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MECHANISM OF ORGANIC REACTIONS. I. THE WANDERING OF ACYL GROUPS IN GLYCEROL ESTERS

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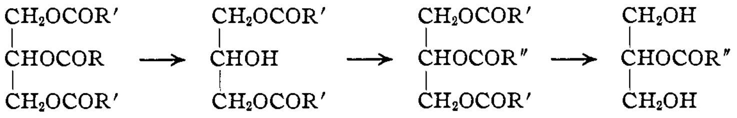
Introduction

Previous methods for the allocation of one or more free hydroxyl groups in derivatives of polyhydroxy compounds have often consisted in a primary esterification with an acid anhydride or halide, followed by selective hydrolysis, oxidation or degradation and, finally, identification of the resulting product as a substance of established constitution. An example of such a procedure is indicated in the following scheme



$$\begin{array}{c} CH_2OCOR' \\ | \\ CHOCOR \\ | \\ CH_2OCOR' \end{array} \longrightarrow \begin{array}{c} CH_2OCOR' \\ | \\ CHOH \\ | \\ CH_2OCOR' \end{array} \longrightarrow \begin{array}{c} CH_2OCOR' \\ | \\ CHOCOR'' \\ | \\ CH_2OCOR' \end{array} \longrightarrow \begin{array}{c} CH_2OH \\ | \\ CHOCOR'' \\ | \\ CH_2OH \end{array}$$

I II III IV

Selective hydrolysis of a glycerol ester of Type I leaves a free hydroxyl group in the β-position of II, which is then "ear-marked" by the introduction of a suitable acid radical —COR″, not readily hydrolyzable. The resulting new glycerol triacyl ester, III, is then further hydrolyzed to the glycerol monoacyl ester, IV, the constitution of which has been previously determined.

Similar schemes have been followed in the determination of the structure of fats[2,3] and of the ring forms of certain sugars and their derivatives.[4]

Conversely, the synthesis of mixed glycerol esters (including fats) has been accomplished by means of a primary esterification of glycerol dichlorohydrins, followed by replacement of the chlorine atoms by acyl groups either directly or through the medium of the free dihydroxy compound, as indicated below[3,5]

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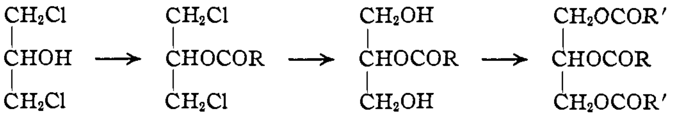
[2] Grün and Corelli, *Z. angew. Chem.*, **25**, 665, 947 (1912); Marcusson, *ibid.*, **26**, 173 (1913).

[3] Grün and Wittka, *Ber.*, **54**, 273 (1921).

[4] For a recent example, see Hickinbottom, *J. Chem. Soc.*, **1928**, 3140.

[5] Grün and Skopnik, *Ber.*, **42**, 3750 (1909); Grün, *ibid.*, **43**, 1288 (1910); Whitby, *J. Chem. Soc.*, **128**, 1458 (1926); Thompson, *Proc. Roy. Soc. Canada*, [iii] **20**, 445 (1926); Brash, *J. Soc. Chem. Ind.*, **46**, 481T (1927).



$$\begin{array}{l} CH_2Cl \\ | \\ CHOH \\ | \\ CH_2Cl \end{array} \longrightarrow \begin{array}{l} CH_2Cl \\ | \\ CHOCOR \\ | \\ CH_2Cl \end{array} \longrightarrow \begin{array}{l} CH_2OH \\ | \\ CHOCOR \\ | \\ CH_2OH \end{array} \longrightarrow \begin{array}{l} CH_2OCOR' \\ | \\ CHOCOR \\ | \\ CH_2OCOR' \end{array}$$

A similar, but more complex process has been utilized by Bergmann, Brand and Dreyer,[6] starting from *n*-dihydroxypropylamine.

