mesityl oxide with other phenolic compounds and of their oxidation products are being carried on.

New York City

[Communication from the Department of Industrial and Cellulose Chemistry, McGill University]

STUDIES ON THE REACTIONS RELATING TO CARBOHYDRATES AND POLYSACCHARIDES.
XV. THE ISOMERIC BENZYLIDENE GLYCEROLS

By Harold S. Hill,[1] Myron S. Whelen[2] and Harold Hibbert[2a]

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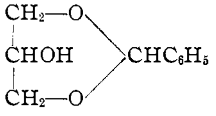
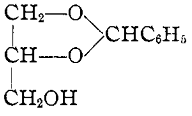
Fischer[3] was the first to describe a definite condensation product from the interaction of glycerol with benzaldehyde and the molecular structure of the cyclic acetal formed was represented as being


I

or


II

The same reaction product was more thoroughly investigated by Irvine, Macdonald and Soutar[4] with a view to determining its structure, and by methods of direct synthesis the material in hand was shown to possess the five membered cyclic configuration (II). While these authors pointed out the possibility of the existence of the isomeric form (I), they were unable to detect its presence in their product. It is because of this fact, together with the generally accepted finished character of their research, that their results have been interpreted as indicating the absence of the six membered benzylidene derivative, and the conclusion that the condensation of benzaldehyde with a poly-alcohol takes place only through *adjacent* hydroxyl groups.

This is especially true since the formula for monobenzylidene α-methyl glucoside was given earlier as containing a five membered acetal ring[5] (A),

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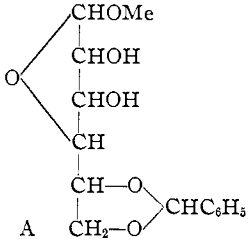
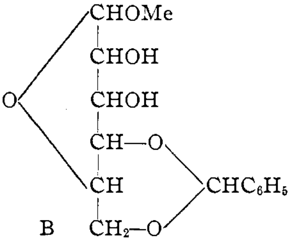
[3] Fischer, *Ber.*, **27**, 1536 (1894).

[4] Irvine, Macdonald and Soutar, *J. Chem. Soc.*, **107**, 337 (1915).

[5] Irvine and Scott, *ibid.*, **103**, 575 (1913).


A


B

a conclusion based partly on the assumption of α-methyl glucoside containing the five membered butylene oxide structure. More recent investigations,[6] however, have brought forth considerable evidence that the transformations of α-methyl glucoside are best explained on the basis of the six membered oxidic form. If the latter view be correct, then formula (A) for the benzylidene derivative becomes less probable than that of a six membered acetal ring (B). The question of the possibility of the formation of the latter grouping is, therefore, of interest.

In view of the great ease of formation of both five and six membered cyclic acetals in general, as shown by various partition experiments carried out by Hibbert and co-workers,[7] it was concluded by these authors that benzylidene glycerol should exist not only in both isomeric forms, but also that in the condensation of benzaldehyde with glycerol a "partition" should take place to give a reaction product consisting of a mixture of a five and six membered cyclic benzylidene glycerol, (I) and (II). The present investigation shows this to be the case and deals with the actual separation and identification of the isomers. The assumption that benzaldehyde condensations involve only adjacent hydroxyl groups is, therefore, unjustified.

Separation of the Isomeric Benzylidene Glycerols.—Glycerol was condensed with benzaldehyde essentially as described by Gerhardt[8] and a product obtained, b. p. 142–147° (2.5 mm.), which proved to be a mixture of the two benzylidene glycerols. A fortunate difference in solubility of the isomers in a mixture of cold ligroin and benzene permitted a fairly quantitative separation, the 1,3-benzylidene glycerol crystallizing out and leaving the 1,2-derivative in solution. The former product melts sharply at 83.5°.

Distillation and fractionation of the mother liquor yields 1,2-benzylidene glycerol as an oil, b. p. 143–144° (2 mm.) which presumably still holds a small amount of the 1,3-isomer in solution.

