was allowed to stand at room temperature for several days. When the ether was removed under reduced pressure, the highly viscous residue (4.5 g.) partly crystallized out, and the crystals separated and dried on a porous plate; m. p. 92–94°.

Anal. Calcd. for $C_7H_{14}O_3$: active (O), 10.95. Found: active (O), 10.00.

The dihydroxydicycloheptyl peroxide was not prepared.

1-Hydroxycycloöctyl Hydroperoxide-1.—A solution of 4.4 g. of cycloöctanone in 120 cc. of 0.55 molal hydrogen peroxide in anhydrous ether was allowed to stand at room temperature for several days. To remove the excess hydrogen peroxide the mixture was then shaken several times with a saturated ammonium sulfate solution until the aqueous layer gave a negative test for hydrogen peroxide. The ether layer was then dried with anhydrous magnesium sulfate, filtered and the ether removed under reduced pressure. A highly viscous semi-solid product, 4.4 g., was obtained which became curdy on standing for several weeks at room temperature, but failed to crystallize even when cooled to −78°.

Anal. Calcd. for $C_8H_{16}O_3$: active (O), 10.00. Found: active (O), 9.65.

1,1′-Dihydroxydicycloöctyl Peroxide-1,1′.—This peroxide was prepared in the same manner as the monocycloöctyl except that the proportions of reagents used were different. A solution of 2.6 g. (0.0206 mole) of cycloöctanone in 22 cc. of 0.55 molal hydrogen peroxide in anhydrous ether was allowed to stand at room temperature for several days. It was then shaken several times with a saturated solution of ammonium sulfate until the latter showed no test for hydrogen peroxide. Finally, the ethereal solution was dried with anhydrous magnesium sulfate, filtered and the ether removed under reduced pressure. A yield of 2.2 g. of highly viscous product was obtained which failed to crystallize.

Anal. Calcd. for $C_{16}H_{30}O_4$: active (O), 5.59. Found: active (O), 5.53.

We are indebted to Dr. R. B. Woodward of Harvard University for supplying the C_7 and C_8 ketones.

Summary

Seventeen cyclane peroxides have been prepared by the interaction of hydrogen peroxide in anhydrous ether with a number of cyclic ketones.

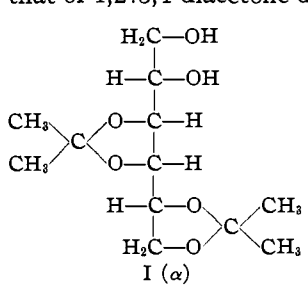
CAMBRIDGE, MASSACHUSETTS RECEIVED JUNE 22, 1939

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

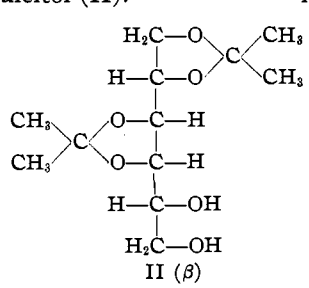
The Structures of the Diacetone Dulcitols[1]

BY RAYMOND M. HANN, W. DAYTON MACLAY AND C. S. HUDSON

Recently Pizzarello and Freudenberg[2] have proposed structures for the two diacetone dulcitols that were originally described by Fischer,[3] assigning to the α-diacetone dulcitol the structure of 3,4:5,6-diacetone dulcitol (I) and to the β-isomer that of 1,2:3,4-diacetone dulcitol (II).



I (α)



II (β)

Pizzarello and Freudenberg point out that the proposed structures are enantiomorphous and they emphasize that the ready separation of the α- and β-diacetone dulcitols by fractional crystallization is thus in conflict with general experience. It also may be added that the substances exhibit very different melting points, solubilities and crystalline forms (as shown by optical crystallographic measurements), all of which facts seem to exclude the idea of enantiomorphism. Neither of them is optically active. The basis of assignment of the enantiomorphous structures was (1) that lead tetraacetate oxidation in benzene solution of both diacetone dulcitols yielded formaldehyde, indicating the presence of contiguous hydroxyl groups, one of which must be primary, in the molecules and (2) that α-diacetone dulcitol could be transformed by alkaline permanganate oxidation to a derivative of D-galactonic acid (potassium diacetone D-galactonate) and (3) that β-diacetone dulcitol under similar oxidative procedure yielded the enantiomorphous derivative of L-galactonic acid (potassium diacetone L-galactonate). A review of the earlier researches of Fischer[3] and of Fischer and Bergmann[4] upon the diacetone dulcitols revealed that these substances undergo several interesting

(1) Publication authorized by the Surgeon General, U. S. Public Health Service.

(2) Pizzarello and Freudenberg, THIS JOURNAL, **61**, 611 (1939).

(3) Fischer, *Ber.*, **48**, 269 (1915).

(4) Fischer and Bergmann, *ibid.*, **49**, 289 (1916).

and unexplained reactions. We have therefore, with the agreement of Dr. Freudenberg, undertaken a further study of the reactions of the isomeric diacetone dulcitols.

The lack of correspondence in physical properties of the α- and β-diacetone dulcitols seems to exclude the possibility of their being enantiomorphous forms, as has been mentioned. Further evidence on this point has now been obtained through the preparation of several of their derivatives. As is apparent from the data recorded in Table I, the melting points of corresponding derivatives are greatly different and the same is true for their crystalline appearances and solubilities; the trityl derivatives have different compositions. None of them exhibits optical activity. It is thus apparent that these derivatives are in no case enantiomorphous forms. One is driven to the conclusion that *the α- and β-diacetone dulcitols are not enantiomorphous substances and hence must be structural isomers.*

TABLE I

MELTING POINTS OF DERIVATIVES OF THE α- AND β-DIACETONE DULCITOLS

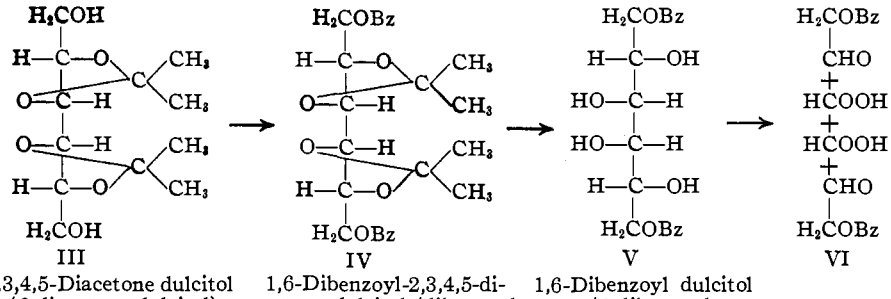
Derivative	From α-diacetone dulcitol	From β-diacetone dulcitol
Diacetate	89°	134°
Ditosylate	101°	165–166°
Trityl (Monotrityl monoacetyl)	107–108°	(Dityrityl) 233–234°
Dibenzoate	82–83°[a]	183–184°[b]

[a] This is the substance which Fischer and Bergmann (ref. 4) designated empirically β-dibenzoyl-diacetone dulcitol. The proof that it is a derivative of α-diacetone dulcitol is presented later in this article. We change its name to dibenzoyl α-diacetone dulcitol. [b] This is the substance which Fischer (ref. 3) designated empirically α-dibenzoyl-diacetone dulcitol. The proof that it is a derivative of β-diacetone dulcitol is presented later in this article. We change its name to dibenzoyl β-diacetone dulcitol.

Our initial investigation of the action of various oxidizing agents on the diacetone dulcitols indicated that hydrolysis occurred readily in the presence of very dilute mineral acids and slowly even when organic acids were present. Periodic acid of 0.4 normality rapidly removed the acetone groups and attacked the free hydroxyls thus formed. On the other hand, sodium periodate in aqueous solution or lead tetraacetate in glacial acetic acid solution was essentially without effect over a period of twenty-four hours at room temperature and thereafter caused a slow oxidation, which presumably was preceded by some hydrolysis of the acetone groups. Evidently the oxidation that was reported by Pizzarello and Freudenberg, which was partly conducted at steam-bath temperatures, involved some hydrolysis of the acetone groups. The failure of either sodium periodate or lead tetraacetate to oxidize the diacetone dulcitols indicates that *there is no glycol grouping present in either of them and therefore the two hydroxyl groups present in each of them are not attached to adjacent carbon atoms.*

It is evident that if the conclusions that have now been reached are correct, neither of the formulas I and II can apply to the structures of either of the diacetone dulcitols.