The validity of the conclusions drawn from such decompositions and syntheses has, in view of an accumulating number of experimental anomalies encountered, been called into question, more especially in recent years. As long ago as 1871, Hübner and Müller[7] described the formation of allyl alcohol from α,α'-dichlorohydrin by the action of sodium in dry ether, pointing to the rearrangement at some stage of the atoms attached to an α-carbon atom. Among the more recent references to supposed migrations of substituents in glycerol derivatives may be cited the observation by Fischer[8] that glycerol α-iodohydrin-α',β-distearate, on the substitution of hydroxyl for iodine, gave glycerol α,α'-distearate. Gilchrist and Purves[9] found that the methylation of glycerol α,α'-dichlorohydrin and subsequent replacement of the chlorine atoms by hydroxyl yielded glycerol α-monomethyl ether instead of the expected β-isomer.[10] Grün and Limpacher,[11] in preparing synthetic cephalin were unable to detect any difference in the physical or chemical properties of the product prepared from either α,α'- or α,β-distearin.

The migration of a benzoyl group from the *p*- to the *m*-position during the hydrolysis of the acetyl groups in 3,5-diacetyl-4-benzoylgallic acid is another similar case.[12]

Attention has frequently been focused on this apparent group migration in the case of acyl derivatives of glycerol,[13] and a method for the avoidance of such in the preparation of glycerol β-esters is to be found in the proposal of Helferich and Sieber[14] to use glycerol α,α'-ditrityl ether as an intermedi-

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[6] Bergmann, Brand and Dreyer, *Ber.*, **54**, 936 (1921).

[7] Hübner and Müller, *Ann.*, **159**, 173 (1871).

[8] Fischer, *Ber.*, **53**, 1621 (1920). It is of interest that the latter compound possesses a melting-point (78.5–79°) very similar to that of the glycerol α-*mono*stearate (76–77°) described by the same investigator, *ibid.*, **53**, 1589 (1920).

[9] Gilchrist and Purves, *J. Chem. Soc.*, **127**, 2735 (1925).

[10] These reactions are under investigation and are to be reported in the near future.

[11] Grün and Limpacher, *Ber.*, **60**, 152 (1927).

[12] Fischer, Bergmann and Lipschitz, *Ber.*, **51**, 45 (1918).

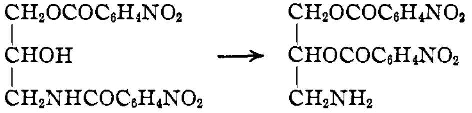
[13] (a) Grün, Wittka and Scholze, *ibid.*, **54**, 273, 290 (1921); (b) Fairbourne and Foster, *J. Chem. Soc.*, **128**, 3148 (1926); (c) Hill, Whelen and Hibbert, THIS JOURNAL, **50**, 2235 (1928); (d) Hibbert and Carter, *ibid.*, **50**, 3120, 3376 (1928). After the present paper had been prepared for publication, a recent and excellent review of the conflicting evidence encountered in the structure of disubstituted glycerols, together with valuable experimental results, has appeared, Fairbourne and Cowdrey, *J. Chem. Soc.*, **1929**, 129.

[14] Helferich and Sieber, *Z. physiol. Chem.*, **170**, 31 (1927).

ate derivative, it being pointed out that trityl chloride (triphenylchloromethane) shows a preferential reactivity toward primary as compared with secondary alcoholic groups.

