a granular crystalline powder which, upon microscopic examination, was found to consist of minute quadrilateral platelets. The amide, which showed a specific rotation $[\alpha]^{20}D$ −5.8° in aqueous solution (*c*, 0.8), melted at 153–154°; it is readily soluble in water and pyridine and nearly insoluble in warm methyl alcohol, acetone and cold ethyl alcohol.

Anal. Calcd. for $C_8H_{17}O_8N$: C, 37.64; H, 6.71; N, 5.49. Found: C, 37.47; H, 6.67; N, 5.31.

In a preparation in which the ammonia was not completely removed from the evaporated solution of the lactone in liquid ammonia and the residue was recrystallized by solution in 10 cc. of warm water and the addition of 5 cc. of alcohol, the amide was hydrolyzed and the product which deposited was the ammonium salt of D-gala-L-gulo-octonic acid. This compound also crystallized in plates, but the melting point was higher than that of the amide, namely, 163–164°, and the specific rotation $[\alpha]^{20}D$ was −6.2°; a mixed melting point determination with the amide depressed the melting point of the ammonium salt to 155–157°.

Anal. Calcd. for $C_8H_{19}O_9N$: C, 35.16; H, 7.01; N, 5.13. Found: C, 34.92; H, 7.01; N, 5.08.

2-[D-Gala-L-gulo-heptahydroxyheptyl]-benzimidazole.—The benzimidazole was prepared from D-gala-L-gulo-octonic lactone by the procedure of Moore and Link.[17] The yield from 2.0 g. of lactone was 0.8 g. (30%). The compound crystallized from 60 parts of hot water as elongated prisms, which melted at 234–235° with decomposition and rotated $[\alpha]^{20}D$ −11.2° in *N* hydrochloric acid (*c*, 0.84); it is soluble in acetic acid and nearly insoluble in alcohol, acetone, ether and cold water.

Anal. Calcd. for $C_{14}H_{20}O_7N_2$: C, 51.21; H, 6.14; N, 8.53. Found: C, 51.19; H, 6.13; N, 8.64.

D-Gala-β-L-gulo-octose.—A solution of 20.0 g. of D-gala-L-gulo-octonic acid lactone in 200 cc. of water was reduced in the usual manner with 2000 g. of 2.5% sodium

amalgam. Following removal of the sodium sulfate, the solution was concentrated to 80 cc. and pipetted into 300 cc. of boiling methyl alcohol; the granular precipitate of sodium salts was separated by filtration and the filtrate was concentrated *in vacuo* to a sirup, which was dissolved in a warm mixture of 10 cc. of water and 25 cc. of methyl alcohol. As the solution cooled the octose crystallized spontaneously; the first crop weighed 9.4 g. and an additional 2.1 g. was obtained from the mother liquor to make the total yield 11.5 g. (57%). The sugar was recrystallized by solution in 2 parts of warm water and the addition of 2 parts of methyl alcohol; it formed small prisms, which melted at 187–188°; it has a very slightly sweet taste and it is not fermented by either bakers' or brewers' yeasts. An aqueous solution of the sugar did not change in rotation for five minutes; thereafter the course of its mutarotation, as shown in Table VII, resembles that of D-gulose in being unimolecular; the velocity coefficient (0.015) is somewhat lower than the value (0.0206) recorded by Isbell for gulose.

Anal. Calcd. for $C_8H_{16}O_8$: C, 40.00; H, 6.71. Found: C, 40.19; H, 6.73.

TABLE VII

MUTAROTATION OF D-GALA-β-L-GULO-OCTOSE IN WATER

Concentration, 0.5061 g. in 25 cc. solution; tube length 4 dm.; $T = 20 \pm 0.5°$

Time after making solution, min.	$[\alpha]^{20}D$	Time, min.	$k_1 + k_2$
2	+24.8	. . .	. . .
5	+24.8	0	. . .
7	+24.4	2	0.016
10	+23.9	5	.015
15	+23.3	10	.014
20	+22.6	15	.014
25	+22.0	20	.015
30	+21.6	25	.015
35	+21.2	30	.014
60	+20.1	55	.014
80	+19.7	75	.014
100	+19.4	95	.015
120	+19.2	115	. . .
24 hrs. (final)	+19.2	∞	. . .