The Structure of β-Diacetone Dulcitol.—The ditosyl derivatives of the diacetone dulcitols were of particular interest since it seemed possible that upon iodination by treatment with sodium iodide and acetone under pressure, iodo compounds of importance for structural determination might be obtained. This expectation was fulfilled when it was discovered that the ditosyl derivative of β-diacetone dulcitol gave a diiodo β-diacetone dulcitol in high yield, allowing the inference that the two tosyl groups were attached to two primary hydroxyl groups and that β-diacetone dulcitol therefore possesses two free primary hydroxyl groups. Support for this inference was obtained when it was found that β-diacetone dulcitol readily formed a ditrityl derivative upon treatment with pyridine and triphenylmethyl chloride. Both results are in agreement with the previously mentioned observation that sodium periodate or lead tetraacetate does not oxidize β-diacetone dulcitol. The evidence from these three sources thus makes it highly probable that β-diacetone dulcitol has free hydroxyl groups on carbons one and six. Conclusive proof of this structure was obtained through the following reactions. The β-diacetone dulcitol (III) was converted to dibenzoyl β-diacetone dulcitol (IV) which in turn was transformed to β-dibenzoyl dulcitol (V) by removal of the acetone groups through acid hydrolysis. A 1,6-dibenzoyl dulcitol, upon oxidation by lead tetraacetate, should consume three moles of oxidant and produce two moles of benzoyl glycolic aldehyde (VI) and two moles of formic acid. The oxidation of the dibenzoate prepared from β-diacetone dulcitol with 3.6 moles of lead tetraacetate in glacial acetic acid solution at room temperature for three and one-half hours consumed 3.15 moles of oxidant per mole of diacyl dulcitol.



III 2,3,4,5-Diacetone dulcitol (β-diacetone dulcitol)

IV 1,6-Dibenzoyl-2,3,4,5-diacetone dulcitol (dibenzoyl β-diacetone dulcitol)

V 1,6-Dibenzoyl dulcitol (β-dibenzoyl dulcitol)

VI

From the reaction mixture benzoyl glycolic aldehyde was isolated as its crystalline semicarbazone in a yield of 79%. The fact that this yield is far above 50% proves that both carbons one and six carry benzoyl groups. In a separate experiment the benzoyl glycolic aldehyde was further identified by its oxidation with bromine water to benzoyl glycolic acid, the melting point of which agreed with that reported by Brigl and Grüner,[5] who prepared the substance from 1,6-dibenzoyl mannitol by alkaline permanganate oxidation. The β-dibenzoyl dulcitol is so slightly soluble in water that the oxidation by aqueous sodium periodate could not be studied, but it was possible to obtain analytical data on the periodate oxidation of the similarly prepared β-diacetyl dulcitol, which is moderately soluble in water. If the substance is 1,6-diacetyl dulcitol, 1 mole of it should consume 3 moles of periodate and generate 2 moles of formic acid; it was found to consume 3 moles of oxidant and the increase in acidity corresponded to the production of 2.05 moles of formic acid. The analytical data are thus in agreement with the formulation that *the β-diacyl dulcitols are 1,6-diacyl dulcitols, and the β-diacetone dulcitol is 2,3,4,-5-diacetone dulcitol.* The attachment of the two acetone groups is limited to three structures, namely, 2,3:4,5, 2,4:3,5 and 2,5:3,4; decision among them must be deferred at this time. Formulas (III) and (IV) indicate provisionally a 2,3:4,5 arrangement of the acetone groups. In any case, the substances of the β-diacetone dulcitol series that are now known possess meso structures, which accounts for their lack of optical activity.

The Structure of α-Diacetone Dulcitol.—It has been mentioned that β-diacetone dulcitol yields a ditosyl derivative which is convertible to a diiodo derivative through the action of sodium iodide in acetone solution. Under similar experimental conditions α-diacetone dulcitol yields a ditosyl derivative, but iodination of this substance yields a mono-iodo monotosyl α-diacetone dulcitol in nearly quantitative yield. The two diacetone dulcitols also show a dissimilar behavior on treatment with triphenylmethyl chloride. As has been stated, the β-isomer forms a dityrityl derivative, but from similar tritylation reactions involving α-diacetone dulcitol no evidence of ditritylation has been observed, and the isolation of a monotrityl monoacetyl α-diacetone dulcitol in 95% yield indicated that none occurred. These results are good evidence that *α-diacetone dulcitol contains only one free primary hydroxyl group*, and are also inclusive independent proofs of the previous decision that the α- and β-diacetone dulcitols are structural isomers rather than enantiomorphous substances. There remains, then, the problem of determining the position of the secondary hydroxyl group in α-diacetone dulcitol.

Reference to Table II, column 2, shows that the maximum number of diacetone dulcitols which have either one or two free primary hydroxyl groups is fifteen. Three of these structures (nos. 1, 4 and 7) are *meso* forms, one of which must represent β-diacetone dulcitol, as has been proved. The remaining twelve structures are those of potentially optically-active substances for which there must be twelve enantiomorphous forms, not shown in the table. Thus the precise enumeration is three *meso* forms and twelve pairs of enantiomorphs. We digress from the argument at this point in order to explain the convention which we shall use in naming these enantiomorphs. The customary use of the word dulcitol with numbered carbon atoms indicating the places of attachment of substituent groups is unobjectionable in the case of *meso* structures for the reason that the name is the same whether the numbering of the dulcitol chain starts at one end or the other.

(5) Brigl and Grüner, *Ber.*, **65**, 643 (1932).

TABLE II

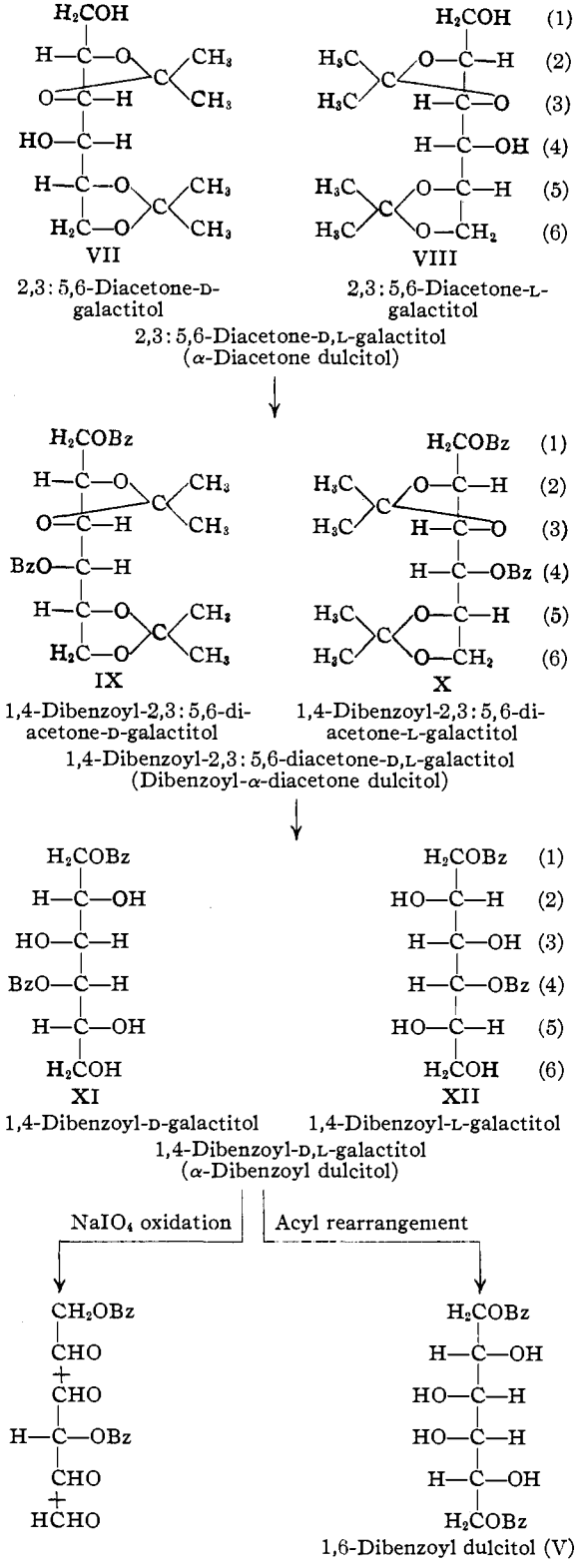
POSSIBLE ARRANGEMENTS OF TWO ISOPROPYLIDENE RESIDUES IN A DIACETONE DULCITOL CONTAINING ONE OR TWO FREE PRIMARY HYDROXYL GROUPS