This tendency of groups to wander is not confined to the glycerol type. Thus the bromine atom in ethyl α-bromo-acetoacetic ester migrates to the γ-carbon atom either on standing alone or in presence of a trace of hydrogen bromide;[15] 1,2-dibromo-3-butene on standing yields an equilibrium mixture with its isomer, 1,4-dibromo-2-butene;[16] the acetyl groups in octa-acetylmaltose are to be considered mobile,[17] and Karrer and Hurwitz[18] cite many acylated acetone sugars to which no definite constitution can be assigned, due to rearrangement of the acyl groups on scission of the cyclic ketal ring. The wandering of the half-acetal ring in the sugars and glucosides from one carbon atom to another is of common occurrence and may even be caused by the preference of acetone for adjacent hydroxyl groups in the formation of diacetone glucose and mannose.[19]

The migration of groups to, or from, atoms other than carbon, is of interest, although possibly of less immediate importance in the present connection. Thus the wandering of a *p*-nitrobenzoyl radical from a nitrogen to an oxygen atom[6]



$$\begin{array}{lcl} CH_2OCOC_6H_4NO_2 & & CH_2OCOC_6H_4NO_2 \\ | & & | \\ CHOH & \longrightarrow & CHOCOC_6H_4NO_2 \\ | & & | \\ CH_2NHCOC_6H_4NO_2 & & CH_2NH_2 \end{array}$$

and the migration of an acyl group brought about by the introduction of a second acyl group[20] are instances of many other examples of this type to be found in the literature.

Migration of Acyl Groups During Cyclic Acetal Hydrolysis

These foregoing examples show that the proof of constitution by "ear-marking" hydroxyl groups in tri- and poly-hydroxy compounds rests on a precarious basis. The investigations on cyclic acetal formation carried out in these Laboratories over a period of several years[13c,d,21] have had for one of their principal objects the accumulation of the necessary experimental data which might throw some light on (A) the true value to be placed on the two

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[15] Hantzsch, *Ber.*, **27**, 355 (1894).

[16] Thorpe, *J. Chem. Soc.*, **1928**, 729.

[17] Freudenberg, Dürr and von Hochstetter, *Ber.*, **61**, 1741 (1928).

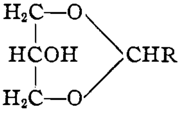
[18] Karrer and Hurwitz, *Helv. Chim. Acta*, **4**, 728 (1921). A recent interesting synopsis of the migration of atoms and radicals is to be found in a series of papers by Gillet, *Bull. soc. chim. belg.*, 1921–1922.

[19] W. N. Haworth, "Constitution of the Sugars," Edward Arnold and Co., London, **1929**, p. 52; Ohle and Erlbach, *Ber.*, **61**, 1870, 1875 (1928).

[20] Raiford and Couture, THIS JOURNAL, **46**, 2305 (1924).

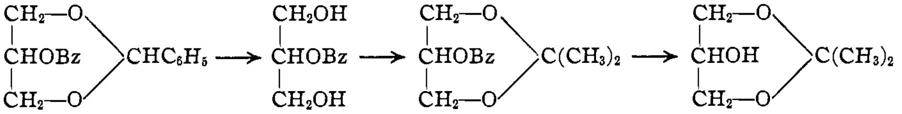
[21] Hibbert and co-workers, *ibid.*, **45**, 734, 2433, 3108, 3117, 3124 (1923); **46**, 1283 (1924); **50**, 1411, 2235, 2242 (1928).

main processes of methylation, namely, (a) use of silver oxide and methyl iodide[22] and (b) dimethyl sulfate and caustic soda[23] as applied to carbohydrates and polysaccharides for the purpose of determining their structure, and (B) the tendency and ease of "ring-shift" in the furanose and pyranose rings present in such derivatives. In the course of these investigations, the constitution of the structurally isomeric cyclic acetals of glycerol was determined by the use as reference compounds of α- and β-monomethyl ethers of glycerol.[13c,d]



A consideration of the structure of a typical six-membered glycerol cyclic acetal would indicate that this should prove a valuable product for the preparation of glycerol β-derivatives as, for example, the pure glycerol β-esters, through the medium of which might be prepared the six-membered cyclic ketal from acetone and glycerol, VII, which has not as yet been obtained.[24] It is true that the type of six-membered ring indicated by Formula VII has already been obtained in the condensation of acetone with 1,3-propanediol,[25a] dihydroxyacetone,[25b] penta-erythritol[25c] and xylose,[19] but it was thought that its labile character in Compound VII, with its adjacent free hydroxyl group, might afford an interesting opportunity for studying the effect of methylating reagents when applied to carbohydrates or glucosides containing the equally labile pyranose ring.

