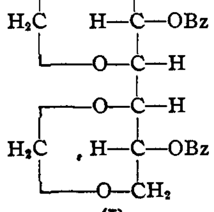
[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

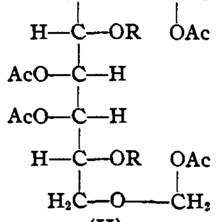
The Acetolysis of Trimethylene-D-mannitol. 2,5-Methylene-D-mannitol

BY A. T. NESS, RAYMOND M. HANN AND C. S. HUDSON

In a previous communication[1] from this Laboratory it was shown that 2,5-dibenzoyl-1,3:4,6-dibenzylidene-dulcitol could be converted in high yield to 2,5-dibenzoyl-1,3,4,6-tetraacetyl-dulcitol by acetolysis with a 2% sulfuric acid acetylation mixture. No migration of the benzoyl groups could be detected. We have since[2] employed the reaction with several benzoylated benzylidene acetals and have obtained corresponding isomeric dibenzoyl-tetraacetyl polyhydric alcohols which are suitable reference substances for the determination of the structures of the acetals of certain of the sugar alcohols. It seemed of interest to test the action of this acetolysis mixture on methylene acetals of sugar alcohols. Recently we[3] have shown that the dimethylene-dulcitol of Weber and Tollens is 1,3:4,6-dimethylene-dulcitol. Its dibenzoate (2,5-dibenzoyl-1,3:4,6-dimethylene-dulcitol) (I) was subjected to the action of the acid acetylating reagent in the expectation that 2,5-dibenzoyl-1,3,4,6-tetraacetyl-dulcitol might be formed. The reaction gave a different product however, a substance which corresponded in composition with a dibenzoyl-di-(acetoxymethyl)-diacetyl-dulcitol. Similar treatment of 2,5-diacetyl-1,3:4,6-dimethylene-dulcitol led to the formation of a tetraacetyl-di-(acetoxymethyl)-dulcitol. The like results in the two cases thus indicate that in these compounds only *one* of the oxygen linkages of each methylene acetal grouping is ruptured and that the resulting potential hydroxymethyl groups undergo acetylation. Although the rupture could conceivably occur at any of the oxygen atoms involved in the acetal structure, the absence of a complicated mixture of products, as shown in each case by the high yield of each pure crystalline di-(acetoxymethyl) compound (quantitative from the dibenzoate, 76% from the diacetate), lends support to the view that the rupture is primarily confined to either the secondary linkages at carbon atoms three and four or the primary linkages at one and six of the dulcitol moiety; should such be the case the resulting compounds would possess either structure II or III, in which R represents the benzoyl or acetyl group present in the original compound. As indicated in the formulas, these structures, insofar as the acetoxymethyl groups are concerned, may be considered as acetylated hemiacetals of orthoformaldehyde in which one hydroxyl group of the orthoaldehyde has been acetylated and the second has been condensed with some hydroxyl group of the dulcitol molecule. True hemiacetals of formaldehyde are unknown and the stability of the two dulcitol compounds is to be ascribed to the presence in their molecular structure of acetylated rather than free hemiacetal groups; in agreement with expectation it was found that upon saponification dibenzoyl-diacetyl-di-(acetoxymethyl)-dulcitol consumed six molecular equivalents of sodium hydroxide and formed dulcitol and formaldehyde. The instability of the methylene hemiacetal to alkali is in striking contrast with the full stability to alkali of the true methylene acetals of sugar alcohols.

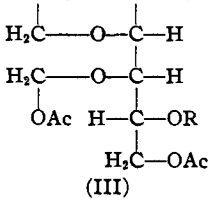

(I)

2,5-Dibenzoyl-1,3:4,6-dimethylene-dulcitol


(II)

1,6-Di-(acetoxymethyl)-2,5-disubstituted-3,4-diacetyl-dulcitol

R = CH_3CO or C_6H_5CO


(III)

1,6-Diacetyl-2,5-disubstituted-3,4-di-(acetoxymethyl)-dulcitol

Since the isolation of either a 1,6- or a 3,4-di-(hydroxymethyl)-dulcitol which would allow a decision between structures II and III was not possible through deacetylation, tetraacetyl-di-(acetoxymethyl)-dulcitol was subjected to mild acid hydrolysis to determine whether the acetyl and acetoxymethyl groups might be hydrolyzed at sufficiently different rates to permit the isolation of a substance that could provide an answer to the structural question; formaldehyde was always observed as a product of the hydrolysis and no crystalline substance other than dulcitol was found. Evidence was therefore lacking to distinguish between II and III at this stage of our work. Recourse was then taken to an independent approach, namely, the action of the acid acetylating solution on the trimethylene-D-mannitol of Schulz

---

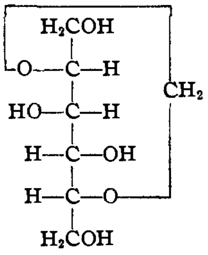
[1] Haskins, Hann and Hudson, THIS JOURNAL, **64**, 134 (1942).

[2] (a) Haskins, Hann and Hudson, *ibid.*, **64**, 137, 139 (1942); (b) Wolfe, Hann and Hudson, *ibid.*, **64**, 1493 (1942); (c) Haskins, Hann and Hudson, *ibid.*, **65**, 1419 (1943).

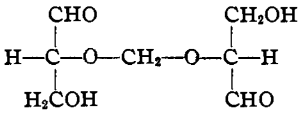
[3] Hann, Haskins and Hudson, *ibid.*, **64**, 986 (1942).

and Tollens.[4] Although the structure of this triacetal had not been established, its acetal linkages must involve two primary and four secondary hydroxyl groups. If the acetolysis reagent causes predominant rupture of the linkages formed through primary hydroxyl groups and has much less effect on those formed through secondary hydroxyl groups, the rupture will occur mainly at positions one and six and a 1,6-diacetyl-di-(acetoxymethyl)-monomethylene-D-mannitol will be obtained, unless the very improbable assumption of a 1,6-methylene grouping in the triacetal be made, in which case a molecule of formaldehyde would be liberated and a 1,6-diacetyl-di-methylene-D-mannitol will result. On the other hand, if the acetal linkages which are more easily ruptured are those formed through secondary alcoholic groups, a molecule of formaldehyde will be lost and a 1,6-di-(acetoxymethyl)-2,3,4,5-tetraacetyl-D-mannitol will result. Treatment of trimethylene-D-mannitol with the acetylating solution under controlled conditions gave an 81% yield of a crystalline compound (m. p., 129–130°; $[\alpha]^{20}\text{D}$ +57.6° in chloroform) which showed correct carbon, hydrogen and saponification values for a diacetyl - di - (acetoxymethyl) - monomethylene - D-mannitol. The isolation of this derivative in such a predominant yield is proof that under the experimental conditions employed the secondary hydroxyl linkages of one of the three acetal groupings are relatively stable; it further suggests that if the same degree of stability applies to the remaining secondary hydroxyl linkages the rupture of the other two acetal groupings does indeed occur at the primary hydroxyls at positions one and six, and the resulting compound may be considered tentatively as being a 1,6-diacetyl-di-(acetoxymethyl)-monomethylene-D-mannitol. Sodium methylate converted the compound quantitatively to a crystalline methylene-D-mannitol (a new substance) melting at 173–174° (cor.) and rotating $[\alpha]^{20}\text{D}$ −51.4° in aqueous solution. This acetal upon oxidation by lead tetraacetate in glacial acetic acid solution reduced only slightly more than one equivalent of the oxidant, indicating that the methylene-D-mannitol contained a single glycol grouping. Upon oxidation with sodium periodate in aqueous solution only slightly more than one molecular equivalent of oxidant was consumed and no formaldehyde or acid was produced. The absence of formaldehyde proves that the glycol grouping is formed from two secondary hydroxyl groups and the absence of formic acid shows that the carbon atoms adjacent to the glycol grouping are concerned in the acetal linkage. The only monoacetal of D-mannitol which can conform to these structural requirements is a 2,5-acetal and *the methylene-D-mannitol is therefore 2,5-methylene-D-mannitol (IV).*