No.	Acetone attachment	Excluded because of	Corresponding dibenzoyl dulcitol
1	2,3:4,5	Two primary OH's	
2	2,3:4,6	.....	1,5
3	2,3:5,6	.....	1,4
4	2,4:3,5	Two primary OH's	
5	2,4:3,6	.....	1,5
6	2,4:5,6	.....	1,3
7	2,5:3,4	Two primary OH's	
8	2,5:3,6	.....	1,4
9	2,5:4,6	.....	1,3
10	2,6:3,4	.....	1,5
11	2,6:3,5	.....	1,4
12	2,6:4,5	.....	1,3
13	3,4:5,6	Contiguous OH's	
14	3,5:4,6	Contiguous OH's	
15	3,6:4.5	Contiguous OH's	

But such is not the case with respect to the non-*meso* (optically active) structures; the numbering for them is formally different for the two ways of numbering dulcitol. This is illustrated by formulas I and II, with the numbering for their names as given by Pizzarello and Freudenberg; while it is clear after an inspection of the formulas that 3,4:5,6- and 1,2:3,4-diacetone dulcitols are enantiomorphous forms, the fact is not immediately apparent from their names alone because they do not have one and the same name to which the D- and L-symbols, which are customary for enantiomorphs, can be prefixed. We suggest for such cases the convention that the numbering be chosen to conform with that of the appropriate D- or L-galactose, since the numbering of the sugars is precise, and that the use of the convention be indicated by employing the name galactitol in place of dulcitol; thus structures I and II would receive the names, respectively, 3,4:5,6-diacetone D-galactitol and 3,4:5,6-diacetone L-galactitol, or 1,2:3,4-diacetone L-galactitol and 1,2:3,4-diacetone D-galactitol. Formulas VII–XII further illustrate this convention of nomenclature, especially its use for the naming of racemic forms. Returning now to the consideration of Table II, the three *meso* forms (nos. 1, 4 and 7) cannot represent α-diacetone dulcitol because the latter has been shown to possess only one primary hydroxyl group. Nos. 13, 14 and 15 also can be excluded because of the presence in them of contiguous hydroxyl groups. One of the remaining nine structures therefore must apply to α-diacetone dulcitol and, since this substance is optically inactive, as are also its derivatives (Table I), it must be a racemate. Upon dibenzoylation of the nine structures, as racemates, nine different dibenzoyl diacetone D,L-galactitols would result, but upon removing the acetone groups from them only three (1,3, 1,4 and 1,5) dibenzoyl D,L-galactitols can be formed; the problem of assigning the position of the free secondary hydroxyl group in α-diacetone dulcitol thus reduces to that of the establishment of the structure of the α-dibenzoyl dulcitol that results when the isopropylidene residues are removed from dibenzoyl-α-diacetone dulcitol. Fortunately it has proved possible to decide this question through a study of the periodate oxidation of the α-dibenzoyl dulcitol. A 1,5-dibenzoyl dulcitol should consume 2 moles of oxidant and yield 1 mole each of formic acid, 2-benzoylglyceric aldehyde, benzoylglycolic aldehyde and water; 1,4-dibenzoyl dulcitol should consume 2 moles of oxidant and produce 1 mole each of formaldehyde, benzoylglycolic aldehyde and benzoyltartronic dialdehyde, and 2 moles of water, *but no formic acid;* and finally 1,3-dibenzoyldulcitol should require 2 moles of oxidant and form 1 mole each of formic acid, formaldehyde, water and 2,4-dibenzoylthreose. It was found that the oxidation of α-dibenzoyldulcitol with sodium periodate in aqueous alcoholic solution consumed 2 moles of oxidant, but that no acid was produced;[6] it is therefore concluded that *α-dibenzoyl dulcitol is 1,4-dibenzoyl* D,L-*galactitol and α-diacetone dulcitol is accordingly 2,3,5,6-diacetone* D,L-*galactitol.* The question of the arrangement of the acetone groups awaits further study. The observed optical inactivity of the various dulcitol derivatives of the α- and β-series is to be ascribed, according to the structure here shown, to the presence of meso forms in the β-series and of racemic forms in the α-series, as previously mentioned. The reactions through which the structure of α-diacetone dulcitol has been disclosed are illustrated in the structural formulas (VII)–(XII), in which the attachment of the acetone residues at positions 2, 3, 5 and 6 is provisionally assumed to be at 2,3 and 5,6.

Rearrangements in the Dulcitol Series.— Upon melting α-dibenzoyl dulcitol in a capillary tube the substance liquefies completely at 170–

(6) As is described in the experimental part, there was found an apparent titratable acidity corresponding to 0.15 mole of formic acid but it is believed that this acidity is negligibly small and that it probably is due to enolization of benzoyl tartronic dialdehyde.



171° and if maintained at this temperature it rapidly resolidifies and then remelts at 202–203°. The closeness of the latter melting point to that of β-dibenzoyl dulcitol, namely, 209°, suggested that an acyl migration had occurred, the enantiomorphous structures (XI) and (XII) rearranging to the *meso* form (V). This hypothesis was verified by melting a larger amount of α-dibenzoyl dulcitol and crystallizing the melt from acetic acid, whereby pure β-dibenzoyl dulcitol was obtained in nearly quantitative yield. Several such migrations of an acyl group have been observed by others and the postulate has been advanced that they occur through the intermediate formation of dioxolone or meta-dioxane ring compounds.[7] The acyl migration in this case seems to be analogous to that of the benzoyl group in 3-benzoyl monoacetone glucose, which readily migrates to form 6-benzoyl monoacetone glucose.[8] The labile nature of the benzoyl group on carbon four in α-dibenzoyl dulcitol thus furnishes an explanation of the observation by Fischer and Bergmann[4] that β-dibenzoyl dulcitol can be obtained by boiling an aqueous solution of α-dibenzoyl dulcitol; this unusual change is now seen to be due to an acyl migration of the benzoyl group from carbon 4 to carbon 6.

We have confirmed the observation of Fischer[3] that α-diacetone dulcitol upon benzoylation with benzoyl chloride and quinoline at 100° yields a dibenzoate melting at 183–184°, which we designate dibenzoyl β-diacetone dulcitol (Formula IV, see also Table I, footnote b) because its debenzoylation yields β-diacetone dulcitol quantitatively. It is evident from the structures which have been developed for the diacetone dulcitols that *an acetone shift has occurred, the enantiomorphous structures (VII) and (VIII) passing on benzoylation to the meso structure (IV)*. This shift is discussed further in the experimental section ("Rearrangements") where it is shown that the rearrangement is catalyzed by such substances as quinoline hydrochloride and (in less degree) pyridine hydrochloride. Hibbert and his co-workers[9] have shown that the 1,1′ and the 1,2 methylidene, benzylidene, and *p*-nitrobenzylidene cyclic acetals of glycerol are interconvertible in the presence of a trace of hydrochloric acid; the catalysis of the isopropylidene shift in the dulcitol derivatives by quinoline and pyridine hydrochlorides appears to be an analogous reaction.

(7) Fischer, *Ber.*, **53**, 1621 (1920); Hibbert and Carter, THIS JOURNAL, **51**, 1601 (1929).