The following synthesis suggested itself (Bz = Benzoyl)



V VI VII

Six-membered 1,3-benzylidene glycerol[13c] yields on benzoylation a pure, crystalline β-benzoate, V, which readily undergoes hydrolysis of its acetal ring under the influence of a trace of acid to yield a glycerol monobenzoate, VI. This should condense with acetone to give a six-membered acetone glycerol benzoate whose ketal ring is considered sufficiently stable toward alkali to withstand the alkaline hydrolysis of the benzoyl group to yield the desired compound, VII.

In carrying out the above scheme, the supposed glycerol β-benzoate was readily obtained, but in accordance with the advice given by Fischer that monoacyl glycerol derivatives intended for subsequent synthesis should not

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[22] Purdie and Irvine, *J. Chem. Soc.*, **83**, 1021 (1903).

[23] Haworth, *ibid.*, **107**, 8 (1915).

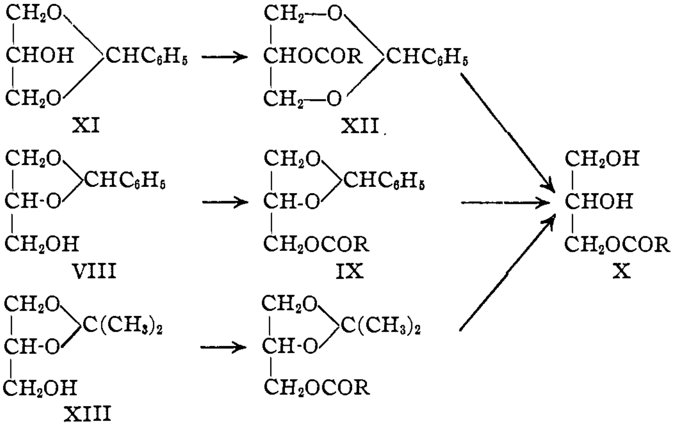
[24] (a) Fischer, Bergmann and Bärwind, *Ber.*, **53**, 1589 (1920); (b) Irvine, Macdonald and Soutar, *J. Chem. Soc.*, **107**, 337 (1915).

[25] (a) Böeseken and Hermans, *Ber.*, **55**, 3758 (1922); (b) Fischer, Taube and Baer, *ibid.*, **60**, 482 (1927); (c) Böeseken, Schaefer and Hermans, *Rec. trav. chim.*, **41**, 722 (1922).

be distilled,[26] no criterion of its purity could be obtained since it would not crystallize. This same compound was recently prepared[14] in an impure, non-crystallizable state by a different method, and was characterized by converting it to the crystalline di-*p*-nitrobenzoate, which melted at 152–152.5°. A sample of the authors' supposed glycerol β-benzoate was *p*-nitrobenzoylated according to the procedure described, and in place of the expected glycerol β-benzoate-α,α'-di-*p*-nitrobenzoate (m. p. 152–152.5°), it yielded instead a *p*-nitrobenzoate melting at 115°, mixed with a small amount of a product with a slightly higher somewhat indefinite melting point. These products were undoubtedly glycerol α-benzoate-β-*p*-nitrobenzoate and glycerol α-benzoate-α,β-di-*p*-nitrobenzoate, melting at 115 and 123°, respectively, as previously recorded by Bergmann, Brand and Dreyer.[6]

It would thus appear that during the hydrolysis of V under *acid* conditions a migration of the *beta*-benzoyl group had taken place, since non-acid media were used in the preparation of V and subsequent *p*-nitrobenzoylation of VI. This tendency of an acyl group to migrate during acid hydrolysis is analogous to that of the change in ring structure of the glycerol cyclic acetal ring itself, brought about under the influence of a trace of dry hydrogen chloride.[13c,d] The solid, crystalline six-membered acetals are in this way converted into an equilibrium mixture of the five- and six-membered isomers.