An independent proof of this structure (IV) was readily obtained through the reduction of the methylene-bis-2-D-glycerose (V) which is formed by the oxidation of methylene-D-mannitol with per-iodic acid. Although this dialdehyde could not be crystallized, its reduction by hydrogen and Raney nickel gave a quantitative yield (based on the methylene mannitol used) of a crystalline substance which proved to be methylene-bis-2-glycerol (VI). This glycerol acetal of formaldehyde, which melted at 85–86° and showed no rotation in aqueous solution (formula (VI) contains no asymmetric carbon atom), was hydrolyzed by hot 2 *N* sulfuric acid with the liberation of formaldehyde; a nearly quantitative yield of glycerol was obtained from the hydrolysis solution.

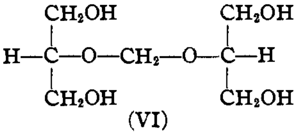


(IV)
2,5-Methylene-D-mannitol



$$\begin{array}{ccccc} & \text{CHO} & & & \text{CH}_2\text{OH} \\ & | & & & | \\ \text{H}- & \text{C} & -\text{O}-\text{CH}_2-\text{O}- & \text{C} & -\text{H} \\ & | & & & | \\ & \text{H}_2\text{COH} & & & \text{CHO} \end{array}$$

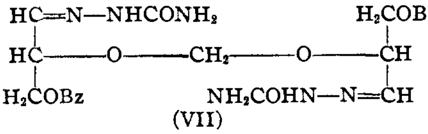
(V)
Methylene-bis-2-D-glycerose



$$\begin{array}{ccccc} & \text{CH}_2\text{OH} & & & \text{CH}_2\text{OH} \\ & | & & & | \\ \text{H}- & \text{C} & -\text{O}-\text{CH}_2-\text{O}- & \text{C} & -\text{H} \\ & | & & & | \\ & \text{CH}_2\text{OH} & & & \text{CH}_2\text{OH} \end{array}$$

(VI)
Methylene-bis-2-glycerol

Further evidence of the correctness of the structure (IV) was obtained by study of the 1,6-dibenzoyl-2,5-methylene-D-mannitol that is obtained from methylene-D-mannitol by differential benzoylation at positions one and six; the limited oxidation at 25° of this dibenzoate by lead tetraacetate proceeded with the consumption of one molecular equivalent of oxidant in thirty hours and from the solution it was possible to prepare the crystalline di-semicarbazone of methylene-bis-2-(3-benzoyl-D-glycerose) (VII) in a yield of 60%; the experimental result is in agreement with that expected for a 2,5-acetal structure solely. It is to be observed that this di-semicarbazone shows optical activity, as is to be expected from formula (VII), which contains two asymmetric carbon atoms and is not a meso structure.



$$\begin{array}{lcr} \text{HC}{=}\text{N}-\text{NHCONH}_2 & & \text{H}_2\text{COBz} \\ | & & | \\ \text{HC}-\!\!\!-\text{O}-\!\!\!- & \text{CH}_2 & -\!\!\!-\text{O}-\!\!\!-\text{CH} \\ | & & | \\ \text{H}_2\text{COBz} & & \text{NH}_2\text{COHN}-\text{N}{=}\text{CH} \end{array}$$

(VII)
Methylene-bis-2-(3-benzoyl-D-glycerose)-di-semicarbazone

It was also possible to confirm the structure of 2,5-methylene-D-mannitol by a synthetic procedure. The known 1,6-dibenzoyl-3,4-benzylidene-D-mannitol,[5] an acetal in which only two hydroxyl

---

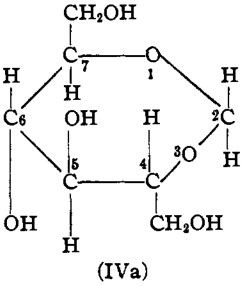
[4] Schulz and Tollens, *Ann.*, **289**, 21 (1896).

[5] Brigl and Grüner, *Ber.*, **65**, 641 (1932); **66**, 931 (1933); *cf.* Haskins, Hann and Hudson, Ref. 2 (c).

groups (those at positions two and five) are available for further condensation, was heated with paraformaldehyde and drierite in benzene at 150°; from the reaction mixture a substance melting at 151–152° and agreeing in composition with that required for 1,6-dibenzoyl-2,5-methylene-3,4-benzylidene-D-mannitol was isolated. The same substance resulted from the condensation of the previously mentioned 1,6-dibenzoyl-2,5-methylene-D-mannitol with benzaldehyde through the action of fused zinc chloride; the condensation product melted at 151–152° and a mixed melting point with the product from the other synthesis showed no depression.

On the basis of the established structure of 2,5-methylene-D-mannitol and the prior considerations regarding the stability of the secondary alcoholic acetal linkages, it seems highly probable that the diacetyl-di-(acetoxymethyl)-methylene-D-mannitol from which the methylene-D-mannitol is derived is 1,6-diacetyl-3,4-di-(acetoxymethyl)-2,5-methylene-D-mannitol. Similar considerations in the case of the products obtained by the acetolysis of the 2,5-diacetyl and 2,5-dibenzoyl-1,3:4,6-dimethylene-dulcitols indicate that they correspond in structure to formula III and may be tentatively assigned the structures of 1,2,5,6-tetraacetyl-3,4-di-(acetoxymethyl)-dulcitol and 1,6-diacetyl - 3,4 - di - (acetoxymethyl) - 2,5 - dibenzoyl-dulcitol, respectively.

The acetal ring structure of 2,5-methylene-D-mannitol is noteworthy; it appears to be the first example of an acetal in the carbohydrate group which contains the C_5O_2 dioxepane ring, previous acetals being C_3O_2 and C_4O_2 ring types. A related known acetal of the same 1,3-dioxepane ring type is the ethylidene-1,4-tetramethylene glycol of Hill and Hibbert.[6] It is possible, though not proved, that the dimethylene acetal of tartaric acid[7] contains the 1,3-dioxepane ring. The formula of 2,5-methylene-D-mannitol, previously written as (IV), may be written in the alternate form (IVa) that applies to 4,7-di-(hydroxymethyl)-5,6-di-(hydroxy)-1,3-dioxepane; in this formula, which is to be viewed as a perspective representation, the space positions of the groups attached to asymmetric carbon atoms 4, 5, 6 and 7 of the dioxepane ring are those pertaining to the corresponding carbon atoms 2, 3, 4 and 5, respectively, of D-mannitol. Viewing the carbon atom 6 of the ring, H is above the plane of the ring and OH is below.