(8) Ohle, *Ber.*, **57**, 406 (1924).

(9) Hill, Whelan and Hibbert, THIS JOURNAL, **50**, 2235 (1928); Hibbert and Carter, *ibid.*, **50**, 3120, 3376 (1928).

We are indebted to Mr. George L. Keenan of the Food and Drug Administration, U. S. Department of Agriculture, for the determination of optical properties of certain compounds, to Dr. W. T. Haskins for micro-analyses performed in connection with this work, and to the Atlas Powder Company for furnishing a supply of dulcitol.

Experimental

In the preparation of the diacetone dulcitols from dulcitol with acetone and dry hydrochloric acid gas, small variations of conditions markedly affect the yields; indeed Fischer and Bergmann have reported that they obtained at times the β-isomer under conditions which previously had yielded the α-derivative without being able to assign a cause for the difference in result. It seems from present knowledge that these variations may be due to cyclic acetal rearrangement of the sensitive α-diacetone dulcitol. We find that a separable mixture of the two diacetone dulcitols may be obtained readily with good regularity under the following conditions. A suspension of 50 g. of finely powdered dulcitol in 975 cc. of dry acetone containing 24.2 g. of dry hydrochloric acid gas was agitated vigorously for twenty-four hours at 20°; the dulcitol dissolved and pure α-diacetone dulcitol (m. p. 144–145°) crystallized in a yield of 24.3 g. (34%). The mother liquor was stirred with 150 g. of basic lead carbonate for one hour, the lead chloride and carbonate were removed by filtration, and the filtrate was concentrated to 275 cc. in the presence of some basic lead carbonate. Following filtration, the solution was seeded with α-diacetone dulcitol and allowed to stand overnight at 5°; a further crop of 10.5 g. of crude α-diacetone dulcitol (m. p. 138–140°) was obtained (yield of α, 48%). The mother liquor was concentrated to a volume of 90 cc., further crystallization occurring during the process; the magma was refrigerated for twenty-four hours and 31.1 g. of impure β-diacetone dulcitol (m. p. 104–108°) was removed by filtration. A further small amount of the same substance (1.4 g., m. p. 102–104°) was recovered from the final mother liquor upon treatment with petroleum ether (yield of β, 45%).

The α-diacetone dulcitol may be recrystallized from 5 parts of 95% alcohol in yields of 90%, separating in well-formed brilliant prisms. The substance melts at 144–145° (corr.) and is optically inactive in alcohol. acetone or chloroform solution. Optical-crystallographic data on this compound were kindly obtained by Mr. George L. Keenan. The refractive indices (determined by the immersion method in organic liquids) are $n_\alpha = 1.503$, $n_\beta = 1.507$, $n_\gamma = 1.538$, $n_\gamma - n_\alpha = 0.035$, all ± 0.003. In parallel polarized light (crossed nicols), the birefringence is strong, the polarization colors are brilliant, many fragments extinguishing sharply and others remaining bright under the same conditions. In convergent polarized light (crossed nicols), partial biaxial figures are frequently seen, one optic axis being perpendicular to many of the fragments.

The crude β-diacetone dulcitol may be purified by solution in 5 parts of acetone and addition of 10 parts of petroleum ether; it separates in groups of elongated prisms. The substance melts at 111° (corr.) and is optically inactive in alcohol, acetone or chloroform solution. The microscopical examination of the compound was made by Mr. Keenan. Its refractive indices are $n_\alpha = 1.478$, $n_\beta = 1.510$, $n_\gamma = 1.518$, $n_\gamma - n_\alpha = 0.040$, all ± 0.003. In parallel polarized light (crossed nicols), the birefringence is strong, some of the fragments extinguish sharply and others remain bright, the polarization colors being of the first order. In convergent polarized light (crossed nicols) biaxial figures showing the acute bisectrix are common, the optic sign being negative, and $2E = 30°$ (approximately). The optical-crystallographic properties are entirely unlike those of the α-diacetone dulcitol, a fact which precludes the possibility that the substances are enantiomorphous forms.

Periodic Acid Oxidation of α-Diacetone Dulcitol.—Pizzarello and Freudenberg identified formaldehyde qualitatively (as its dinitrophenylhydrazone) as an oxidation product from the action of lead tetraacetate on α-diacetone dulcitol in benzene solution. We have verified this qualitative observation but we doubt its interpretation in terms of structure because of the fact that the oxidation was partly conducted at elevated temperature and there is the possibility that α-diacetone dulcitol may have been hydrolyzed. It was found that at 20° lead tetraacetate in glacial acetic acid solution, or sodium periodate in aqueous solution, oxidized α-diacetone dulcitol to only a slight and negligible extent in twenty hours, but that aqueous periodic acid oxidizes it rapidly at 20°. To a solution of 0.4078 g. of α-diacetone dulcitol in 27 cc. of water, 19.97 cc. of 0.623 *M* periodic acid (8 moles) was added and the volume of the solution adjusted to 50 cc. Analysis of 5-cc. subsamples at fifteen and thirty minutes, one, four and twenty-two hours, indicated that 1.83, 2.77, 3.68, 5.01 and 5.17 moles of oxidant had been consumed at 20°. The results indicate that the acetone groups were hydrolyzed and the dulcitol which was thus liberated was completely oxidized. Such a series of reactions should consume 5.00 moles of periodic acid.

Sodium Periodate Oxidation of α-Diacetone Dulcitol.—To a solution of 0.2838 g. of α-diacetone dulcitol in 30 cc. of water, 12.38 cc. of 0.306 *M* sodium periodate solution (3.5 moles) was added and the volume adjusted to 50 cc. Analysis of 5-cc. subsamples at the expiration of fifteen, thirty and one hundred and forty-five minutes indicated that no oxidation had occurred at 20° and a similar analysis at twenty hours showed that only 0.35 mole of oxidant had been consumed. Evidently the acidity of sodium periodate is so low that hydrolysis is greatly retarded; and the oxidant appears to be without action on unhydrolyzed α-diacetone dulcitol.

Lead Tetraacetate Oxidation of α-Diacetone Dulcitol.—To a solution of 0.1347 g. of α-diacetone dulcitol in 73 cc. of glacial acetic acid, 25 cc. of 0.1282 *N* lead tetraacetate glacial acetic acid solution (3.2 moles) was added and the volume adjusted to 100 cc. with glacial acetic acid. Analysis of 10-cc. subsamples at fifteen, thirty and one hundred and twenty minutes showed that no oxidation had occurred at 20°, and similar analyses at nineteen and forty-five hours indicated that only 0.08 and 0.23 mole of oxidant had been consumed. Lead tetraacetate thus also appears to be without action on unhydrolyzed α-diacetone dulcitol.

Periodic Acid Oxidation of β-Diacetone Dulcitol.—To a solution of 0.3982 g. of β-diacetone dulcitol in 25 cc. of water, 19.44 cc. of 0.625 *M* periodic acid (8 moles) was added and the solution diluted to 50 cc. with water. At the expiration of one hour at 20°, 0.94 mole of oxidant had been utilized and in fifty hours 5.3 moles had been consumed, indicating the conversion of the diacetone dulcitol to free dulcitol and the complete oxidation of the latter compound.

Sodium Periodate Oxidation of β-Diacetone Dulcitol.—To a solution of 0.2692 g. of β-diacetone dulcitol in 25 cc. of water, 11.59 cc. of 0.31 *M* sodium periodate solution (3.5 moles) was added and the solution diluted to 50 cc. with water. Subsamples of 5 cc. were analyzed after the expiration of fifteen and thirty minutes, one and six hours, and at the end of four days, but no sodium periodate was consumed during this period at 20°. Evidently the β-isomer is considerably more resistant than the α-form to hydrolysis.