This wandering of an acyl (benzoyl) group during acid hydrolysis of the cyclic acetal ring was further confirmed in a more rigorous manner, as indicated below



Each of the structurally isomeric benzylidene glycerols VIII and XI was converted under non-acid conditions into a suitable ester of Types IX and XII, respectively. The acetal ring of each was then carefully hydrolyzed

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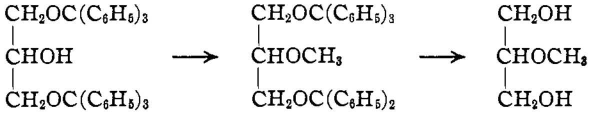
[26] Fischer, *Ber.*, **53**, 1613 (1920).

so as to leave the newly introduced acyl group intact, resulting in a glycerol mono-ester. Both isomers yielded the same glycerol α-ester, X, indicating that a migration of the β-acyl group had taken place between stages XII and X. The identity of the glycerol α-ester was further confirmed by its synthesis from acetone glycerol, XIII, as indicated.

Two parallel sets of experiments were carried out, where R was *p*-nitrophenyl and *p*-bromophenyl, respectively, in order to ensure the presence of crystalline compounds and concomitant strict parallelism in regard to homogeneity at each stage; the benzylidene acetal was chosen on account of its ready ease of hydrolysis. In each case the migration of the acyl group was observed.

Additional proof of the structure of glycerol α-*p*-nitrobenzoate is afforded by its synthesis[27] from α-sodium glyceroxide and *p*-nitrobenzoyl chloride, as well as from the oxidation of the *p*-nitrobenzoate of allyl alcohol. The recent isolation[28] of glycerol β-*p*-nitrobenzoate with a melting point (121°) fourteen degrees higher than its α-isomer should prevent any confusion in the identification of the two isomers. The structure of the intermediate compound, XIV, through which glycerol β-*p*-nitrobenzoate was obtained, has been linked up with the authors' investigations of glycerol β-derivatives by the following series of reactions



$$\begin{array}{lclcl} CH_2OC(C_6H_5)_3 & & CH_2OC(C_6H_5)_3 & & CH_2OH \\ | & & | & & | \\ CHOH & \longrightarrow & CHOCH_3 & \longrightarrow & CHOCH_3 \\ | & & | & & | \\ CH_2OC(C_6H_5)_3 & & CH_2OC(C_6H_5)_2 & & CH_2OH \\ \text{XIV} & & \text{XV} & & \end{array}$$

On methylation of glycerol α,α′-ditrityl ether, XIV, a crystalline glycerol α,α′-ditrityl-β-methyl ether, XV, was obtained, from which the two trityl groups were readily removed by hydrobromic acid at 0°, yielding liquid glycerol β-methyl ether. The latter compound was then definitely identified by the method described in a previous communication.[29]

The above proof of the migration of β-acyl groups in glycerol, as well as that relating to the structure of the cyclic acetals themselves,[13c,d,24b] is based on the non-migration of the *ether*-linked methyl radical. Although extensive studies have been made on the wandering of alkyl and aryl radicals from *carbon* to *carbon* in the pinacolin transformation, and other similar cases[30] are known, the ether-linked alkyl groups seem to possess a very remarkable degree of stability and lack of tendency toward migration.[31] An excellent example of such inertness is afforded by the very recent ob-

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[27] Fairbourne and Foster, *J. Chem. Soc.*, **127**, 2759 (1925); **128**, 3146 (1926).