D-Gala-L-gulo-octose Phenylhydrazone.—To a cold solution of 1.0 g. of D-gala-L-gulo-octose in 10 cc. of water was added 1.0 cc. of phenylhydrazine and 0.5 cc. of glacial acetic acid; in a few minutes precipitation of D-gala-L-gulo-octose phenylhydrazone occurred and after five hours the precipitate (1.2 g., 86%) was separated by filtration and recrystallized from 50 parts of boiling water. The hydrazone formed small needles which melted with decomposition at 191–192°; it is nearly insoluble in cold pyridine and in boiling methyl and ethyl alcohols, acetone and acetic acid. Upon heating its aqueous solution with phenylhydrazine and acetic acid it is converted to phenyl-D-gala-L-gulo-octosazone.

Anal. Calcd. for $C_{14}H_{22}O_7N_2$: C, 50.90; H, 6.71; N, 8.48. Found: C, 51.03; H, 6.65; N, 8.51.

Phenyl-D-gala-L-gulo-octosazone.—A solution of 2.0 g. of D-gala-L-gulo-octose in a mixture of 4 cc. of phenylhydrazine, 2 cc. of glacial acetic acid and 50 cc. of water was heated under reflux for forty-five minutes. The precipitate of fine yellow needles of the osazone which crystallized on cooling the solution was separated by filtration and recrystallized from 50 cc. of 50% alcohol. The compound, which is nearly insoluble in cold methyl and ethyl alcohols, acetone, benzene and acetic acid, melted with decomposition at 204–205°; it is soluble in cold pyridine and in this solvent it shows mutarotation from $[\alpha]^{20}D$ +17° (ten minutes after solution) to −44° in five days.

Anal. Calcd. for $C_{20}H_{26}O_6N_4$: C, 57.40; H, 6.26; N, 13.39. Found: C, 57.44; H, 6.13; N, 13.20.

(22) Hann and Hudson, THIS JOURNAL, 56, 957 (1934).

D-Gala-L-gulo-octitol.—A solution of 2.0 g. of D-gala-L-gulo-octose in 50 cc. of water was agitated at 80° with Raney nickel and hydrogen under a pressure of 100 atmospheres for four hours; the catalyst was removed by filtration and the filtrate, which did not reduce Fehling solution, was concentrated *in vacuo* to dryness. The crystalline residue was dissolved in 3 cc. of warm water and the solution was diluted with 10 cc. of alcohol; upon cooling, clusters of elongated glistening prisms were deposited in the solution. The yield of product, which rotated [α]^{20}D +2.4° in aqueous solution (*c*, 1.6) was nearly quantitative; it melted at 153–154° and a mixed melting point with D-gluco-L-gala-octitol showed the same melting point; an optical examination of the two compounds by Mr. George L. Keenan disclosed no difference. The identity of this octitol from the two sources constitutes definitive proof by one of Fischer's classical methods of the configurations of D-gluco-L-gala-octose and D-gala-L-gulo-octose and by the epimeric relationship it proves the configurations of D-gluco-L-talo-octose and D-gala-L-ido-octonic acid.

Octaacetyl-D-gala-L-gulo-octitol.—This compound was prepared by the acetylation of 0.5 g. of the alcohol with acetic anhydride and fused sodium acetate. The yield was 0.8 g. (67%). It was recrystallized from 3 parts of alcohol with a recovery of 0.7 g. (88%). The compound melted at 88–89° and this melting point was not depressed upon admixture of octaacetyl-D-gluco-L-gala-octitol; it showed a specific rotation [α]^{20}D +20.5° in chloroform (*c*, 1.5). A microanalytical optical examination by Mr. Keenan proved it to be identical microscopically with octaacetyl-D-gluco-L-gala-octitol. This proof of identity confirms the conclusions previously stated regarding the configurations of the octose sugars in the glucose and galactose series.