Lead Tetraacetate Oxidation of β-Diacetone Dulcitol.—To a solution of 0.1067 g. of β-diacetone dulcitol in 73 cc. of glacial acetic acid, 25 cc. of 0.1282 *N* lead tetraacetate acetic acid solution (3.2 moles) was added and the solution diluted to 100 cc. with the same solvent. Subsamples of 10 cc., which were analyzed at the expiration of fifteen, thirty and one hundred and thirty-five minutes, showed no consumption of oxidant at 20°; after twenty hours 0.03 mole of lead tetraacetate had been consumed and after eight days only 0.8 mole.

Summarizing, these oxidation experiments indicate that the diacetone dulcitols are stable toward two oxidizing agents that are known to attack specifically a glycol grouping, provided that the reagent itself is not acidic enough to cause hydrolysis of the isopropylidene residues.

Derivatives of β-Diacetone Dulcitol (2,3,4,5-Diacetone Dulcitol)

Diacetyl-β-diacetone Dulcitol (1,6-Diacetyl-2,3,4,5-diacetone Dulcitol).—To a solution of 1 g. of β-diacetone dulcitol in 5 cc. of pyridine 5 cc. of acetic anhydride was added. A slight warming occurred and within five minutes the formation of a crystalline deposit, which increased rapidly in amount on standing, was noted. After twenty-four hours the solid was removed by filtration, washed with alcohol, and dried; yield 1.3 g. (quantitative). The compound may be recrystallized from 10 parts of alcohol, separating in prisms which melt at 134° (corr.) and show no rotation in chloroform (*c*, 1.28).

Anal. Calcd. for $C_{16}H_{26}O_8$: C, 55.48; H, 7.57. Found: C, 55.62; H, 7.45.

The relative insolubility of diacetyl β-diacetone dulcitol in the acetylating mixture offers an easy procedure for the separation of a mixture of α- and β-diacetone dulcitols.

In a typical experiment, 10 g. of a mixture of m. p. 104–108° was acetylated in 50 cc. of pyridine and 50 cc. of acetic anhydride. Within two hours the β-diacetate began to crystallize and on standing overnight in the refrigerator 8.9 g. of the substance had separated. The diacetyl α-diacetone dulcitol was obtained in a yield of 3.4 g. by pouring the mother liquors into ice and water. The total recovery of acetate was 93%. The respective diacetone dulcitols were obtainable in quantitative yield upon deacetylation with either sodium or barium methylate.

Ditosyl-β-diacetone Dulcitol (1,6-Ditosyl-2,3,4,5-diacetone Dulcitol).—To a solution of 8.3 g. of *p*-toluenesulfonyl chloride (2.2 mols) in 23.6 cc. of pyridine (15 mols) cooled in an ice-bath, 5.1 g. of finely powdered β-diacetone dulcitol was added. Solution occurred readily and was followed by a separation of characteristic crystals of pyridine hydrochloride. The reaction mixture was then held at 40° for seventy-two hours. The solid mass was broken up with addition of 100 cc. of water and the precipitate removed by filtration and washed well with water; yield 10.5 g. (96%). The compound was recrystallized from 7.5 parts of glacial acetic acid, being obtained in small oblique plates which melted at 165–166° (corr.) and showed no rotation in chloroform (*c*, 1.36).

Anal. Calcd. for $C_{26}H_{34}O_{10}S_2$: C, 54.72; H, 6.00. Found: C, 54.75; H, 6.21.

Dityrityl-β-diacetone Dulcitol (1,6-Dityrityl-2,3,4,5-diacetone Dulcitol).—To a solution of 4.7 g. (2.2 mols) of triphenylmethyl chloride in 25 cc. of pyridine, 2.0 g. of finely powdered β-diacetone dulcitol was added. The solution was allowed to stand at room temperature for seventy-two hours and then crystallization of the dityrityl derivative was induced by gradual addition of 100 cc. of water. The precipitate weighed 6.3 g. (theory 5.7 g.) and was contaminated by triphenylcarbinol. The pure dityrityl compound was obtained, after several recrystallizations from 200 parts of acetone, in the form of small elongated glistening prisms which decomposed at 233–234° (corr.) and showed no rotation in chloroform (*c*, 0.39).

Anal. Calcd. for $C_{50}H_{50}O_6$: C, 80.40; H, 6.75. Found: C, 80.39; H, 6.76.

Diiodo-β-diacetone Dulcitol (1,6-Di-iodo-2,3,4,5-diacetone Dulcitol).—A solution of 5.0 g. of ditosyl-β-diacetone dulcitol and 3.9 g. (3 moles) of sodium iodide in 125 cc. of acetone was heated for two hours at 100° in a pressure bottle. The separated sodium salt of *p*-toluenesulfonic acid (2.5 g.; theory for 2 moles, 3.1 g.) was removed by filtration and the acetone mother liquors were concentrated to dryness by an air current. The dry residue was treated with 25 cc. of water and the insoluble portion filtered off and dried: yield, 4.4 g.; m. p., 102–103° (theory, 4.2 g.). By an initial recrystallization from acetone and a second from alcohol the compound was obtained in fine needles which melted at 108–109° (corr.) and showed no optical activity in chloroform solution (*c*, 1.36).

Anal. Calcd. for $C_{12}H_{20}O_4I_2$: C, 29.89; H, 4.18. Found: C, 29.88; H, 4.22.

β-Dibenzoyl Dulcitol (1,6-Dibenzoyl Dulcitol).—Four grams of dibenzoyl-β-diacetone dulcitol, which was prepared from β-diacetone dulcitol, benzoyl chloride and quinoline by the directions of Fischer and Bergmann[4] (see also the later section on "Rearrangements"), was refluxed for half an hour in 100 cc. of 80% acetic acid. On cooling, 2.6 g. of the desired deacetonated product crystallized and a further 0.4 g. was obtained from the reaction mixture upon concentration; yield, 3.0 g. (91%). Upon recrystallization from 25 parts of

glacial acetic acid it separated in shining platelets which melted at 209° (corr.) and showed no optical activity in acetic acid solution. Fischer reported a melting point of 210° and designated the compound α-dibenzoyl dulcitol, because it was the first dibenzoyl dulcitol isolated. It seems advisable, however, to name it a member of the β-series, particularly since we later describe a dibenzoyl dulcitol of the α-series.

Tetraacetyl-β-dibenzoyl Dulcitol (1,6-Dibenzoyl-2,3,4,5-tetraacetyl Dulcitol).—The solution of 2.0 g. of β-dibenzoyl dulcitol in 10 cc. of pyridine and 10 cc. of acetic anhydride was completed by refluxing the mixture for fifteen minutes. The desired acetate separated in a yield of 2.9 g. (quantitative) upon addition of water. The substance may be recrystallized from 10 parts of glacial acetic acid, and separates in diamond-shaped plates which melt at 225–226° (corr.) and show no rotation in chloroform solution (*c*, 1.40).

Anal. Calcd. for $C_{28}H_{30}O_{12}$: C, 60.21; H, 5.41. Found: C, 60.09; H, 5.44.

β-Diacetyl Dulcitol (1,6-Diacetyl Dulcitol).—A suspension of 5 g. of diacetyl β-diacetone dulcitol in 100 cc. of water and 10 cc. of acetic acid was refluxed for one hour, during which time solution gradually occurred. The solution was concentrated *in vacuo* to dryness and the dry residue transferred to a filter funnel with 35 cc. of warm absolute alcohol. The yield of 1.8 g. (m. p. 155–156°) was increased by 0.5 g. (m. p. 154–155°) by further recovery from the mother liquors (60%). The crude material, which apparently contained some dulcitol, was recrystallized from 10 parts of water; it separated in pure condition in large flat plates, melting at 167–168° (corr.) and showing no rotation in chloroform solution (*c*, 0.28).

Anal. Calcd. for $C_{10}H_{18}O_8$: C, 45.11; H, 6.81. Found: C, 45.06; H, 6.95.

Lead Tetraacetate Oxidation of β-Diacetyl Dulcitol.—A sample of 0.1120 g. of β-diacetyl dulcitol was dissolved in 70 cc. of glacial acetic acid, 25 cc. of 0.1267 *N* lead tetraacetate (8 moles) solution in acetic acid was added and the total volume adjusted to 100 cc. Subsamples of 10 cc. were analyzed at the expiration of fifteen and thirty minutes, one, two, eighteen and sixty-seven hours when 2.01, 2.64, 2.82, 2.89, 2.99 and 3.18 moles of lead tetraacetate were found to have been consumed. The expected consumption for 1,6-diacetyl dulcitol would be 3.00 moles.