(IVa)

2,5-Methylene-D-mannitol (IV) shown as 4,7-di-(hydroxymethyl)-5,6-di-(hydroxy)-1,3-dioxepane[8]

In the course of the work an interesting example of what appears to be an intramolecular aldol condensation was observed.[9] An oxidation of 2,5-methylene-D-mannitol was performed with aqueous per-iodic acid and the resulting solution of methylene-bis-2-D-glycerose (V) was made alkaline with hot saturated barium hydroxide solution followed by the addition of acid to neutrality, to precipitate the barium salts; after removal of the salts the solution was found to be levorotatory whereas it had been dextrorotatory before the addition of alkali. It was concentrated in the presence of barium carbonate to a small volume, clarified with carbon and reduced with hydrogen and Raney nickel. The crystalline reduction product was not the methylene-bis-2-glycerol (VI) melting at 85–86° which has been described earlier, but a substance which melted at 139–140°. The composition of the compound agreed with that expected for a 2,5-methylene-D-mannitol, but in contrast to the latter substance, which rotates −51.4° in water, it showed a specific rotation $[\alpha]^{20}D$ +39.7° in aqueous solution. Further, it was not oxidized by sodium periodate or lead tetraacetate and hence its structure does not include a glycol grouping, a conclusion which excludes the possibility that this substance is a derivative of a stereoisomer of mannitol. Upon acetylation it formed a crystalline acetate which melted at 93–94° and rotated $[\alpha]^{20}D$ +12.4° in chloroform solution; this acetate showed the same content of carbon, hydrogen and acetyl that is found for a tetraacetyl-methylene-mannitol; both substances possess the formula $C_7H_{10}O_6(CH_3CO)_4$. A molecular weight estimation by the Rast method gave a value of 313 (theory, 362) indicating that the tetraacetate and the parent compound from which it was derived are monomeric substances. It seemed likely that the compound was formed by an internal condensation of the methylene-bis-2-D-glycerose (V). It could not have resulted as a product of a condensation of the benzoin type, since the reduction of the ketone obtained in such a reaction would yield a methylene-hexitol which would be oxidized by glycol-splitting reagents. The products of a Cannizzaro dismutation of methylene-bis-2-D-glycerose, except the methylene-bis-2-glycerol obtained in this investigation and shown to be devoid of optical activity, would be acidic in nature. Consideration of these facts led to the hypothesis that under the slightly alkaline conditions of the experiment the primary oxidation product, methyl-

---

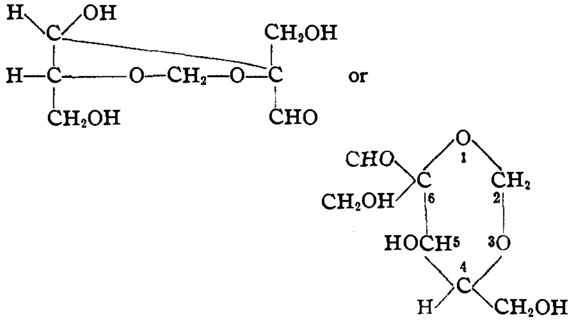
(6) Hill and Hibbert, THIS JOURNAL, **45**, 3115 (1923).

(7) Lobry de Bruyn and Van Ekenstein, *Rec. trav. chim.*, **20**, 335 (1901).

(8) Ring Index No. 248 of Patterson and Capell, "The Ring Index," Reinhold Publishing Corporation, New York, N. Y., 1940.

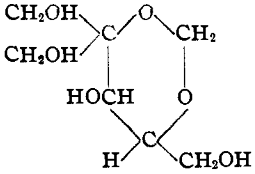
(9) Examples of dialdehydes undergoing an intramolecular aldol condensation are numerous. See Wohl and Schweitzer, *Ber.*, **39**, 896 (1906); Read and Hibbert, THIS JOURNAL, **46**, 990, 1281 (1924).

ene-bis-2-D-glycerose (V), was converted by an intramolecular aldol condensation to the isomeric cyclic aldehyde, 4-hydroxymethyl-5-hydroxy-6-formyl, hydroxymethyl-1,3-dioxane[10] (VIII), which was then reduced to form 4-hydroxymethyl-5-hydroxy-6-di-(hydroxymethyl)-1,3-dioxane (IX), an isomer of 2,5-methylene-D-mannitol (IV), both substances possessing the empirical formula $C_7H_{14}O_6$. To test this hypothesis a neutral solution of methylene-bis-2-D-glycerose was adjusted to 0.1 *N* alkalinity with sodium hydroxide and the changes in rotatory power of the solution were observed. In a typical experiment it was found that at 20° the specific rotation of the aldehyde solution changed rapidly from an initial value of +10° to a maximum negative value of −54.6° in one hundred and fifty minutes and then decreased slightly to a value of −52.9°, at which it remained constant for sixty minutes; at this time the solution was neutralized and reduced with hydrogen and Raney nickel; from the reduced solution a yield of 40% of the crystalline substance which we believe to be 4-hydroxymethyl-5-hydroxy-6-di-(hydroxymethyl)-1,3-dioxane (IX) was obtained. In a comparable experiment the neutral solution of methylene-bis-2-D-glycerose was reduced without addition of alkali and an 80% yield of crystalline methylene-bis-2-glycerol was obtained. The isolation of the two different compounds under the outlined conditions thus supports the hypothesis that first an intramolecular condensation takes place in the alkaline solution, resulting in the formation of a 1,3-dioxane ring to which a formyl group is attached, and that in the second stage this formyl group is then reduced to the hydroxymethyl group. The stability of the dioxane ring appears to be the factor responsible for this intramolecular aldol condensation.



(VIII)

4-Hydroxymethyl-5-hydroxy-6-formyl, hydroxymethyl-1,3-dioxane[11]



(IX)

