

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

## The Relationship between Structures and Configurations of Various Methylene and Benzylidene Acetals of Polyhydroxy Alcohols

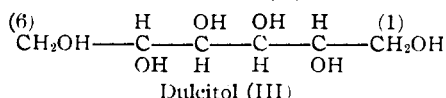
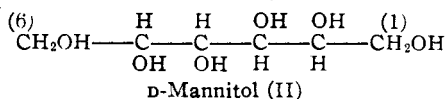
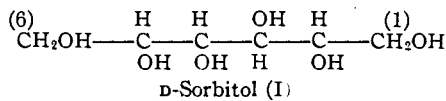
BY RAYMOND M. HANN AND C. S. HUDSON

The recent proof that the trimethylene cyclic acetals of D-mannitol and D-sorbitol differ in structure, the former being 1,3:2,5:4,6-trimethylene-D-mannitol<sup>1</sup> and the latter 1,3:2,4:5,6-trimethylene-D-sorbitol,<sup>2</sup> indicates clearly the great influence of configuration on the type of acetal that is favored. It is the purpose of the present article to discuss the structures of the methylene and benzylidene cyclic acetals of the polyhydroxy alcohols upon the basis of the experimental facts that are now known. In the customary formation of cyclic methylene polyacetals from hexitols, pentitols, etc., the polyhydroxy alcohol reacts with acidified aqueous solutions of formaldehyde; in the general case there is a succession of reactions, some of which may be in competition, and a state of reversible equilibrium involving a number of acetals is finally attained. If one of the acetals crystallizes during the reaction, as is often the case, the equilibrium conditions may cause this solid phase to be the principal product that is isolated. Similar considerations apply to the benzylidene acetals. The data concerning such equilibria are so meager that it does not seem possible at present to pass beyond an indication of the importance of the question of equilibrium and solid phases in these reactions; recognizing this limitation we venture upon the present attempt to obtain some generalizations concerning the relationship between the configurations of a considerable number of the polyhydroxy alcohols and the structures of the methylene and benzylidene acetals that have been produced so far from them.

Cyclic acetals of the polyhydric alcohols have been known since 1861, when Wurtz<sup>3</sup> described ethylidene glycol. Meunier's discovery of the crystalline benzylidene derivative of D-sorbitol<sup>4</sup> led to the recognition of this class of compounds as valuable derivatives for the isolation, purification and characterization of the sugar alcohols; however, it is only within recent years that extensive knowledge of their molecular structures has been gained. These advances have resulted from the application to the acetals of a combination of certain new chemical reactions and the related analytical procedures. The oldest of the new methods, that of the conversion of a tosyl derivative of the acetal to an iodohydrin by the Oldham-Rutherford technique, supplies a strong indication of the presence of a free primary hydroxyl group in the acetal<sup>5</sup>; a definitive proof of

such an inference may often be obtained by reduction of the halogen compound to a desoxy derivative<sup>6</sup> which is capable, either directly or after hydrolysis, of yielding acetaldehyde when oxidized by periodate<sup>7</sup>; the acetaldehyde is estimated by the analytical procedure of Nicolet and Shinn.<sup>8</sup> A second reaction, restricted at present to methylene acetals, is of particular interest because it offers evidence whether one or more of the primary hydroxyl groups of an alcohol participate in the formation of the cyclic methylene acetal; this reaction is the limited acetolysis of methylene acetals to produce a rapid rupture of those hemiacetal linkages which are formed through primary hydroxyl groups, while those formed through secondary hydroxyl groups are relatively stable; examples of the reaction are the formation of 1,2,5,6-tetraacetyl-3,4-di-(acetoxymethyl)-dulcitol<sup>1</sup> from 1,3:4,6-dimethylene-dulcitol<sup>9</sup> and of 1,6-diacetyl-3,5-di-(acetoxymethyl)-2,4-methylene-D-sorbitol from 1,3:2,4:5,6-trimethylene-D-sorbitol<sup>2</sup>; the alkaline hydrolysis of the acetoxymethyl compounds generates dulcitol in the one example and 2,4-methylene-D-sorbitol in the other one. Finally, the application to acetals of the periodate and lead tetraacetate selective oxidative procedures for the analysis of compounds containing contiguous hydroxyl groups, has been of special importance in the determination of acetal structures.