Sodium Periodate Oxidation of β-Diacetyl Dulcitol.—This experiment was performed to obtain quantitative analytical data on the production of formic acid in the oxidation reaction. A sample of 0.4496 g. of the diacetyl compound was dissolved in 80 cc. of water, 16.51 cc. of 0.307 *M* sodium periodate (3 mols) solution added, and the volume adjusted to 100 cc. After forty-five minutes a 5-cc. subsample was titrated with 0.1 *N* sodium hydroxide, using methyl red as indicator, and found to require 1.72 cc., equivalent to 2.05 mols of formic acid. The expected production from 1,6-diacetyl dulcitol would be 2.00 mols.

Lead Tetraacetate Oxidation of β-Dibenzoyl Dulcitol.—(1) An amount of 0.1017 g. of β-dibenzoyl dulcitol was dissolved in 170 cc. of glacial acetic acid, 24.5 cc. of 0.1275 *N* lead tetraacetate (6 mols) solution in glacial acetic acid added, and the volume adjusted to 200 cc. Subsamples of 20 cc. were analyzed at the end of fifteen and thirty minutes, one, two, four, six and twenty-three hours, and 1.50, 2.21, 2.75, 2.94, 2.98, 3.01 and 3.19 mols of oxidant shown to be utilized progressively. After a further ninety-six hours, 4.32 mols had been consumed and a final analysis at the end of ten days showed 4.90 mols of oxidant had been consumed. The latter figure compares favorably with that expected, namely, 5.00 mols, if the benzoyl groups had been hydrolyzed completely.

(2) A suspension of 0.8062 g. of β-dibenzoyl dulcitol in 127.5 cc. of 0.1167 *N* lead tetraacetate (3.6 mols) acetic acid solution was agitated for three and one-half hours at room temperature whereby solution was completed. Analysis showed that 3.15 mols of oxidant had been consumed. To a subsample of 50 cc. of the oxidized solution, equivalent to 0.266 g. of benzoyl glycolic aldehyde, 0.8 g. of semicarbazide hydrochloride and 2 g. of sodium acetate were added, and on slight warming crystallization of the semicarbazone of benzoyl glycolic aldehyde occurred. After refrigerating overnight the precipitate was separated by filtration and obtained in a yield of 0.284 g. (79%). The fine needles which were thus produced melted at 193–194°, in close agreement with Aoyama's[10] value of 194–195° for benzoyl glycolic aldehyde semicarbazone, and showed the correct analysis.

Anal. Calcd. for $C_{10}H_{11}O_3N_3$: C, 54.29; H, 5.01. Found: C, 54.15; H, 5.04.

(3) To a suspension of 3.01 g. of β-dibenzoyl dulcitol in 50 cc. of glacial acetic acid, 11.3 g. of crystalline lead tetraacetate (3.3 mols) was added and the reaction mixture agitated for five hours, at which time analysis indicated that all the oxidant had been consumed. A small amount (0.2 g.) of unchanged dibenzoyl compound was removed and the residual solution, containing 2.24 g. of benzoyl glycolic aldehyde, was diluted with water and neutralized with sodium carbonate. It was then extracted successively with four 100-cc. portions of ether and the ether extract concentrated to a sirup. The sirup was dissolved in 100 cc. of water and 10 g. of strontium carbonate and 1.8 cc. of bromine added. After the solution had stood for twenty hours the excess bromine was removed by aeration and the strontium carbonate by filtration, and the solution acidified by addition of 10 cc. of *N* sulfuric acid. The benzoyl glycolic acid was extracted by treatment with four 100-cc. portions of ether, and the ether extract concentrated to dryness, crystallization occurring during the process. The dry residue was redissolved in 15 cc. of ether, the solution clarified, and 15 cc. of petroleum ether added. Upon slow evaporation at room temperature 0.84 g. (34%) of benzoyl glycolic acid was obtained in the form of large rhombs which showed a melting point of 110–111° (corr.). Brigl and Grüner[5] report a melting point of 112° for benzoyl glycolic acid isolated from 1,6-dibenzoyl mannitol.

Anal. Calcd. for $C_9H_8O_4$: C, 60.00; H, 4.48. Found: C, 60.20; H, 4.69.

(10) Aoyama, *J. Pharm. Soc. Japan*, **27**, 539 (1927).

Derivatives of α-Diacetone Dulcitol (2,3,5,6-Diacetone-D,L-galactitol)

Diacetyl-α-diacetone Dulcitol (1,4-Diacetyl-2,3,5,6-diacetone-D,L-galactitol).—A solution of 1 g. of α-diacetone dulcitol in a mixture of 5 cc. of pyridine and 5 cc. of acetic anhydride was allowed to stand overnight at room temperature, no crystallization taking place (contrast the behavior of the β-isomer). The reaction mixture was poured into 50 cc. of water, whereupon crystallization readily occurred, the desired diacetate being obtained in a yield of 1.3 g. (quantitative). It was recrystallized from 10 parts of 50% alcohol and obtained in colorless needles which melted at 89° (corr.) and showed no rotation in chloroform solution (*c*, 1.40).

Anal. Calcd. for $C_{16}H_{26}O_8$: C, 55.48; H, 7.57. Found: C, 55.53; H, 7.54.

Ditosyl-α-diacetone Dulcitol (1,4-Ditosyl-2,3,5,6-diacetone-D,L-galactitol).—The tosylation of α-diacetone dulcitol was carried out as described for that of β-diacetone dulcitol, a yield of 9.3 g. (85%) of the ditosyl derivative being obtained. It crystallized from its solution in 5 parts of alcohol in clusters of minute needles which melted at 101° (corr.) and were optically inactive in chloroform solution (*c*, 1.32).

Anal. Calcd. for $C_{26}H_{34}O_{10}S_2$: C, 54.72; H, 6.00. Found: C, 54.89; H, 5.94.

Monotrityl-monoacetyl-α-diacetone Dulcitol (1-Trityl-4-acetyl-2,3,5,6-diacetone-D,L-galactitol).—To a solution of 2.3 g. (1.1 mole) of triphenylmethyl chloride in 25 cc. of pyridine, 2 g. of finely powdered α-diacetone dulcitol was added and the resulting reaction mixture allowed to stand at room temperature for seventy-two hours. It was then cooled in a freezing mixture, 25 cc. of acetic anhydride added, and again allowed to stand for twenty-four hours at room temperature. Upon addition of water, the monoacetate precipitated in a yield of 4.0 g. (95%). The substance was recrystallized several times from 5 parts of alcohol to remove traces of triphenylcarbinol acetate, and was finally obtained in prisms melting at 107–108° (corr.). It is optically inactive in chloroform solution.

Anal. Calcd. for $C_{33}H_{38}O_7$: C, 72.50; H, 7.01. Found: C, 72.33; H, 6.95.

Mono-iodo-monotosyl-α-diacetone Dulcitol (1-Iodo-4-tosyl-2,3,5,6-diacetone-D,L-galactitol).—A solution of 2.9 g. of ditosyl-α-diacetone dulcitol and 2.3 g. of sodium iodide (3 mols) in 75 cc. of acetone was heated for one and one-half hours at 100° in a pressure bottle. The separated sodium *p*-toluenesulfonate (1.0 g., theory for 1 mol, 0.9 g.) was removed by filtration, the filtrate concentrated to dryness by an air current, and the dry residue treated with 50 cc. of water to remove the excess of sodium iodide. The insoluble crude reaction product weighed 2.6 g. (96%) and was recrystallized from 10 parts of methyl alcohol from which it separated in thick quadratic prisms. The pure compound melted at 120–121° and was optically inactive in chloroform solution (*c*, 1.04).

Anal. Calcd. for $C_{19}H_{27}O_7SI$: C, 43.35; H, 5.17. Found: C, 43.52; H, 5.12.