The benzoate of the crystalline isomer, prepared by means of benzoyl chloride in dry pyridine solution, is a well crystallized product, m. p. 103°, whereas that from the liquid 1,2-benzylidene glycerol is an oil.

It is of interest to compare the above results with those obtained by Irvine and co-workers, who also followed Gerhardt's patent in their prepa-

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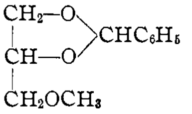
[6] A review of the subject by W. N. Haworth is to be found in *Chem. Soc. Annual Reports*, **1926**, pp. 74–92.

[7] Hill and Hibbert, THIS JOURNAL, **45**, 3117 (1923).

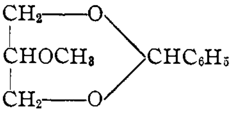
[8] Gerhardt, German patent 255,083 (1913).

ration of benzylidene glycerol. They obtained only one product, a benzylidene glycerol whose melting point was originally 65°, but which rose on standing to 76° and which was proved beyond question to be the 1,2-derivative. In the present investigation it is shown that the crystalline benzylidene glycerol, m. p. 83.5°, is a pure 1,3-isomer and that the liquid product is a mixture of a small amount of this with the 1,2-derivative as the main product. The liquid isomer would not crystallize even on long cooling either alone or from solvents. This difference from Irvine's 1,2-benzylidene glycerol may be due to the fact that although it has the same ring system, it represents the alternate *cis* or *trans* geometric isomer. On the other hand, the small amount of the 1,3-derivative present may prevent crystallization.

Determination of Structure.—For the identification of the isomeric benzylidene glycerols the methylation–hydrolysis method of Irvine and co-workers was followed. The use of dimethyl sulfate and sodium hydroxide as a methylating agent[9] proved to be unsuitable, owing to extensive hydrolysis of the acetal group. Methylating with silver oxide and methyl iodide, however, gave satisfactory yields of the corresponding benzylidene glycerol methyl ethers



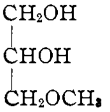
III



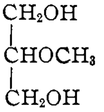
IV

the crystalline benzylidene glycerol, m. p. 83.5°, giving exclusively the new six membered acetal ether (IV) as a crystalline product, whereas the liquid isomer yielded an oil identical with Irvine's benzylidene glycerol methyl ether which was shown by him to have the five membered cyclic structure (III).

Hydrolysis of the latter product gave glycerol α-methyl ether (V), identical with that described by Irvine. Hydrolysis of the isomeric benzylidene glycerol ether (IV) yielded a new glycerol monomethyl ether, VI, quite different from the α-derivative and which must, therefore, be glycerol β-methyl ether,



$$\begin{array}{l} CH_2OH \\ | \\ CHOH \\ | \\ CH_2OCH_3 \end{array} \quad V$$



$$\begin{array}{l} CH_2OH \\ | \\ CHOCH_3 \\ | \\ CH_2OH \end{array} \quad VI$$

It is now possible to assign definitely to the crystalline benzylidene glycerol, m. p. 83.5°, the six membered cyclic acetal structure (I) and to the liquid isomer the alternate formula (II). It should be noted that while the liquid benzylidene glycerol, by the above methylation–hydrolysis method,

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[9] Haworth, *J. Chem. Soc.*, **107,** 8 (1915).

yielded for the most part glycerol α-methyl ether, it also gave a small amount of the β-ether, showing that the liquid acetal still holds some of its isomer in solution.

Glycerol β-methyl ether, as isolated above, marks the first definite β-derivative of glycerol to be recorded in the literature, and for this reason it should prove to be a reference compound of some importance. Its physical constants in comparison with glycerol α-methyl ether are given in the following table.