4-Hydroxymethyl-5-hydroxy-6-di-(hydroxymethyl)-1,3-dioxane

The isolation of 2,5-methylene-D-mannitol as a saponification product of the diacetyl-di-(acetoxymethyl)-methylene-D-mannitol that is obtained by the acetolysis of the trimethylene-D-mannitol of Schulz and Tollens indicates that one of the acetal groups of the trimethylene-mannitol is attached to the 2,5-positions. It seems reasonable to assume that the other two acetal groups occupy the 1,3- and 4,6-positions and that the trimethylene-D-mannitol is 1,3:2,5:4,6-trimethylene-D-mannitol. While a definite proof of this hypothesis is lacking at present, some support for it is available. First, it has been shown[12] that a dimethylene-D-mannitol (m. p. 204–208° (cor.); $[\alpha]^{20}_D$ −91.0° in water) which is limited in structure to 1,3:4,6 or 1,3:5,6-dimethylene-D-mannitol, can be isolated in a yield of 12.6% from the mother liquor in the preparation of trimethylene-D-mannitol by the method of Schulz and Tollens. Second, it has been found that this dimethylene-D-mannitol, upon solution in a mixture of ten parts of concentrated hydrochloric acid and twelve and one-half parts of formaldehyde at 50°, formed a precipitate of trimethylene-D-mannitol in forty-five minutes while 2,5-methylene-D-mannitol and D-mannitol itself under the same experimental conditions first showed precipitation of the triacetal in one hundred and five and one hundred and eighty-five minutes, respectively; at a temperature of 25° and the same acid and formaldehyde concentrations the precipitation of the triacetal from solutions of dimethylene-D-mannitol, 2,5-methylene-D-mannitol and D-mannitol was first observed after three, twenty-one and forty-five hours, respectively. The relatively short time periods required for the formation of the triacetal from the diacetal suggest that the latter substance is the usual precursor of the trimethylene-D-mannitol. Since trimethylene-D-mannitol contains a 2,5-methylene union its rapid formation from the diacetal supports an inference that dimethylene-D-mannitol is 1,3:4,6- rather than 1,3:5,6-dimethylene-D-mannitol, and also supports the previously expressed view that Schulz and Tollens' trimethylene-D-mannitol is 1,3:2,5:4,6-trimethylene-D-mannitol.

Experimental

The Acetolysis of 2,5-Dibenzoyl-1,3:4,6-dimethylene-dulcitol.—A suspension of 1.0 g. of 2,5-dibenzoyl-1,3:4,6-dimethylene-dulcitol[3] in 25 cc. of an acid acetylating mixture, prepared by adding 2 cc. of concentrated sulfuric acid dropwise to an ice-cold mixture of 70 cc. of acetic anhydride

---

[10] The numbering is that of the dioxane ring rather than that of the original mannitol. It will be noticed that in formula (VIII) the carbon atom to which groups H and OH are attached has become asymmetric as a result of the aldol condensation; two forms of (VIII) are, therefore, possible, each of which on reduction passes to the corresponding form of (IX). We plan to study further this condensation and its stereochemical aspects, the discussion of which is postponed for the present.

[11] Ring Index No. 189 of Patterson and Capell, "The Ring Index."

[12] Haskins, Hann and Hudson, This Journal, 65, 67 (1943).

and 30 cc. of glacial acetic acid, was agitated on a shaking machine at 25° and when solution of the dibenzoate was complete (thirty minutes) the reaction mixture was poured upon crushed ice; the crystalline precipitate (1.5 g.; quantitative) was separated by filtration and upon recrystallization from ten parts of alcohol it formed prisms which melted at 87–88°. The compound is insoluble in water, readily soluble in cold chloroform and acetone and warm methyl and ethyl alcohols, and relatively insoluble in cold alcohol. An analysis for carbon and hydrogen agreed with that required for a dibenzoyl-diacetyl-di-(acetoxymethyl)-dulcitol. Upon saponification by the method of Kunz[13] the compound consumed six molecular equivalents of 0.1 N alkali; this analytical result is in agreement with the observation recorded in the following paragraph that dulcitol is obtained in quantitative yield by the action of sodium methylate on dibenzoyl-diacetyl-di-(acetoxymethyl)-dulcitol.

Anal. Calcd. for $C_{30}H_{34}O_{14}$: C, 58.25; H, 5.54; theory for six saponifiable groups, 9.75 cc. 0.1 N NaOH for 0.1005 g. substance. Found: C, 58.26; H, 5.56; 0.1005 g. substance consumed 9.68 cc. 0.1 N NaOH.

The Action of Sodium Methylate on 2,5-Dibenzoyl-diacetyl-di-(acetoxymethyl)-dulcitol.—To a solution of 2.0 g. of 2,5-dibenzoyl-diacetyl-di-(acetoxymethyl)-dulcitol in 20 cc. of chloroform, 2 cc. of 0.2 N sodium methylate was added and the reaction mixture was allowed to stand at room temperature for eighteen hours; the dulcitol (0.6 g.; m. p. 184–185°; quantitative) which had deposited was separated by filtration and recrystallized from 8 parts of 50% alcohol; the recrystallized product (0.5 g.; 83%) melted at 187–188° and a mixed melting point with dulcitol showed no depression. The chloroform mother liquor from which the dulcitol had been separated was poured into water and the chloroform removed by concentration *in vacuo* (bath temperature 35°). An aliquot of the solution, equivalent to 0.25 g. of 2,5-dibenzoyl-diacetyl-di-(acetoxymethyl)-dulcitol, upon neutralization and treatment with dimethone, formed 0.2161 g. of formaldehyde dimethone, corresponding to 1.83 molecular equivalents of formaldehyde.

The Acetolysis of 2,5-Diacetyl-1,3:4,6-dimethylene-dulcitol.—A solution of 2.0 g. of 2,5-diacetyl-1,3:4,6-dimethylene-dulcitol in 20 cc. of the acid acetylating mixture was allowed to stand for six hours at 20° and then poured upon crushed ice; the precipitate which formed was separated by filtration, washed with water, and recrystallized from ten parts of alcohol; the yield of recrystallized product was 2.6 g. (76%). The substance, which agreed in composition with a tetraacetyl-di-(acetoxymethyl)-dulcitol, crystallized in well formed prisms of melting point 93–94°; it showed no rotation in chloroform solution (c, 1.0); it was readily soluble in chloroform, ethylene dichloride, ethyl acetate and warm alcohol, and insoluble in water. Upon saponification by the Kunz[13] method it consumed six molecular equivalents of 0.1 N NaOH, and upon saponification with sodium methylate it gave a quantitative yield of dulcitol.

Anal. Calcd. for $C_{20}H_{30}O_{14}$: C, 48.58; H, 6.12; theory for six saponifiable groups, 16.09 cc. 0.1 N NaOH for 0.1326 g. substance. Found: C, 48.80; H, 6.22; 0.1326 g. substance consumed 16.14 cc. 0.1 N NaOH.