**Methylene Acetals of the Hexitols and Pentitols.**—Consider the definitive structures of the methylene acetals of D-sorbitol (I), D-mannitol (II) and dulcitol (III) as set forth in Table I.



It is apparent from the table that there is a correlation between the structures of the acetals and the *cis* or *trans* relationship of the pairs of secondary hydroxyl groups of these three hexitols: (I)

(6) Fischer and Zach, *Ber.*, **45**, 3761 (1912); Freudenberg and Raschig, *ibid.*, **60**, 1633 (1927); Levene and Compton, *J. Biol. Chem.*, **111**, 326 (1935).

(7) Ness, Hann and Hudson, *THIS JOURNAL*, **64**, 982 (1942).

(8) Nicolet and Shinn, *J. Biol. Chem.*, **135**, 91 (1941); *THIS JOURNAL*, **63**, 1456 (1941).

(9) Hann, Haskins and Hudson, *ibid.*, **64**, 986 (1942).

(1) Ness, Hann and Hudson, *THIS JOURNAL*, **65**, 2215 (1943).

(2) Ness, Hann and Hudson, *ibid.*, **66**, 665 (1944).

(3) Wurtz, *Compt. rend.*, **53**, 378 (1861); *Ann.*, **120**, 328 (1861).

(4) Meunier, *Ann. chim. phys.*, [6] **22**, 412 (1891).

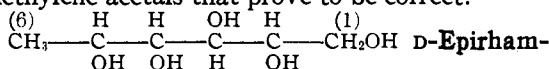
(5) Oldham and Rutherford, *THIS JOURNAL*, **54**, 366 (1932); Oldham, *J. Chem. Soc.*, **127**, 2840 (1925).

TABLE I  
 KNOWN STRUCTURES OF THE METHYLENE ACETALS OF THREE HEXITOLS

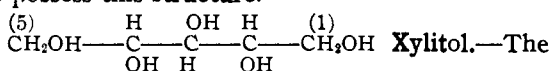
Alcohols	Structures of known acetals from alcohol, acid and formaldehyde	Configurations and positions of pairs of secondary hydroxyls <sup>a</sup>		
		2,4( $\beta$ )	3,5( $\beta$ )	2,5( $\gamma$ )
D-Sorbitol	1,3:2,4 and 1,3:2,4:5,6	<i>cis</i> (F)	<i>trans</i> (U)	<i>cis</i> (U)
D-Mannitol	1,3:4,6 and 1,3:2,5:4,6	<i>trans</i> (U)	<i>trans</i> (U)	<i>trans</i> (F)
Dulcitol	1,3:4,6	<i>trans</i> (U)	<i>trans</i> (U)	<i>cis</i> (U)

<sup>a</sup> The terms *cis* and *trans* are here used only in the sense that they specify the configurational relations that are exhibited by the plane projections of the conventional formulas of Fischer; the actual positions in space of the atoms comprising the molecules of the polyhydroxy alcohols are unknown.

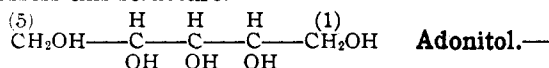
in the case of secondary hydroxyl groups of  $\beta$ -position a *cis* relationship is favorable (F) to acetal formation, but a *trans* relationship is unfavorable (U); (2) in the case of secondary hydroxyl groups of  $\gamma$ -position a *trans* relationship is favorable to acetal formation, but a *cis* relationship is unfavorable; (3) a primary and a secondary alcohol group in  $\beta$ -position are favorable for acetal formation. A primary alcohol group may also form an acetal with a secondary hydroxyl in  $\alpha$ -position in case the one in  $\beta$ -position is not available, as in 1,3:2,4:5,6-trimethylene-D-sorbitol. Although these correlations are inferred from the behavior of only three hexitols, it will now be shown that their application to several other alcohols leads to predictions concerning the structures of the derived methylene acetals that prove to be correct.