[28] Helferich and Sieber, *Z. physiol. Chem.*, **175**, 311 (1928).

[29] Hibbert, Whelen and Carter, This Journal, **51**, 302 (1929).

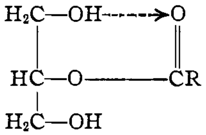
[30] Levy, *Bull. soc. chim.*, **33**, 1655 (1923); see also Cohen, "Organic Chemistry," Part II, Edward Arnold and Co., London, **1924**, p. 377.

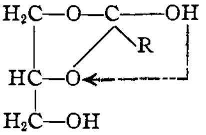
[31] Hirst and Smith, *J. Chem. Soc.*, **1928**, 3149.

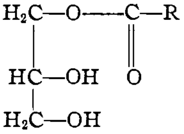
servation in this Laboratory[32] that the vinyl ether of glycol, $CH_2{=}CHOCH_2CH_2OH$, under the influence of a trace of hydrogen ion undergoes a molecular rearrangement with explosive violence, to form ethylidene glycol, the change involving a migration of the hydroxyl hydrogen atom. On the other hand, the corresponding vinyl methyl ether is quite stable under both acid and alkaline conditions.[33]

Mechanism of the Change Involved in the Migration of Acyl Groups

If the spatial configuration and nature of the polarities of the various groupings present in a glycerol β-derivative of Type XVI be considered, it is reasonable to assume that the strongly negative carbonyl group must have a strong affinity for the hydrogen atom of the α-hydroxyl group, resulting in the formation, under the catalytic influence of hydrogen ion, of the intermediate, unstable, five-membered cyclic acetal ring, XVII, postulated by Fischer.[8]


XVI

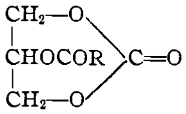

XVII


XVIII

This can then undergo ring scission, and with accompanying migration of the hydrogen atom in question, yield the α-derivative, XVIII. The *cause* of the "tendency toward migration" would seem to be the fact that the energy relations in glycerol derivatives seem best satisfied when the *primary* alcoholic groups are interacting. In agreement with this idea the ready formation of α,α′-derivatives from glycerol α-derivatives, such as the chlorohydrins, trityl ethers, sodium glyceroxides and others may be noted. If this theory be correct, then the more positive the substituent, **R**, the less should be the tendency toward migration. Thus the β-trichloro-acetyl group might be expected to wander readily; the β-trimethylacetyl group only with difficulty or not at all.[34]

[32] Hill, This Journal, 50, 2725 (1928).

[33] It is proposed, having in mind the recent work of Haworth[19] on the sugar carbonates, to attempt the synthesis of a compound of the type shown. The ring of such a compound undergoes scission by the action of alkalies, and it will be of interest to ascertain if, under these alkaline conditions, migration of the acyl group from the β- to the α-position takes place.



[34] The possibility of isolating the intermediate compound, XVII, is at present under investigation in these Laboratories. Thus the condensation of methyl formate with glycerol might be expected to yield a stable derivative with the same ring structure as shown in Formula XVII (where R represents hydrogen). Hydrolysis of the methyl group should then lead to ring scission with simultaneous formation of glycerol α-monoformate. On the other hand, condensation of glycerol with carbonyl chloride, followed by catalytic reduction of the carbonyl group to a secondary alcohol, would

Conclusion

The experimental evidence submitted clearly indicates that in any operation where the acyl esters of tri- or poly-hydroxy compounds are subjected to acid conditions, great care is necessary in drawing any conclusions as to the constitution of the resulting compounds. It is equally true that conclusions regarding the structure of polysaccharides and carbohydrates drawn from a consideration of the structure of their acylated derivatives must also be regarded with suspicion. If, in addition to this, the remarkable ease of change in such ring structures is recalled, it is evident that great care is necessary in drawing conclusions from either acylation or methylation experiments, especially when there is any possibility of the latter having been carried out in the presence of a slight hydrogen-ion concentration, as advocated by certain workers.[35]

Experimental Part

The first two reactions described below for the attempted synthesis of 1,3-isopropylidene glycerol (2,2-dimethyl-5-*m*-dioxanol) follow the procedure adopted in a former investigation of the benzylidene glycerols,[13c] except for some slight modifications which considerably increase the yields.