TABLE I

PHYSICAL PROPERTIES OF ETHERS

Glycerol α-methyl ether (Irvine)	Glycerol α-methyl ether (The authors)	Glycerol β-methyl ether (The authors)
B. p., 110–111° (13 mm.)	B. p., 110–111° (13 mm.)	B. p., 123° (13 mm.)
$d_{4°}^{17°} = 1.1197$	$d_{4}^{17°} = 1.1202$	$d_{4}^{17°}$ 1.1306
$n_{D}^{17°} = 1.4460$	$n_{D}^{17°} = 1.4449$	$n_{D}^{17°}$ 1.4505

Partition and Interconversion of the Isomeric Benzylidene Glycerols.—Taking advantage of the fact that the crystalline 1,3-benzylidene glycerol is practically insoluble in a strongly cooled mixture of ligroin and benzene, while the other isomer remains in solution, it is possible by carefully controlled conditions to determine the relative amounts of the isomers present in the primary reaction product. In the material isolated by the use of Gerhardt's method, it was found that the five membered cyclic form (II) exceeds that of the six membered (I) in the ratio of 7.5 to 1. On the other hand, if the preparation of benzylidene glycerol was carried out by a different method, namely, by heating glycerol and benzaldehyde with a small amount of 40% sulfuric acid, a mixture was obtained in which the same isomers were present in a ratio of 3 to 1.

Obviously the "partition" varies somewhat with the conditions used in the preparation, and it is even possible that in some cases the above ratio might be reversed. The fact remains, however, that both isomers are always formed and that in all cases investigated the smaller ring structure predominates.

In this connection it seemed desirable to ascertain whether the "partition" was the result of chance formation of varying amounts of the isomers, or whether it represented a state of equilibrium between the two forms. If the latter interpretation be correct, then, as shown previously in other cases, either isomer, when treated with a trace of acid, should be transformed into the other until an equilibrium mixture results, and for a given set of conditions the same ratio of products should be obtained, regardless of which isomer is used, and this is found to be the case. When 1,3-benzylidene glycerol is treated with a trace of dry hydrogen chloride and heated at 100° for one hour, a mixture is obtained in which the ratio of the five membered cyclic acetal to the six is 5:1. Starting with 1,2-benzylidene glycerol, the ratio of these isomers found in the equilibrium product is 5.5:1.

This transformation is rapid and takes place even under very mild conditions. Thus crystalline 1,3-benzylidene glycerol treated with a trace of dry hydrogen chloride and warmed to 30° liquefies immediately as a result of its partial conversion into the 1,2-isomer.

On the other hand, 1,2-benzylidene glycerol, when allowed to stand for one month at room temperature with a trace of dry hydrogen chloride, reaches approximately the same equilibrium with its 1,3-isomer as when heated to 100°, the ratio being 5.7 to 1.

These interconversion experiments are to be considered as being more of a qualitative than an exact quantitative nature, since it is admittedly impossible to separate all of the crystalline isomer from the liquid. The possibility of *cis-trans* interconversions in the same ring system must also be considered as a complicating factor.

These results are significant, however, since they bring out the labile character of these carbon–oxygen cyclic structures, many closely related examples of which exist in various sugar and polysaccharide derivatives. The marked ease of transformation of one form into the other emphasizes the need for great caution in assigning a definite structure to an original compound on the basis of the structure of one of its derivatives, especially if the latter has been prepared under conditions involving an acid medium as, for example, in the case of the two different cellobiosans obtained by Bergmann and Knehe, *Ann.*, **448,** 76 (1926), and Hess and Friese, *Ann.*, **450,** 40 (1926); **456,** 38 (1927), respectively.

It is believed that the formation of isomeric glycerol methyl ethers by the methylation–hydrolysis method, as applied to the corresponding ethylidene glycerols, lends considerable support to the claims of Irvine and coworkers regarding their method of methylation technique based on Purdie's original observations.

Their procedure of complete methylation, subsequent hydrolysis and identification of the resulting methylated sugars is taken as indicating the positions of the free hydroxyls and of the point of union in the original polysaccharide. In such reasoning there is always the possibility that a rearrangement in the oxide ring of the sugar residues may take place under the conditions of methylation. The present investigation with the simpler glycerol derivatives shows that under these same conditions the relatively sensitive five and six membered acetal rings involved undergo no change, one into the other, and that the methylated products obtained are an authentic proof of the constitution of the parent substances.