Summary

A new crystalline gala-octose, which was obtained by application of the Fischer cyanohydrin synthesis to D-gala-L-gluco-heptose, has been reduced to an octitol, which proves to be identical with the octitol obtained by reduction of Fischer's α-gluco-octose. The identity of the alcohols constitutes a definitive proof that (1) Fischer's long known α-gluco-octose is D-gluco-L-gala-octose and its recently described epimer is D-gluco-L-talo-octose, and (2) that the new crystalline gala-octose is D-gala-L-gulo-octose. Extensive data on the comparison of similar sugars and derivatives are presented. The usefulness of several empirical rules in aiding the planning of the synthesis of higher carbon sugars is illustrated. The present data in the octose series lead to a very simple additional proof of the configurations of glucose and galactose.

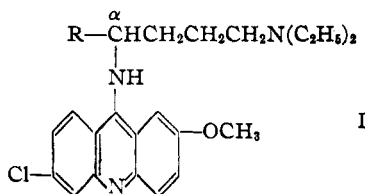# Synthesis of Atabrine Analogs Having Various Aliphatic α-Substituents in the Side Chain[1]

BY DAVID S. BRESLOW, ROBERT S. YOST, HOWARD G. WALKER AND CHARLES R. HAUSER
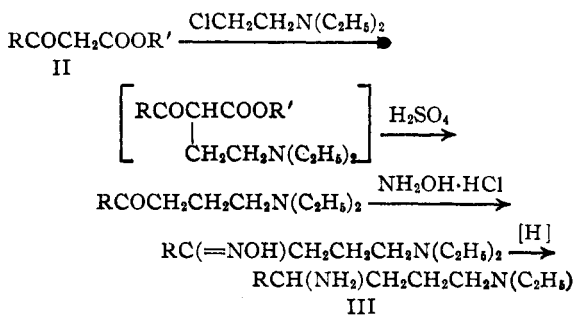
Although many analogs of atabrine (I, R = CH$_3$) have been synthesized relatively few have

$$\overset{\alpha}{R}\!-\!CHCH_2CH_2CH_2N(C_2H_5)_2$$

been described which have the same length of carbon side chain as atabrine but with a different α-substituent, R.[2] The present paper describes the synthesis of various atabrine analogs in which the α-substituents are alkyl groups higher than methyl.

Since 5-diethylamino-2-aminopentane, which yields atabrine when coupled with 2-methoxy-6,9-dichloroacridine, is generally synthesized from ethyl acetoacetate, the appropriate β-keto esters of type (II) were used in the preparation of the desired side chains (III). These β-keto esters were prepared by various methods. The conversion of

(1) The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Duke University.

(2) Of course it is possible that certain of these compounds were prepared by I. G. Farbenindustrie in their survey of acridine compounds but, if so, the results have not been made available.

the β-keto esters to the side chains may be represented by the transformation.

$$RCOCH_2COOR' \xrightarrow{ClCH_2CH_2N(C_2H_5)_2}$$

II

$$\left[\begin{array}{c} RCOCHCOOR' \\ | \\ CH_2CH_2N(C_2H_5)_2 \end{array}\right] \xrightarrow{H_2SO_4}$$

$$RCOCH_2CH_2CH_2N(C_2H_5)_2 \xrightarrow{NH_2OH \cdot HCl}$$

$$RC(\!=\!NOH)CH_2CH_2CH_2N(C_2H_5)_2 \xrightarrow{[H]}$$

$$RCH(NH_2)CH_2CH_2CH_2N(C_2H_5)$$

III

The alkylation of the β-keto esters with β-diethylaminoethyl chloride was carried out in benzene or dioxane and the alkylated product, without isolation, was subjected to ketonic cleavage in the presence of dilute sulfuric acid. The yields of ketones in these two steps (Table I) were in general better than those obtained using alcohol as a solvent for the alkylation. The ketones were converted in excellent yields to the corresponding oximes (Table II), which were reduced in good yields to the corresponding diamines (Table III). The reduction was effected with sodium in butyl alcohol or catalytically in the presence of Raney nickel; the latter method is preferable.