Condensation of Benzaldehyde with Glycerol.—One hundred g. of benzaldehyde and 88.5 g. of glycerol (1% excess over the theoretical amount) were placed in a 300-cc. Claisen distillation flask and five drops of concd. hydrochloric acid added. The mixture was then heated to 85–90° at 60–70 mm., that is, sufficiently high to allow the water produced in the condensation to distil off with a minimum loss of unchanged benzaldehyde. In twenty minutes the reaction was complete, as evidenced by the non-separation of two layers when the flask was cooled to 10°. The condensation product was diluted with half its volume of ether and then well shaken with 800 cc. of a 1% solution of potassium carbonate to remove the acid catalyst and any remaining glycerol. The ether solution, without further washing, was dried over fused potassium carbonate and the ether removed by gentle heating under diminished pressure, leaving a mixture of the isomeric 1,2- and 1,3-benzylidene glycerols as a slightly viscous, yellowish oil; yield, 150.5 g. (87%). A solution (saturated at 30°) of this oil in a mixture of ligroin (b. p. 80–90°) and benzene in the proportion of 4:3, deposited the 1,3-isomer as white, fine, silky needles which acted much like wet absorbent cotton when being removed from the flask for filtration. The oily 1,2-benzylidene glycerol (2-phenyl-1,3-dioxolane-4-carbinol) remains dissolved in the mother liquor. The 1,3-benzylidene glycerol (2-phenyl-5-*m*-dioxanol) after recrystallization from ether at −10° melted at 83°, in agreement with that of previous preparations.

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yield Compound XVII (where R represents hydrogen) directly, which would presumably then undergo a similar transformation to glycerol α-monoformate under the influence of an acid. A third, more direct, method is based on the observation by Tanasescu [*Bull. Soc. stiinte cluj*, **2**, 369 (1925)] that *o*-nitrobenzylidene gylcol undergoes a re-arrangement in direct sunlight, to 2-*o*-nitrosophenyl-2-hydroxy-1,3-dioxolane, which contains the same type of configuration as Compound XVII. Preliminary experiments with the corresponding glycerol derivatives are in progress.

[35] Haworth, "Constitution of the Sugars," Edward Arnold and Co., London, **1929**, p. 55.

Preparation of 1,3-Benzylidene Glycerol 2-Benzoate (2-Phenyl-5-*m*-dioxanol Benzoate).—Twenty g. of crystalline 1,3-benzylidene glycerol was dissolved in 25 g. of dry pyridine and a solution of 18 g. of benzoyl chloride in 15 g. of dry pyridine added, with constant stirring. The heat of reaction was slowly allowed to dissipate, after which the mixture stood for forty-eight hours at 18°. The semi-liquid product was poured into one liter of cold water, causing the separation of a mass of crystalline granules which were washed with water and dried at 60° under reduced pressure. Recrystallization from 300 cc. of a saturated, boiling ether solution yielded the pure benzoate as large, colorless, prismatic needles melting at 103°. Evaporation of the mother liquor to 100 cc. and cooling to −10° yielded a second crop with m. p. 99–100°. Total yield, 29 g. (93%).

Hydrolysis of 1,3-Benzylidene Glycerol 2-Benzoate to Glycerol Monobenzoate.—Twenty g. of the benzoate was allowed to simmer in an open beaker at 80° for thirty minutes with 200 cc. of a 50% aqueous solution of ethyl alcohol containing 0.5 cc. of concd. hydrochloric acid. Benzaldehyde was freely evolved. After careful neutralization with 10% potassium carbonate, the alcohol, water and remaining benzaldehyde were removed by heating under diminished pressure and the residue was extracted from the inorganic salts with 150 cc. of ether. Drying over calcium chloride, followed by removal of the solvent, left 8 g. of a slightly brown, viscous oil which could not be induced to crystallize; yield, 60%. It was redistilled for the following experiments.