Experimental Part

Preparation and Separation of Isomeric Benzylidene Glycerols.—One hundred fifty g. of *pure* benzaldehyde and 120 g. of glycerol were heated in an atmosphere of carbon dioxide with stirring for one hour at 145–155°, and then for thirty minutes at 165°. The product upon fractionation under reduced pressure yielded 170 g. of a crude mixture,

b. p. 140–149° (3 mm.). This was taken up in ether, washed several times with water to remove traces of glycerol, dried over solid potassium carbonate and refractionated; yield, 120 g. of mixed benzylidene glycerols, b. p. 142–147° (2.5 mm.); $d^{17°}_{4°}$, 1.19838; n_D, 1.5400.

Anal. Subs., 0.2244: CO_2, 0.5464; H_2O, 0.1340. Calcd. for $C_{10}H_{12}O_3$: C, 66.67; H, 6.67. Found: C, 66.41; H, 6.66.

Sixty g. of mixed benzylidene glycerols from the above preparation was dissolved in a mixture of 150 cc. of ligroin (b. p. 60–70°) and 90 cc. of benzene and cooled to −15° until crystallization had taken place. Enough benzene was slowly added, with shaking, until there was no longer undissolved oil present with the precipitated crystals. After standing at −15° for one hour, the crystals were filtered from the cold solution and washed with 40 cc. of a cold mixture of equal parts of ligroin and benzene; yield, 7 g. Recrystallization from ligroin-benzene mixture with practically no loss gave pure 1,3-benzylidene glycerol, m. p. 83.5°.

Anal. Subs., 0.2020: CO_2, 0.4947; H_2O, 0.1182. Calcd. for $C_{10}H_{12}O_3$: C, 66.67; H, 6.67. Found: C, 66.79; H, 6.50.

Benzylidene glycerol was also prepared using sulfuric acid as a catalyst.

Method.—One hundred fifty-nine g. of benzaldehyde, 150 g. of glycerol and 2 cc. of 40% sulfuric acid were heated on a steam-bath for eight hours in an atmosphere of carbon dioxide. The product was taken up in ether, neutralized with potassium carbonate and dried over this reagent. Fractionation yielded 105 g. of mixed benzylidene glycerols, b. p. 163–168° (11 mm.).

Fifty g. of this mixture, separated as described above, gave 13 g. of crystalline 1,3-benzylidene glycerol, m. p. 83°. In another experiment 28 g. of the mixture yielded 7 g. of 1,3-benzylidene glycerol.

1,2-Benzylidene Glycerol.—The ligroin–benzene mother liquor from the above separation of 1,3-benzylidene glycerol was evaporated under reduced pressure, taken up in ether, washed with concentrated potassium carbonate solution to remove traces of acid and dried over the solid carbonate. Fractionation gave pure 1,2-benzylidene glycerol, b. p., 143–144° (2 mm.); $d^{17°}_{4°}$, 1.1916; n_D, 1.5389. This product showed no tendency to crystallize.

Anal. Subs., 0.2170: CO_2, 0.5295; H_2O, 0.1301. Calcd. for $C_{10}H_{12}O_3$: C, 66.67; H, 6.67. Found: C, 66.55; H, 6.66.

Benzoates of Benzylidene Glycerol.—The respective benzylidene glycerols were benzoylated by dissolving each of them at room temperature in four times the weight of dry pyridine containing the theoretical amount of benzoyl chloride and allowing the reaction, with development of heat, to proceed spontaneously for about twenty minutes. On pouring into water, the product from 1,3-benzylidene glycerol crystallized at once, while that from 1,2-benzylidene glycerol remained as an oil. The benzoate of 1,3-benzylidene glycerol was recrystallized from ligroin, m. p. 103°.

Analysis of the Benzoate from 1:2-Benzylidene Glycerol.—Subs. 0.2153: CO_2, 0.5674; H_2O, 0.1103. Calcd. for $C_{17}H_{16}O_4$: C, 71.83; H, 5.63. Found: C, 71.87; H, 5.69.