Only one pair of secondary hydroxyl groups is in favorable position for acetal formation, namely 2,4 (*cis*). The primary alcohol group and the one in  $\beta$ -position to it are free to form an acetal; hence epirhamnitol is to be expected to form a 1,3:2,4-dimethylene acetal. Its known acetal, which has been prepared both by the condensation of D-epirhamnitol and formaldehyde and by the reduction of 6-desoxy-6-iodo-1,3:2,4-dimethylene-D-sorbitol, has been proved<sup>10</sup> to possess this structure.



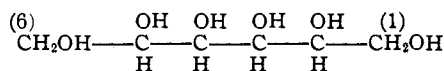
The only favorable pair of secondary hydroxyl groups is 2,4 (*cis*); a primary alcohol group and the secondary one in  $\beta$ -position are free to form an acetal; hence the compound to be expected is the racemic mixture D,L-1,3:2,4-dimethylene-xylitol. The known dimethylene-xylitol has been proved<sup>11</sup> to possess this structure.



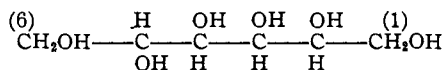
The same relationships hold here as in the case of xylitol and the racemic mixture D,L-1,3:2,4-dimethylene-adonitol is to be expected. The condensation of adonitol with formaldehyde by acid catalysis has been found to yield 18% of a dimethylene-adonitol<sup>12</sup> which has this structure. In addition, 2,4-methylene-adonitol, a compound of

*meso* structure, has been obtained in relatively high yield (63%) from the mother liquor of the dimethylene acetal preparation. This fact suggests that cyclic acetals involving secondary hydroxyl groups which are  $\beta$  in position and *cis* in configuration are more stable than those formed from a primary and secondary hydroxyl group in  $\beta$ -position.

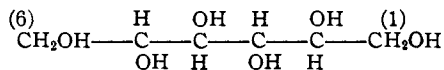
**Allitol, Talitol and Iditol.**—Three of the possible six hexitols have been discussed in connection with the study of Table I. The application of the generalizations to the methylene acetals of the remaining three is indicated in Table II.



Allitol (IV)



D-Talitol (V)



D-Iditol (VI)

 TABLE II  
 SUGGESTED STRUCTURES OF METHYLENE ACETALS OF ALLITOL, TALITOL AND IDITOL

Alcohols	Acetal structures indicated by the generalizations	Configurations and positions of pairs of secondary hydroxyl groups		
		2,4( $\beta$ )	3,5( $\beta$ )	2,5( $\gamma$ )
	(1) 2,4:3,5 ( <i>meso</i> )			
Allitol	(2) D,L-1,3:2,4	<i>cis</i> (F)	<i>cis</i> (F)	<i>cis</i> (U)
	(3) D,L-1,3:2,4:5,6			
	(1) 1,3:2,4			
Talitol	(2) 1,3:2,4:5,6	<i>cis</i> (F)	<i>trans</i> (U)	<i>trans</i> (F)
	(3) 1,3:4,6			
	(4) 1,3:2,5:4,6			
	(1) 2,4:3,5			
	(2) 1,3:2,4			
Iditol	(3) 1,3:2,4:5,6	<i>cis</i> (F)	<i>cis</i> (F)	<i>trans</i> (F)
	(4) 1,3:4,6			
	(5) 1,3:2,5:4,6			

Study of Table II brings to light a factor which was not prominent among the data of Table I, namely, the question of competitive structures. In the case of iditol, for instance, the favored positions for the condensation of formaldehyde with its secondary hydroxyl groups are expected to be the 2,4, the 3,5 and the 2,5-positions; obviously the 2,5-ring cannot coexist with either of the other

(10) Ness, Hann and Hudson, THIS JOURNAL, 66, 1235 (1944).