α-Dibenzoyl Dulcitol (1,4-Dibenzoyl-D,L-galactitol).—A solution of 8 g. of dibenzoyl-α-diacetone dulcitol, the preparation of which from α-diacetone dulcitol, benzoyl chloride and pyridine has been described by Fischer and Bergmann[4] (see also the later section on "Rearrangements"), in 100 cc. of 80% acetic acid was refluxed for thirty minutes and allowed to cool; there crystallized 0.6 g. of β-dibenzoyl dulcitol (m. p. 206–207°). The mother liquors were diluted with 500 cc. of water and allowed to stand overnight in the refrigerator, whereupon 2.4 g. of crude α-dibenzoyl dulcitol (m. p. 165–166°) crystallized, and a further yield of 2.4 g. of the same compound was obtained upon concentrating the solution to dryness and crystallizing the residue from 30 cc. of 50% alcohol (yield of the β-isomer, 9.1%; of the α-isomer, 72.7%). The production of some of the β-isomer in this reaction apparently is due to an acyl migration. The crude α-isomer is purified readily by recrystallization from 15 parts of alcohol, separating in clusters of fine needles which show no rotation in chloroform solution (*c*, 1.10). Upon heating in a capillary tube, it melts at 170–171° (corr.), resolidifies, and then remelts at 202–203° (corr.) (see also the later section on "Rearrangements").

Anal. Calcd. for $C_{20}H_{22}O_8$: C, 61.53; H, 5.68. Found: C, 61.35; H, 5.83.

Tetraacetyl-α-dibenzoyl Dulcitol (2,3,5,6-Tetraacetyl-1,4-dibenzoyl-D,L-galactitol).—Acetylation of the α-dibenzoyl dulcitol in pyridine solution by acetic anhydride at room temperature during twenty-four hours produced the tetraacetate in nearly quantitative yield. The compound was recrystallized from 10 parts of alcohol, separating in needles which melted at 113° (corr.) and showed no optical activity in chloroform solution (*c*, 0.82).

Anal. Calcd. for $C_{28}H_{30}O_{12}$: C, 60.21; H, 5.41. Found: C, 60.00; H, 5.57.

Lead Tetraacetate Oxidation of α-Dibenzoyl Dulcitol.—To a solution of 0.2000 g. of α-dibenzoyl dulcitol in 15 cc. of acetic acid, 33.4 cc. of 0.1105 *N* lead tetraacetate (3.6 mols) acetic acid solution was added and the volume adjusted to 50 cc. Subsamples of 5 cc. were analyzed at the end of fifteen and thirty minutes, one, two and nineteen hours and it was found that 1.94, 1.95, 1.95, 1.96 and 2.03 mols of oxidizing agent had been consumed. A 1,4-diacyl dulcitol should consume 2 mols of lead tetraacetate.

Sodium Periodate Oxidation of α-Dibenzoyl Dulcitol.—To a cooled solution of 0.1049 g. of α-dibenzoyl dulcitol in 15 cc. of alcohol, 1.84 cc. of 0.307 *M* sodium periodate (2.1 mols) was added and the solution volume adjusted to 25 cc. with water. Analyses of 5-cc. subsamples at the expiration of fifteen and thirty minutes indicated that 2.05 mols of oxidant had been consumed. Titration of a further 5-cc. subsample with 0.1 *N* sodium hydroxide required 0.08 cc. to obtain a decided alkaline reaction with methyl red indicator. This acidity, equivalent to 0.15 mol of formic acid in the sample, may be due to enolization of benzoyl tartronic dialdehyde; in any event it appears that the observed acidity is negligibly small. The formation of one mol of formic acid would require 0.53 cc. of 0.1 *N* alkali for neutralization of 5 cc. of the oxidized solution.

Rearrangements in the Dulcitol Series

1,6-Dibenzoyl Dulcitol from 1,4-Dibenzoyl-D,L-galactitol.—One gram of 1,4-dibenzoyl-D,L-galactitol

(Fischer and Bergmann's low melting dibenzoyl dulcitol) was heated in a small flask for fifteen minutes at 210° and the melt then recrystallized from 25 cc. of glacial acetic acid. Characteristic glistening platelets of 1,6-dibenzoyl dulcitol melting at 209° (corr.) were obtained in a yield of 90%.

Benzoylation of α-Diacetone Dulcitol (2,3,5,6-Diacetone-D,L-galactitol) in Quinoline.—Following the directions of Fischer, 10 g. of α-diacetone dulcitol was benzoylated with 2.2 mols of quinoline and 2 mols of benzoyl chloride for six hours at 100°. The reaction mixture was then refluxed for a few minutes with 120 cc. of alcohol to complete the solution of quinoline hydrochloride, refrigerated overnight, and the separated solid was removed by filtration: yield 11.8 g.; m. p. 183–184° (corr.); 66%. Fischer reported a melting point of 185–186° and a yield of 60% and called this substance dibenzoyl-α-diacetone dulcitol. The mother liquor was concentrated *in vacuo* to remove the alcohol, 300 cc. of water was added, and the oily suspension extracted four times with 25 cc. of carbon tetrachloride. The extract was washed successively four times with 100 cc. of ice cold 1% hydrochloric acid, twice with dilute sodium carbonate solution, and twice with water, and then concentrated to a dry sirup. The sirupy residue was dissolved in 20 cc. of 85% alcohol and upon standing for several days 2.0 g. (11%) of the isomeric dibenzoyl diacetone dulcitol of melting point 82–83° crystallized from the solution. The latter substance was not reported by Fischer and Bergmann as being obtained by benzoylation of α-diacetone dulcitol in the presence of quinoline, but they did obtain it when pyridine was employed in the diacylation. The isolation of *two* isomeric dibenzoyl diacetone dulcitols upon benzoylation of α-diacetone dulcitol indicated that a rearrangement had occurred in the course of diacylation.

Identification of the Dibenzoate Melting at 183–184° (Fischer and Bergmann's Dibenzoyl-α-diacetone Dulcitol) as a Derivative of β-Diacetone Dulcitol.—The dibenzoate of melting point 183–184° that was obtained from the benzoylation of α-diacetone dulcitol as just described, was recrystallized from 20 parts of carbon tetrachloride. It still melted at 183–184° (corr.) and was optically inactive in chloroform (*c*, 1.60).

Anal. Calcd. for $C_{26}H_{30}O_8$: C, 66.37; H, 6.43. Found: C, 66.28; H, 6.32.

A solution of 5 g. of it in 250 cc. of chloroform was cooled in ice and salt, and 21.9 cc. of 0.972 *N* sodium methylate (2 mols) added dropwise. After standing overnight at 5° the solution was held at 50° for one hour and the separated sodium benzoate removed by filtration. The filtrate was concentrated to dryness and the dry residue dissolved in 30 cc. of acetone. Upon addition of 30 cc. of petroleum ether the typical crystals of β-diacetone dulcitol separated in a yield of 1.0 g. (m. p. 110–111°) and a further amount of 1.0 g. was obtained by working up the mother liquors; yield, quantitative. A similar quantitative debenzoylation to β-diacetone dulcitol occurs if barium methylate be employed as the deacylation agent. Fischer and Bergmann's dibenzoyl-α-diacetone dulcitol (m. p. 183–184°) is therefore a derivative of β-diacetone dulcitol and is 1,6-dibenzoyl-2,3,4,5-diacetone dulcitol; its formation from α-diacetone dulcitol (2,3,5,6-diacetone-D,L-galactitol) results from a molecular rearrangement.

Identification of the Dibenzoate Melting at 82–83° (Fischer and Bergmann's Dibenzoyl-β-diacetone Dulcitol) as a Derivative of α-Diacetone Dulcitol.—This dibenzoate, the preparation of which was described above, is recrystallized conveniently from 6 parts of 85% alcohol, crystallization being rather slow and markedly hindered by presence of impurities. It separates in the form of needles and is optically inactive in chloroform solution (*c*, 1.52). Upon debenzoylation with barium methylate, α-diacetone dulcitol (m. p. 144–145°) was obtained in quantitative yield; the dibenzoate of melting point 82–83° is evidently 1,4-dibenzoyl-2,3,5,6-diacetone-D,L-galactitol.