Methylation of 1,3-Benzylidene Glycerol.—Fifty-four g. of crystalline 1,3-benzylidene glycerol was recrystallized from ligroin–benzene solution (1:1), pressed as dry as possible on a suction filter and methylated immediately in the usual manner, using 115 g. of silver oxide and 230 g. of methyl iodide. The reaction mixture was thoroughly extracted with ether from which, on partial evaporation and cooling, benzylidene glycerol methyl ether separated. Recrystallization from mixture of ligroin–benzene (1:1) yielded 31 g. of long, coarse, transparent needles, m. p. 52°. No other substance could be isolated from the reaction product.

Anal. Subs., 0.1446: CO_2, 0.3570; H_2O, 0.0878. Calcd. for $C_{11}H_{14}O_3$: C, 68.04; H, 7.22. Found: C, 67.38; H, 6.79.

Hydrolysis of Benzylidene Glycerol β-Methyl Ether.—Twenty-seven g. of benzylidene glycerol β-methyl ether (m. p. 52°) was hydrolyzed by boiling under reflux for seventy minutes with 220 cc. of 75% aqueous ethyl alcohol containing 3 cc. of concd. hydrochloric acid; 65 cc. of water was added and the alcohol removed under reduced pressure. Three or four extractions with ether removed benzaldehyde. The aqueous solution was neutralized by shaking with lead carbonate, filtered, concentrated and fractionated under diminished pressure. Redistillation yielded 9.8 g. (64%) of pure β-methyl glycerol ether, b. p. 123° (13 mm.); $d^{17°}_{4°}$ = 1.1300; $n^{17°}_{D}$ = 1.4505.

Anal. Subs., 0.1419: CO_2, 0.2350; H_2O, 0.1176. Calcd. for $C_4H_{10}O_3$: C, 45.28; H, 9.27. Found: C, 45.17; H, 9.27.

Methylation of 1,2-Benzylidene Glycerol.—Seventy-five g. of the liquid 1,2-benzylidene glycerol was methylated in the usual manner with 145 g. of freshly prepared silver oxide and 290 g. of methyl iodide. Extraction of the reaction mixture with ether and fractionating gave 50 g. of a mixture, b. p. 139–145° (10 mm.).

Fraction I	28 g. b. p. 138–139° (10 mm.)	$n^{17°}_{D}$ = 1.5128
Fraction II	12 g. b. p. 139–141° (10 mm.)	$n^{17°}_{D}$ = 1.5135
Fraction III	8 g. b. p. 141–145° (10 mm.)	$n^{17°}_{D}$ = 1.5159

Analysis of the lower and higher fractions showed both to be benzylidene glycerol methyl ether.

Anal. Fraction I. Subs., 0.2281: CO_2, 0.5678; H_2O, 0.1472. Calcd. for $C_{11}H_{14}O_3$: C, 68.04; H, 7.22. Found: C, 67.89; H, 7.17.

Anal. Fraction III. Subs., 0.2180: CO_2, 0.5127; H_2O, 0.1408. Calcd. for $C_{11}H_{14}O_3$: C, 68.04; H, 7.22. Found: 67.92; 7.19.

Hydrolysis of Benzylidene Glycerol α-Methyl Ether.—Twenty-eight g. of benzylidene glycerol α-methyl ether (fraction (I) above), hydrolyzed in the same manner as the β-derivative, yielded 13.4 g. (87%) of glycerol α-methyl ether, b. p. 110° (13 mm.), $d^{17°}_{4°}$ = 1.1202; n^{17}_{D} = 1.4449.

Anal. Subs., 0.2073: CO_2, 0.3424; H_2O, 0.1747. Calcd. for $C_4H_{10}O_3$: C, 45.28; H, 9.43. Found: C, 45.05; H, 9.36.

Hydrolysis of the higher boiling fractions from the preparation of 1,2-benzylidene glycerol α-methyl ether gave for the most part glycerol α-methyl ether, b. p. 112° (13 mm.), $n^{17°}_{D}$ = 1.4446, but also a smaller fraction, b. p. 112–118°, indicating the presence of a small amount of the higher boiling β-methyl glycerol ether.