Trimethylene-D-mannitol from D-Mannitol, Formaldehyde and Concentrated Hydrochloric Acid.—Schulz and Tollens[4] prepared trimethylene-D-mannitol by heating "equal parts" of D-mannitol, formaldehyde and concentrated hydrochloric acid on the steam-bath for forty-five minutes; the yield of product, which melted at 227° and rotated −103.9° in chloroform, was not stated. An experiment conducted under these reaction conditions with 10 g. of D-mannitol, 10 cc. of commercial formaldehyde (specific gravity 1.09; 0.468 g. of formaldehyde per cc. = 2.84 molecular equivalents) and 10 cc. of concentrated hydrochloric acid gave a yield of 4.8 g. (40%) of trimethylene-D-mannitol which melted at 232–233° (cor.) and rotated $[\alpha]^{20}_{D}$ −104.2° in chloroform (c, 2.19), 1.4 g. of the previously described[12] dimethylene-D-mannitol melting at 204–208° (cor.) and rotating $[\alpha]^{20}_{D}$ −91.0° in water (c, 0.9) and 3.0 g. of a sirup which could not be crystallized. Increasing the amount of formaldehyde to 12.5 cc. (3.54 molecular equivalents) increased the yield of triacetal to 7.0 g. (58%); further increase in the amount of formaldehyde did not improve the yield, presumably because of the resulting lowering of the acid concentration; however, when the last named proportions of reactants were allowed to stand at 50° for four days the yield of triacetal was 9.1 g. (76%) and a further 0.4 g. (3%) of product was obtained by allowing the mother liquor to stand an additional four days at 50°. The above results indicate that in the liquid phase, several mutually dependent reversible reactions move toward an equilibrium in which mannitol and its various methylene acetals are present; one of these (the trimethylene acetal), being of relatively low solubility and readily crystalline in habit, soon begins to crystallize and the system becomes a heterogeneous one. With sufficient time, and in the presence of sufficient catalyst (acid), the heterogeneous system reaches the equilibrium that holds for the temperature of the system; the triacetal is present in the pure state as the crystalline phase; the liquid phase contains an equilibrium mixture consisting of some of the triacetal (corresponding to its solubility at the particular temperature), and the amounts of the other acetals and mannitol, all of relatively high solubility, that are in equilibrium in solution with this amount of dissolved triacetal. The only one of these other acetals that has been identified through isolation from the solution is the dimethylene-D-mannitol. Our experiments relating to this equilibrium have been directed only to the practical question of finding suitable conditions for obtaining high yields of trimethylene-D-mannitol; they are summarized in Table I. The first crop of triacetal was obtained by heating the reactants at 50° for five days, cooling the mixture to 5° and filtering; the filtrates were then kept at 50° for four days to obtain the second crop. A yield of 94% of triacetal was obtained by using a mixture of 10 g. of D-mannitol, 20 cc. of formaldehyde solution and 20 cc. of concentrated hydrochloric acid.

TABLE I

YIELDS OF TRIMETHYLENE-D-MANNITOL FROM D-MANNITOL (10 G.) WITH VARYING CONCENTRATIONS OF FORMALDEHYDE AND HYDROCHLORIC ACID

37% Formaldehyde, cc.	Concd. hydrochloric acid, cc.	Trimethylene-D-mannitol 1st crop, g.	2nd crop, g.	%
12.5	5 (+5 cc. H_2O)	1.9	0.9	23
12.5	6.7 (+3.3 cc. H_2O)	3.9	1.3	43
12.5	5	4.0	1.0	42
12.5	10	9.1	0.4	79
12.5	20	9.2	.1	78
15.0	20	10.8	.03	90
17.5	20	11.1	.03	93
20.0	20	12.2	.06	94

Diacetyl-di-(acetoxymethyl)-2,5-methylene-D-mannitol from Trimethylene-D-mannitol.—Five grams of finely powdered trimethylene-D-mannitol was dissolved in 25 cc. of an ice-cold acid acetylating mixture prepared by adding 1 cc. of concentrated sulfuric acid to an ice-cold mixture of 70 cc. of acetic anhydride and 30 cc. of glacial acetic acid. Within fifteen minutes the reaction mixture set to a magma of needle-like crystals. The mass was broken up, poured into 600 cc. of ice water, and after standing for eighteen hours in the refrigerator the precipitate (7.3 g.; 75%) was separated; a chloroform extract of the mother liquor yielded a further 0.6 g. of product to make the total yield 7.9 g. (81%). The substance was recrystallized from 12 parts of alcohol or 20 parts of 50% alcohol; the needles melted at 129–130° and rotated $[\alpha]^{20}_{D}$ +57.6° in chloro-

---

(13) Kunz, THIS JOURNAL, 48, 1982 (1926).

form (*c*, 1.1).[14] It was insoluble in water, ether and heptane, moderately soluble in benzene, and readily soluble in acetone, glacial acetic acid and dioxane.

Anal. Calcd. for $C_{17}H_{26}O_{12}$: C, 48.34; H, 6.20; theory for four saponifiable groups, 15.02 cc. of 0.1 *N* NaOH for 0.1586 g. substance. Found: C, 48.44; H, 6.19; 0.1586 g. substance consumed 15.04 cc. 0.1 *N* NaOH.

2,5-Methylene-D-mannitol from Diacetyl-di-(acetoxymethyl)-2,5-methylene-D-mannitol.—A solution of 10 g. of diacetyl-di-(acetoxymethyl)-2,5-methylene-D-mannitol in 100 cc. of chloroform was cooled to 0° and 10 cc. of 0.2 *N* sodium methylate was added; in one hour the solution deposited a crystalline precipitate and after standing for eighteen hours at 5° the product (4.6 g.; quantitative) was separated by filtration and recrystallized from 15 parts of alcohol. The acetal crystallized as prismatic needles which melted at 173–174° (cor.) and rotated $[\alpha]^{20}$D $-51.4°$ in water (*c*, 1.2). It was readily soluble in water and hot methyl alcohol, moderately soluble in pyridine, and nearly insoluble in cold ethyl and methyl alcohols, chloroform, acetone and ether.

Anal. Calcd. for $C_7H_{14}O_6$: C, 43.29; H, 7.27. Found: C, 43.38; H, 7.35.

1,3,4,6-Tetraacetyl-2,5-methylene-D-mannitol.—The tetraacetate was obtained by acetylation of 2,5-methylene-D-mannitol in pyridine solution with acetic anhydride. The yield was 57%. The compound crystallizes from its solution in 6 parts of alcohol in the form of prismatic needles melting at 117–118° and rotating $[\alpha]^{20}$D $-1.3°$ in chloroform (*c*, 1.2). It is insoluble in water, fairly soluble in methyl and ethyl alcohols, and readily soluble in chloroform and acetone.

Anal. Calcd. for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12; CH_3CO, 47.5. Found: C, 49.71; H, 6.02; CH_3CO, 47.4.

1,3,4,6-Tetrabenzoyl-2,5-methylene-D-mannitol.—The benzoylation of 2,5-methylene-D-mannitol in pyridine solution with benzoyl chloride gave an 85% yield of the desired tetrabenzoate. The compound was recrystallized from 25 parts of alcohol; it formed needles which melted at 107–109° and rotated $[\alpha]^{20}$D $-7.5°$ in chloroform (*c*, 1.6). It is insoluble in water, cold methyl and ethyl alcohols and soluble in chloroform, acetone, pyridine, benzene and dioxane.

Anal. Calcd. for $C_{35}H_{30}O_{10}$: C, 68.84; H, 4.95; C_6H_5CO, 68.8. Found; C, 68.79; H, 5.01; C_6H_5CO, 68.9.

1,3,4,6-Tetratosyl-2,5-methylene-D-mannitol.—Ice-cold solutions of 2.0 g. of 2,5-methylene-D-mannitol in 20 cc. of pyridine and 12.0 g. of *p*-toluene sulfonyl chloride in 20 cc. of pyridine were mixed and the reaction mixture was allowed to stand at 20° for six days; the addition of 800 cc. of water caused the deposition of a heavy sirup, which gradually crystallized. The product was a mixture, but after two recrystallizations from 20 parts of 1:1 chloroform–alcohol, pure 1,3,4,6-tetratosyl-2,5-methylene-D-mannitol was obtained in the form of fine needles melting at 177–178° (cor.) and rotating $[\alpha]^{20}$D $+3.5°$ in chloroform (*c*, 1.1); yield, 2.5 g. (30%). Further recrystallization did not change these constants.