(11) Hann, Ness and Hudson, *ibid.*, 66, 670 (1944).(12) Hann and Hudson, *ibid.*, 66, 1906 (1944).

two in a polyacetal. In such cases, the relative stability of the various rings needs to be considered. There is much evidence, and particularly the evidence from acetolysis, that rings which involve two secondary hydroxyls in  $\beta$ - or  $\gamma$ -position are more resistant to rupture than those which involve a primary hydroxyl; one may therefore regard as improbable in Table II, under iditol, the structures (2), (3) and (4). Data on the relative stability of the types of structure that are represented by the remaining (1) and (5) need to be known. We have recently condensed L-iditol with formaldehyde by slow evaporation of a solution of it in aqueous formaldehyde and concentrated hydrochloric acid; the principal reaction product is a crystalline dimethylene-L-iditol ( $[\alpha]_D^{20} +39.2^\circ$  in water, m. p.  $264^\circ$  (dec.)) which is presumably the acetal (m. p.  $262^\circ$ ) that Lobry de Bruyn and Van Ekenstein<sup>13</sup> described. Oxidation of it is found to yield the dimethylene-L-idosaccharic acid which Haworth, Jones, Stacey and Wiggins<sup>14</sup> obtained by the epimerization, at carbon 5, of 2,3,4,5-dimethylene-D-glucosaccharic acid. The latter acid has been shown by Haworth and Wiggins<sup>15</sup> to be an oxidation product of the dimethylene-D-sorbitol which has recently been shown<sup>16</sup> to be 2,4:3,5-dimethylene-D-sorbitol.<sup>17</sup> Since the above-mentioned epimerization is a change in configuration rather than in structure, we conclude that the dimethylene-L-iditol is 2,4:3,5-dimethylene-L-iditol, the structure (1) of Table II. It seems possible that the structure (5) may exist in the trimethylene-iditol<sup>18</sup> or tribenzylidene-iditol<sup>19</sup> that have been reported. Our studies on iditol, from which the above data are taken, will be published later.

In the case of talitol, as indicated in Table II, the 2,4 and 2,5 secondary hydroxyl pairs are both favorable; however, they are in competition. The behavior of iditol suggests that structures (1) and (2) under talitol are favored over (4). Structure (3) seems improbable for reasons already stated. No methylene acetal of talitol has been reported; a tribenzylidene acetal has been described<sup>20</sup> but its structure is unknown. The generalizations indicate that it is probably (2) or (4).

In allitol, the 2,4 and 3,5 hydroxyls are not in competition and the *meso* 2,4:3,5-dimethylene-

(13) Lobry de Bruyn and Van Ekenstein, *Rec. trav. chim.*, **19**, 1, 180 (1900).

(14) Haworth, Jones, Stacey and Wiggins, *J. Chem. Soc.*, 61 (1944).

(15) Haworth and Wiggins, *ibid.*; 58 (1944).

(16) Hann, Wolfe and Hudson, *THIS JOURNAL*, **66**, 1898 (1944).

(17) It is to be noticed that this 2,4:3,5-dimethylene-sorbitol has not been found among the acetals that result from the system sorbitol-formaldehyde-water-acid, to which the generalizations have reference, but is instead the result of a "forced" condensation of formaldehyde with 1,6-dibenzoyl sorbitol, followed by removal of the benzoyl groups by alkali.

(18) Bertrand and Lauzenberg, *Bull. soc. chim.*, [3] **35**, 1073 (1906).

(19) Fischer and Fay, *Ber.*, **28**, 1979 (1895).