Interconversion of the Benzylidene Glycerols.—Several bubbles of dry hydrogen chloride were passed into 3 g. of 1,2-benzylidene glycerol contained in a tube so small that there was very little free air space when stoppered. This was heated for one hour at 100°, allowed to stand at room temperature for twelve hours and taken up with 10 cc. of ether. The solution was shaken with 0.5 g. of solid potassium carbonate to neutralize the acid, filtered and evaporated under reduced pressure. The residue was taken up with 15 cc. of a 50% mixture of ligroin (b. p. 60–70°) and benzene and cooled to −15° for one hour. The crystals of 1,3-benzylidene glycerol which separated were filtered from the cold solution, washed with 10 cc. of the cold ligroin-benzene mixture and dried in a vacuum; yield, 0.5 g. (m. p. 81°). It was recrystallized with practically no loss and then melted at 83.5°.

Three g. of 1,3-benzylidene glycerol, when subjected to an as nearly as possible parallel treatment, as above, yielded 0.46 g. of unchanged 1,3-benzylidene glycerol, m. p. 80–82°.

An experiment carried out with 3 g. of 1,2-benzylidene glycerol, similarly treated with dry hydrogen chloride but without any preliminary heating and allowed to stand for one month at room temperature, yielded 0.45 g. of 1,3-benzylidene glycerol.

Summary

1. The preparation, isolation, quantitative separation and interconversion of the isomeric 1,2- and 1,3-benzylidene glycerols are described.

2. The corresponding methyl ethers have been prepared and their physical constants determined.

3. The remarkably labile character of the oxygen ring is shown by the ease of partial transformation of either of the acetals into the corresponding isomer at a low temperature under the influence of traces of gaseous hydrochloric acid. The bearing of this on polysaccharide investigations is pointed out.

4. Glycerol β-methyl ether has been isolated for the first time in a pure state. It is apparently the first pure β-derivative of glycerol to be reported in the literature.

MONTREAL, CANADA

[COMMUNICATION FROM THE DEPARTMENT OF INDUSTRIAL AND CELLULOSE CHEMISTRY, McGILL UNIVERSITY]

STUDIES ON THE REACTIONS RELATING TO CARBOHYDRATES AND POLYSACCHARIDES.

XVI. SEPARATION AND IDENTIFICATION OF THE ISOMERIC ETHYLIDENE GLYCEROLS[1]

BY HAROLD S. HILL,[2] ALLAN C. HILL[3] AND HAROLD HIBBERT[4]

RECEIVED APRIL 14, 1928 PUBLISHED AUGUST 4, 1928

The importance of the cyclic acetal and ketal glycerols has long attracted the interest of investigators in the field of carbohydrate chemistry. Such workers as Tollens,[5] Fischer,[6] Karrer,[7] Irvine,[8] and more recently

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[1] This work was presented by Mr. Allan C. Hill to the Graduate Department, McGill University, in April, 1927, in partial fulfilment of the requirements for the degree of Master of Science.

[2] Research Fellow, Canadian Pulp and Paper Association.

[3] Research Chemist attached to Pulp and Paper Division, Forest Products Laboratories of Canada.

[4] This paper represents the second of a forthcoming series of publications carried out under the joint auspices of the Canadian Pulp and Paper Association, the Pulp and Paper Division of the Forest Products Laboratories of Canada and the Department of Industrial and Cellulose Chemistry, McGill University. The authors wish to express their keen appreciation of the generous facilities placed at their disposal by the three coöperating agencies.

[5] Schulz and Tollens, *Ann.*, **289**, 29 (1896).

[6] Fischer, *Ber.*, **27**, 1536 (1897).

[7] Karrer, *Helv. Chim. Acta*, **4**, 728 (1921).

[8] Irvine, Macdonald and Soutar, *J. Chem. Soc.*, **107**, 337 (1915).