Anal. Calcd. for $C_{35}H_{38}O_{14}S_4$: C, 51.84; H, 4.72; S, 15.81. Found: C, 51.99; H, 4.87; S, 15.80.

Lead Tetraacetate Oxidation of 2,5-Methylene-D-mannitol.—To a solution of 0.1040 g. of 2,5-methylene-D-mannitol in 15 cc. of glacial acetic acid, 30 cc. of 0.0581 *M* solution of lead tetraacetate in glacial acetic acid (3.25 molecular equivalents) was added and the volume was adjusted to 50 cc. with glacial acetic acid. Analysis of 5 cc. aliquots at the end of one, three, nineteen and seventy hours indicated that 0.14, 0.45, 0.99 and 1.07 molecular equivalents, respectively, of lead tetraacetate had been consumed. The analytical results indicate that 2,5-methylene-D-mannitol contains one glycol grouping in its structure.

Sodium Periodate Oxidation of 2,5-Methylene-D-mannitol.—To an ice-cold solution of 1.0056 g. of 2,5-methylene-D-mannitol in 25 cc. of water, 15 cc. of a 0.570 *M* sodium periodate solution (1.65 molecular equivalents) was added; the solution was allowed to warm to 20° and the volume was adjusted to 50 cc. with water. Analysis of 5 cc. aliquots at the end of twenty and forty minutes and at nineteen hours indicated that 1.10, 1.14 and 1.10 molecular equivalents of oxidant had been consumed. No formaldehyde could be detected in the oxidation solution by the sensitive dimethone reagent and no acid was produced. As previously mentioned, these facts prove that the glycol grouping is formed by two secondary hydroxyl groups and that it is situated between the carbon atoms of the D-mannitol moiety which are involved in the acetal linkage; hence the methylene-D-mannitol is 2,5-methylene-D-mannitol.

Methylene-bis-2-glycerol (VI).—To a solution of 5.0 g. of 2,5-methylene-D-mannitol in 60 cc. of water, 40 cc. of 0.675 *M* per-iodic acid (1.05 molecular equivalents) was added. Analysis of 5 cc. aliquots at fifteen and sixty minutes showed that 0.53 and 0.98 molecular equivalent, respectively, of oxidant had been reduced. After six hours the solution was cooled to 0° and after careful neutralization with *N* sodium hydroxide, avoiding any alkalinity, a slight excess of barium chloride solution was added; the mixture was allowed to stand at 0° for one hour and then filtered to remove the precipitated barium salts. The filtrate was strongly reducing to Fehling solution and it showed a specific rotation $[\alpha]^{20}$D $+10.5°$ based on the calculated content of methylene-bis-2-D-glycerose (V). The solution was agitated at room temperature for eighteen hours in a bomb with Raney nickel and hydrogen under a pressure of 133 atmospheres. The catalyst was separated by filtration and the filtrate, which did not reduce Fehling solution and was optically inactive, was concentrated *in vacuo* to a thick sirup which crystallized completely on standing a few hours. The compound was recrystallized from 5 parts of absolute alcohol, forming fine needles which melted at 85–86°; the yield was nearly quantitative. The substance is optically inactive in aqueous solution (*c*, 1.3); it is soluble in alcohol, pyridine and warm dioxane, and insoluble in ether, acetone, benzene and chloroform.

Anal. Calcd. for $C_7H_{16}O_6$: C, 42.85; H, 8.22. Found: C, 42.91; H, 8.22.

Hydrolysis of Methylene-bis-2-glycerol.—A solution of 1.0 g. of the acetal in 25 cc. of 2 *N* sulfuric acid was allowed to stand at room temperature for eighteen hours and then boiled under a reflux for six hours; the solution, which then had a strong odor of formaldehyde, was freed of sulfate ions by treatment with barium hydroxide, and concentrated *in vacuo* to a dry sirup. The sirup was dissolved in 10 cc. of pyridine, the solution was cooled to 0° and 4.5 cc. of benzoyl chloride (3.6 molecular equivalents) was added dropwise; after standing eighteen hours at room temperature the mixture was poured into 400 cc. of ice water and the crystalline precipitate (4.1 g.) which deposited was recrystallized several times from ten parts of methanol; the product (2.3 g.; 56%), which melted at 73–74°, gave a correct analysis for tribenzoyl glycerol and did not depress the melting point of an authentic sample of this substance.

Anal. Calcd. for $C_{24}H_{20}O_6$: C, 71.28; H, 4.99; C_6H_5CO, 78.0. Found: C, 71.27; H, 5.06; C_6H_5CO, 78.4.

Tetrabenzoyl-methylene-bis-2-glycerol.—The tetrabenzoate was prepared by benzoylation of methylene-bis-2-glycerol in pyridine solution by benzoyl chloride. The product, which separated as a sirup upon pouring the reaction mixture into water, did not crystallize at this stage; it was then dissolved in 5 parts of methyl alcohol and the solution was allowed to evaporate slowly in the refrigerator; after two months crystallization occurred. The compound was recrystallized from 15 parts of methanol in the form of elongated thin plates which melted at 69–71°

---

[14] All 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.

and showed no rotation in chloroform (*c*, 1.0). It was insoluble in water and cold ethanol and soluble in chloroform, ether, benzene, acetone and dioxane. The yield was quantitative.

Anal. Calcd. for $C_{35}H_{32}O_{10}$: C, 68.62; H, 5.27; C_6H_5CO, 68.6. Found: C, 68.41; H, 5.22; C_6H_5CO, 68.6.

1,6-Dibenzoyl-2,5-methylene-D-mannitol.—A solution of 5.0 g. of 2,5-methylene-D-mannitol in 50 cc. of pyridine was cooled in an ice-bath and 6.0 cc. (two molecular equivalents) of benzoyl chloride was added dropwise. After standing at 20° for three hours the reaction mixture was poured into 400 cc. of ice water and the precipitated dibenzoate (7.4 g.) was separated by filtration; an additional 1.4 g. of product was obtained by extracting the mother liquor with chloroform, the total yield of crude product being therefore 8.8 g. (85%). The compound crystallized from its solution in 5 parts of methyl alcohol as fine needles, which melted at 119–120° and rotated $[\alpha]^{20}\mathrm{D}$ −70.3° in chloroform (*c*, 1.1). It was insoluble in water, but dissolved readily in chloroform, acetone, ethyl acetate and ether.

Anal. Calcd. for $C_{21}H_{22}O_8$: C, 62.68; H, 5.51; C_6H_5-CO, 52.2. Found: C, 62.45; H, 5.42; C_6H_5CO, 52.0.