(20) Fischer, *ibid.*, **27**, 1524 (1894); Lobry de Bruyn and Van Ekenstein, *Rec. trav. chim.*, **18**, 150 (1899).

allitol (1) appears to be the favored structure. The racemic allitol acetals (2) and (3) that are listed in Table II seem improbable structures for reasons already stated. The preparation of acetals of allitol has not been reported.

As one proceeds higher in the series to heptitols and beyond, the questions of competing acetal structures and the insolubility of intermediate acetals become more important; we defer application of the generalizations to such alcohols until more experimental data are available for guidance.

#### Benzylidene Acetals of Hexitols and Pentitols.

—Although the structures of only a few of the benzylidene acetals are known, the data which are available show agreement with these generalizations from the methylene acetals. The benzylidene acetals that are derived from D-sorbitol are 2,4-benzylidene-D-sorbitol,<sup>21</sup> 1,3:2,4-dibenzylidene-D-sorbitol<sup>22</sup> and 1,3:2,4:5,6-tribenzylidene-D-sorbitol.<sup>23</sup> In contrast to D-sorbitol, dulcitol forms a 1,3:4,6-dibenzylidene derivative,<sup>24</sup> as would be expected since its secondary hydroxyls which are  $\beta$  in position are *trans* in configuration and the 2,5 pair has *cis* configuration, both of which are unfavorable. The known tribenzylidene-D-mannitol has been assigned a 1,2:3,4:5,6-triacetal structure,<sup>24</sup> but we have failed to find any recorded evidence for this assumed structure, and it seems to us more likely that the 1,3:2,5:4,6-structure, analogous to that of trimethylene-D-mannitol, applies to the substance. Considering next the pentitol acetals, the one that has been obtained from D-arabitol and benzaldehyde is a mono-acetal possessing a 1,3 structure,<sup>25</sup> while those derived from xylitol<sup>26</sup> and adonitol<sup>27</sup> are diacetals; according to the generalizations, arabitol (hydroxyls 2 and 4 *trans*) would not be expected to form a 2,4-acetal, but rather a 1,3 or 3,5-mono-acetal. A diacetal of arabitol (1,3:4,5 or 1,2:3,5) appears to be capable of formation, though none has been reported. It is suggested that the known dibenzylidene acetals from xylitol and adonitol probably have the D,L-1,3:2,4 structures that are like the known structures of the corresponding dimethylene acetals of these pentitols.

The benzylidene acetals are far more complicated than the methylene acetals because of the presence in each benzylidene acetal ring of a new asymmetric carbon atom,<sup>28</sup> which is not the case for the methylene acetal ring. There is only one substance that is defined as 1,3:2,4:5,6-trimethylene-D-sorbitol but there are eight possible stereochemical formulas for the known 1,3:2,4:5,6-tribenzylidene-D-sorbitol.

(21) Vargha, *Ber.*, **68**, 18, 1377 (1935).

(22) Angyal and Lawler, *THIS JOURNAL*, **66**, 837 (1944).

(23) Haskins, Hann and Hudson, *ibid.*, **64**, 132 (1942).

(24) Tollens-Elsner, "Kurzes Handbuch der Kohlenhydrate," Johann Ambrosius Barth, Leipzig, 1935, p. 317.

(25) Steiger and Reichstein, *Helv. Chim. Acta*, **19**, 1016 (1936).

(26) E. Fischer, *Ber.*, **27**, 2487 (1894).

(27) E. Fischer, *ibid.*, **26**, 663 (1893).

(28) E. Fischer, *ibid.*, **27**, 1524 (1894).

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.

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## 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<sup>1</sup> 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.<sup>2</sup> 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 enantiomorphous form of the glucoheptose 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- $\alpha$ -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.<sup>3</sup>

Fischer's second D-glucoheptose (designated  $\beta$  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-mannoheptitol) is the enantiomorph of his D-mannoheptitol (D-manno-L-gala-heptitol), a conclusion which would have established at that early date the configurations of the epimeric pairs of D-galaheptoses 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<sup>3</sup>; 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).