Anal. Calcd. for $C_{26}H_{30}O_8$: C, 66.37; H, 6.43. Found: C, 66.36; H, 6.36.

Benzoylation of α-Diacetone Dulcitol in Pyridine.—To a solution of 20.8 g. of α-diacetone dulcitol in 18 cc. of pyridine (2.8 mols), 20.4 cc. of benzoyl chloride (2.2 mols) was added, and the reaction mixture heated for three hours at 100°. The reaction products were dissolved in 200 cc. of chloroform and the chloroform solution washed successively with ice cold 0.1% aqueous hydrochloric acid, 2% sodium carbonate solution, and water. The chloroform solution was concentrated *in vacuo* to dryness. Upon attempting to dissolve the dry residue in 180 cc. of 85% alcohol, crystalline dibenzoyl-β-diacetone dulcitol (1.5 g., m. p. 178–180°, 4%) was recovered as an insoluble precipitate. From the alcoholic solution 32 g. (86%) of dibenzoyl-α-diacetone dulcitol (m. p. 82–83°) was recoverable. These results indicate that some rearrangement also occurs upon benzoylation of α-diacetone dulcitol in pyridine at 100°. The failure of Fischer and Bergmann to obtain the β-derivative by the pyridine method of acylation at 100° appears to be due to a far smaller production of it with pyridine than with quinoline.

The Isopropylidene Rearrangement.—From the structural evidence which has been presented it is certain that the α-diacetone dulcitol, which we know to be 2,3,5,6-diacetone-D,L-galactitol, upon benzoylation under the experimental conditions cited, yields both 1,4- and 1,6-dibenzoyl derivatives, namely, 1,4-dibenzoyl-2,3,5,6-diacetone-D,L-galactitol and 1,6-dibenzoyl-2,3,4,5-diacetone dulcitol. The formation of the latter derivative could take place only if there occurred a cyclic acetal shift of an isopropylidene residue, which in terms of the formulas VII, VIII and III is from carbons 5,6 to 4,5 of the galactitol chain. It was found that the shift does not occur after the 1,4-dibenzoyl-2,3,5,6-diacetone-D,L-galactitol is produced. Two grams of the pure substance was heated in quinoline (2.8 moles) and benzoyl chloride (2.2 moles) at 100° for six hours, but no formation of the β-isomer could be demonstrated. In further experiments the pure substance was melted and the melt held at 100° for several hours; neither from this melt nor from a similar one, through which dry hydrochloric acid gas was bubbled, could any β-isomer be isolated. It was sought next to determine whether the isopropylidene shift is caused by a change of α-diacetone dulcitol to its β-isomer through heating at 100° in quinoline alone. Since the isolation of the diacetone dulcitols from quinoline solution did not appear to be feasible, we selected the following experimental test. Five grams of α-diacetone dulcitol was

heated in quinoline (2.5 moles) at 100° for six hours and the solution was then cooled in ice and benzoyl chloride (2.2 mols) was added. After standing for four hours at 0°, followed by twenty-four hours at 25°, the reaction product yielded by customary procedure 0.4 g. (4.4%) of 1,6-dibenzoyl-2,3,4,5-diacetone dulcitol and 6.5 g. (72.5%) of 1,4-dibenzoyl-2,3,5,6-diacetone-D,L-galactitol. The rearrangement in this test is so slight that the cause of the extensive rearrangement which occurs when the benzoylation reaction is carried out at 100°, cannot be attributed to an action of the quinoline alone, particularly if the result of the next experiment be considered. It was carried out with the same quantities of materials but some anhydrous quinoline hydrochloride (1.2 mols) was present during the period of heating at 100°; it yielded 3.8 g. (42.4%) of 1,6-dibenzoyl-2,3,4,5-diacetone dulcitol and 3.5 g. (39%) of 1,4-dibenzoyl-2,3,5,6-diacetone-D,L-galactitol. It appears therefore that the rearrangement is catalyzed by such substances as quinoline hydrochloride and (in less degree) pyridine hydrochloride.

Summary

It is shown that the properties of the α- and β-diacetone dulcitols, as well as those of several new derivatives of these substances, exclude the possibility that they can be enantiomorphous substances and prove that they are structural isomers. Evidence has been obtained from periodate and lead tetraacetate oxidations that neither α- nor β-diacetone dulcitol contains a glycol grouping. The results of a study of the ditosyl, diiodo and dityrityl derivatives of β-diacetone dulcitol indicate that it contains two free primary hydroxyl groups, and a study of the oxidation of the diacyl dulcitols, derivable from it, proves that its structure is that of 2,3,4,5-diacetone dulcitol, a *meso* form. The results of a study of the ditosyl, monotosyl-mono-iodo, and monotrityl-monoacetyl derivatives of α-diacetone dulcitol indicate that it contains one free primary hydroxyl group and one free secondary hydroxyl group, and a study of the oxidation of the dibenzoyl dulcitol derived from it proves that it is 2,3,5,6-diacetone-D,L-galactitol, a racemic form. An acyl migration by which 1,4-dibenzoyl-D,L-galactitol (a racemic form) passes to 1,6-dibenzoyl dulcitol (a *meso* form) has been demonstrated. A cyclic acetal shift has been shown to be the cause of the interesting and unusual changes which Fischer and Bergmann noticed upon acylation of α-diacetone dulcitol. The shift occurs as a stage in the benzoylation of α-diacetone dulcitol with benzoyl chloride and quinoline or pyridine at elevated temperatures and it is catalyzed by quinoline hydrochloride or pyridine hydrochloride. In structural terms it is represented as the passage of 2,3,5,6-diacetone-D,L-galactitol to 1,6-dibenzoyl-2,3,4,5-diacetone dulcitol. Reasons have been given for preferring the name galactitol to dulcitol in designating non-*meso* structures of derivatives of dulcitol which carry in their names a numbering of its carbon atoms.

WASHINGTON, D. C. RECEIVED JUNE 19, 1939

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY OF PRINCETON UNIVERSITY]

Procedure for Preparation of Fully Methylated Carbohydrates and their Derivatives

BY EUGENE PACSU AND S. M. TRISTER[1]

For investigation of certain structural problems in carbohydrate chemistry, it is often necessary to methylate all free hydroxyl groups in the molecule. Methylation usually is carried out either with methyl iodide and silver oxide,[2] dimethyl sulfate and alkali solution,[3] alkali metals in liquid ammonia and methyl iodide,[4] or with the thallium salts of the carbohydrates and methyl iodide.[5]

However, none of these methods, if used alone, gives entirely satisfactory results for various reasons. For complete methylation usually a combination of two of these methods is necessary. In most instances first the dimethyl sulfate–alkali procedure is employed and the products obtained are then repeatedly treated with silver oxide and methyl iodide.

In this Laboratory excellent results were obtained from combination of Haworth's dimethyl sulfate–alkali procedure with a slightly modified process of Freudenberg and Hixon.[6] These

(1) Research Assistant on Special Funds from the Rockefeller Foundation.

(2) Purdie and Irvine, *J. Chem. Soc.*, **83**, 1021 (1903).

(3) (a) Haworth, *ibid.*, **107**, 8 (1915); (b) Haworth and Leitch, *ibid.*, **113**, 188 (1918); (c) West and Holden, THIS JOURNAL, **56**, 930 (1934).

(4) (a) Muskat, *ibid.*, **56**, 693, 2449 (1934); (b) Hendricks and Rundle, *ibid.*, **60**, 2563 (1938).

(5) (a) Fear and Menzies, *J. Chem. Soc.*, 937 (1926); (b) Purves and Hudson, THIS JOURNAL, **59**, 49, 1170 (1937); (c) Hirst and Jones, *J. Chem. Soc.*, 496 (1938); (d) Barker, Hirst and Jones, *ibid.*, 169 (1938).

(6) Freudenberg and Hixon, *Ber.*, **56**, 2119 (1923).