Lead Tetraacetate Oxidation of 1,6-Dibenzoyl-2,5-methylene-D-mannitol.—To a solution of 0.1011 g. of 1,6-dibenzoyl-2,5-methylene-D-mannitol in 20 cc. of glacial acetic acid, 25 cc. of 0.058 *M* lead tetraacetate (5.77 molecular equivalents) solution in glacial acetic acid was added, and the volume adjusted to 50 cc. Aliquots of 5 cc. were analyzed at the end of three, six, twenty-four and thirty hours and 0.20, 0.40, 0.92 and 1.00 molecular equivalents of oxidant were found to have been used progressively. After a further forty-two hours, 1.44 equivalents had been consumed and an analysis after one month showed a consumption of 4.92 equivalents. The latter figure compares favorably with that expected, namely, 5.00 equivalents, if the primary oxidation product, the 3-benzoyl-D-glyceric aldehyde acetal of formaldehyde, had been hydrolyzed and completely oxidized.

Di-semicarbazone of the Formaldehyde Acetal of 3-Benzoyl-D-glyceric Aldehyde (VII).—A solution of 0.6481 g. of 1,6-dibenzoyl-2,5-methylene-D-mannitol in 20 cc. of glacial acetic acid was added to 30.5 cc. of a 0.058 *M* acetic acid solution of lead tetraacetate (1.1 molecular equivalents) and the oxidation allowed to proceed for thirty hours at room temperature. At the expiration of this time, 0.8 g. of semicarbazide hydrochloride and 2.0 g. of sodium acetate were added and the reaction mixture was again allowed to stand for twenty-four hours. The precipitated lead chloride was separated by filtration and the filtrate was diluted with 50 cc. of water and, after standing for several days at 5°, it deposited 0.2 g. of the di-semicarbazone. An additional 0.3 g. of the compound was obtained by evaporating the acetic acid filtrate to dryness and recrystallizing the residual solid from dilute acetic acid. The total yield was 60%. The di-semicarbazone was recrystallized from 40 parts of 25% acetic acid as well formed prisms which melted at 193–195° (cor.) and rotated $[\alpha]^{20}\mathrm{D}$ +83.6° in glacial acetic acid (*c*, 0.9). The substance is practically insoluble in chloroform or water.

Anal. Calcd. for $C_{23}H_{26}O_8N_6$: C, 53.69; H, 5.09; N, 16.34. Found: C, 53.62; H, 4.94; N, 16.12.

1,6-Dibenzoyl-2,5-methylene-3,4-benzylidene-D-mannitol from 1,6-Dibenzoyl-2,5-methylene-D-mannitol, Benzaldehyde and Zinc Chloride.—A mixture of 1.0 g. of 1,6-dibenzoyl-2,5-methylene-D-mannitol, 1.0 g. of fused zinc chloride and 5 cc. of benzaldehyde was agitated on a shaking machine at room temperature; solution of the dibenzoate occurred with noticeable slight warming and after thirty minutes fine needles began to deposit rapidly from the solution and the reaction mixture set to a sludge; after standing overnight, the mass was thinned with 5 cc. of alcohol and filtered. The yield was 1.0 g. (83%). The mixed diacetal was recrystallized from five parts of alcohol and it formed long silky needles which melted at 151–152° and rotated $[\alpha]^{20}\mathrm{D}$ +61.2° in chloroform (*c*, 1.1). It was readily soluble in cold acetone and benzene, warm methyl and ethyl alcohols and was insoluble in water.

Anal. Calcd. for $C_{28}H_{26}O_8$: C, 68.56; H, 5.34; C_6H_5-CO, 4.08 cc. of 0.1 *N* alkali for 100 mg. substance. Found: C, 68.49; H, 5.36; C_6H_5CO, 4.04 cc. of 0.1 *N* alkali consumed for 100 mg. substance.

1,6-Dibenzoyl-2,5-methylene-3,4-benzylidene-D-mannitol from 1,6-Dibenzoyl-3,4-benzylidene-D-mannitol and Paraformaldehyde.—A mixture of 1.0 g. of 1,6-dibenzoyl-3,4-benzylidene-D-mannitol,[5] 1.0 g. of paraformaldehyde which had been dried over phosphorus pentoxide, 5 g. of drierite and 50 cc. of benzene was heated in a bomb at 150° for eight hours; the drierite was separated by filtration and the residue remaining after evaporation of the benzene was dissolved in 5 cc. of warm alcohol; as it cooled the solution deposited 0.2 g. (20%) of impure 1,6-dibenzoyl-2,5-methylene-3,4-benzylidene-D-mannitol in the form of silky needles which melted at 144–145°. Four recrystallizations from alcohol raised the melting point to 151–152° and a mixed melting point determination with the previously described diacetal prepared from 1,6-dibenzoyl-2,5-methylene-D-mannitol and benzaldehyde showed no depression.

4-Hydroxymethyl-5-hydroxy-6-di-(hydroxymethyl)-1,3-dioxane (IX) from 2,5-methylene-D-mannitol.—(1) A solution containing 10.0 g. of 2,5-methylene-D-mannitol in 50 cc. of water and 100 cc. of 0.675 *M* per-iodic acid (1.3 molecular equivalents) was allowed to stand at room temperature for twenty hours; the specific rotation $[\alpha]^{20}\mathrm{D}$ of the solution, calculated on the basis of the expected oxidation product, methylene-bis-2-D-glycerose (V), was +10° (dextrorotation). Hot saturated barium hydroxide solution was added in slight excess and the mixture then carefully neutralized with dilute sulfuric acid, cooled to 0°, and filtered to remove the precipitated barium salts; the filtrate, which was strongly reducing to Fehling solution and now showed a specific rotation of −14° (levorotation), was concentrated *in vacuo* in the presence of barium carbonate and yielded 8.5 g. of a sirup which did not crystallize. The sirup was dissolved in 50 cc. of water and agitated in a bomb for eight hours at 100° with Raney nickel and hydrogen under a pressure of 133 atmospheres; the catalyst was removed by filtration and the filtrate, which did not reduce Fehling solution and exhibited a rotation of +24°, was concentrated *in vacuo* and it deposited a sirupy slurry of crystals (8.2 g.). The product was recrystallized several times from 5 parts of alcohol and yielded 3.7 g. (37%) of prisms, melting at 139–140° and rotating $[\alpha]^{20}\mathrm{D}$ +39.7° in water (*c*, 1.1).

(2) To a solution containing 1.49 g. of methylene-bis-2-D-glycerose in 75 cc. of water, 10 cc. of 1.0 *N* sodium hydroxide was added and the volume was adjusted to 100 cc. with water. Polarimetric observation of the solution at the end of five, fifteen, thirty, sixty, ninety, one-hundred fifty, two-hundred ten and two-hundred seventy minutes gave readings $[\alpha]^{20}\mathrm{D}$ −43.6, −48.8, −51.1, −53.4, −54.0, −54.6, −52.9 and −52.9°, respectively. Sulfuric acid equivalent to the alkali was added and the solution was adjusted in volume to 200 cc.; it was reducing to Fehling solution and showed a specific levorotation of −27.9° based on the original aldehyde content. The solution was agitated with hydrogen and Raney nickel at 133 atmospheres pressure for eighteen hours at room temperature. Following removal of the catalyst, the solution, which was found to be non-reducing to Fehling solution and to be dextrorotatory (+20.8°), was concentrated *in vacuo* and yielded 1.5 g. of a sirup; a solution of the sirup in 15 cc. of absolute alcohol deposited 0.6 g. (40%) of the crystalline 1,3-dioxane derivative melting at 139–140°. This substance was not oxidized by lead tetraacetate or sodium periodate. It corresponded in composition with 2,5-methylene-D-mannitol and, as described in the next paragraph, it formed a crystalline tetraacetyl derivative, as does the latter substance. These properties are in agreement with the structure of 4-hydroxymethyl-5-hydroxy-6-di-(hydroxymethyl)-1,3-dioxane assigned to the compound

but they exclude the possibility that it could be 2,5-methylene-D-mannitol or a stereoisomer of that substance.

Anal. Calcd. for $C_7H_{14}O_6$: C, 43.29; H, 7.27. Found: C, 43.15; H, 7.27.

4-Acetoxymethyl-5-acetoxy-6-di-(acetoxymethyl)-1,3-dioxane.—A solution of 1.0 g. of the substituted 1,3-dioxane in a mixture of 10 cc. of pyridine and 15 cc. of acetic anhydride was allowed to stand overnight at room temperature and then poured into 500 cc. of ice water. The aqueous solution was extracted with chloroform and the washed and dried extract upon concentration yielded 1.7 g. (89%) of a sirup which crystallized readily. The compound, which is soluble in acetone, chloroform, ether, pyridine, benzene and dioxane and insoluble in water, was recrystallized from 10 parts of alcohol in the form of rods, melting at 93–94° and showing a specific rotation $[\alpha]^{20}_{D}$ +12.4° in chloroform (*c*, 1.0) and +20.4° in acetone (*c*, 1.0).

Anal. Calcd. for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12; CH_3CO, 47.5; molecular weight, 362. Found: C, 49.73; H, 6.24; CH_3CO, 47.3; molecular weight (Rast), 313.

Summary

The acetolysis of 2,5-diacetyl and 2,5-dibenzoyl-1,3:4,6-dimethylene-dulcitols yields a tetraacetyl-di-(acetoxymethyl)-dulcitol and a 2,5-dibenzoyl-diacetyl-di-(acetoxymethyl)-dulcitol, respectively. The acetolysis of the trimethylene-D-mannitol of Schulz and Tollens yields a diacetyl-di-(acetoxymethyl)-methylene-D-mannitol. Upon saponification of the latter compound 2,5-methylene-D-mannitol, a new type of acetal of a carbohydrate, is formed. The isolation of this substance indicates that under the conditions of acetolysis employed, the methylene hemiacetal linkages that are formed through primary hydroxyl groups are more easily ruptured than those formed through secondary hydroxyl groups and suggests the tentative structural assignments of 1,2,5,6-tetraacetyl-3,4-di-(acetoxymethyl)-dulcitol, 1,6-diacetyl-2,5-dibenzoyl-3,4-di-(acetoxymethyl)-dulcitol, and 1,6-diacetyl-2,5-methylene-3,4-di-(acetoxymethyl)-D-mannitol to the acetolysis products.

Proof of the structure of 2,5-dimethylene-D-mannitol has been obtained (1) through its oxidation by per-iodic acid to form sirupy methylene-bis-2-D-glycerose, which upon reduction is converted into a crystalline methylene-bis-2-glycerol; (2) through the lead tetraacetate oxidation of its 1,6-dibenzoyl derivative to produce the formaldehyde acetal of 3-benzoyl-D-glyceric aldehyde, which was characterized as the crystalline disemicarbazone; and (3) through the condensation of its 1,6-dibenzoyl derivative with benzaldehyde to yield 1,6-dibenzoyl-2,5-methylene-3,4-benzylidene-D-mannitol which proved to be identical with the mixed diacetal prepared by condensing the known 1,6-dibenzoyl-3,4-benzylidene-D-mannitol with paraformaldehyde.

Evidence is presented for the assignment of 1,3:2,5:4,6-trimethylene-D-mannitol as the structural formula for the long known trimethylene-D-mannitol of Schulz and Tollens.

An interesting reaction, apparently an intramolecular aldol condensation of methylene-bis-2-D-glycerose to produce 4-hydroxymethyl-5-hydroxy-6-formyl, hydroxymethyl-1,3-dioxane, which upon reduction yields crystalline 4-hydroxymethyl-5-hydroxy-6-di-(hydroxymethyl)-1,3-dioxane, has been described.

BETHESDA, MARYLAND RECEIVED AUGUST 16, 1943

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF WINTHROP CHEMICAL COMPANY, INC.]

2,4-Diamino-5-(4-methyl-5-β-hydroxyethylthiazolium chloride)-methylpyrimidine Hydrochloride, a New Analog of Thiamin

BY WOLFGANG HUBER

Within the last seven years well over two score homologs and analogs of thiamin have been prepared. These compounds can be conveniently classified into the following groups indicating the place of change in comparison with the original thiamin molecule: (1) change of substituents in the pyrimidine ring[1,2,3,4,5]; (2) change of substituents in the thiazole ring[1,6,3,7,8,5]; (3) change of substituents in the pyrimidine and the thiazole rings[3,5]; (4) change of the carbon bridge connecting the pyrimidine and thiazole rings[3]; (5) replacement of either the pyrimidine or thiazole ring by another ring system.[9,10,11,12,13] The pharmacological and biochemical evaluation of a large number of thiamin homologs and analogs has been reported in the literature.[3,5,12,14] One cannot fail to draw the conclusion from these reports that the antineuritic specificity of the vitamin is shared by a surprisingly large number of more or less related compounds although the actual activity of the vitamin is duplicated only in the very closely related homologs and some of the esters.

(1) Todd and Bergel, *J. Chem. Soc.*, 1559 (1936).

(2) Andersag and Westphal, *Ber.*, **70**, 2043 (1937).

(3) Schultz, *Z. physiol. Chem.*, **265**, 113 (1940).

(4) Perina and Ziegel, *Proc. Sci. Inst. Vitamin Research*, U. S. S. R., **3**, No. 1, 94 (1941); *C. A.*, **36**, 3008.

(5) Stein, Sampson, Cline and Stevens, THIS JOURNAL, **63**, 2059 (1941).

(6) Buchman and Richardson, *ibid.*, **61**, 891 (1939).

(7) Slobodin and Ziegel, *J. Gen. Chem.* (U. S. S. R.), **11**, 1019 (1941).

(8) Price and Pickel, THIS JOURNAL, **63**, 1067 (1941).

(9) Schmelkes and Joiner, *ibid.*, **61**, 2562 (1939).

(10) Finkelstein and Elderfield, *J. Org. Chem.*, **4**, 365 (1939).

(11) Tracy and Elderfield, *ibid.*, **6**, 54 (1941).

(12) Baumgarten and Dornow, *Ber.*, **73**, 44, 353 (1940).

(13) Tota and Elderfield, *J. Org. Chem.*, **7**, 309 (1942).

(14) Robbins, *Proc. Nat. Acad. Sci.* U. S., **27**, 419 (1941).