Identification of the Supposed Glycerol β-Benzoate.—One g. of the distilled oil, dissolved in 5 g. of dry pyridine, was added to a solution of 1.9 g. (two equivalents) of *p*-nitrobenzoyl chloride in 12 g. of dry pyridine. After standing for twenty-four hours at 18° the reaction mixture was poured into 400 cc. of cold water, which caused the separation of a gummy, yellowish mass. Upon vigorous stirring with fresh quantities of water, the product slowly became almost solid and was taken up in 50 cc. of chloroform, washed with cold, saturated potassium bisulfate and sodium bicarbonate solutions, then dried over fused potassium carbonate. Upon dilution of the chloroform solution with petroleum ether until it was cloudy at room temperature, then cooling slowly to −10°, a few small, white, nodular aggregates with indefinite m. p. 119–121° separated, followed by a deposit of straw-colored clusters of microscopic needles melting sharply at 115°. The amount of the higher-melting compound did not permit of further recrystallization, but its melting point corresponds closely to that of glycerol α-benzoate-α′,β-di-*p*-nitrobenzoate (123°), while the lower-melting compound was evidently glycerol α-benzoate-β-*p*-nitrobenzoate.[6] Analyses were not made.

***p*-Nitrobenzoylation of 1,3-Benzylidene Glycerol.**—Two g. of 1,3-benzylidene glycerol was dissolved in 5 g. of dry pyridine and added to a solution of 2 g. of *p*-nitrobenzoyl chloride (slightly less than one equivalent, to avoid possible formation of *p*-nitrobenzoic anhydride)[36] in 10 g. of dry pyridine. The mixture was allowed to stand for fifteen hours at 30° and then poured into 400 cc. of cold water. The flocculent, pale yellow material which separated out on stirring was taken up in 50 cc. of chloroform, the solution washed with cold saturated potassium bisulfate and sodium bicarbonate solutions, and dried over fused potassium carbonate. Removal of the solvent left a crystalline mass which on recrystallization from ethyl acetate by cooling to −10° yielded 2 g. of straw-colored clusters of prisms. This compound, 1,3-benzylidene glycerol-2-*p*-nitrobenzoate (2-phenyl-5-*m*-dioxanol-*p*-nitrobenzoate), melts sharply at 156° and is apparently a new derivative. It is soluble in most organic solvents except alcohol, petroleum ether and ligroin and is insoluble in water.

Anal. Calcd. for $C_{17}H_{15}O_6N$: N, 4.25. Found (Micro-Dumas): 4.12, 4.38.

***p*-Nitrobenzoylation of 1,2-Benzylidene Glycerol.**—Thirteen and one-half g. of the

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[36] See in this connection, Stather, *Ber.*, **57**, 1392 (1924).

1,2-benzylidene glycerol recovered from the benzene–ligroin mother liquor in the condensation of benzaldehyde and glycerol previously described, and which had been distilled within the range prescribed in a previous communication,[13c] was treated with 13.3 g. (slightly less than one equivalent) of *p*-nitrobenzoyl chloride in exactly the same manner as its 1,3-isomer. Upon cooling the ethyl acetate solution of the crude product, 3 g. of the isomer melting at 156° was obtained, identical with that obtained in the previous experiment.[37] The solvent was removed from the mother liquor under reduced pressure and replaced by an acetone–alcohol mixture of approximately equal parts by volume which, by cooling to −10° and slowly adding water, a few drops at a time with shaking, yielded 8.3 g. of yellowish crystals with a very indefinite m. p. of 80–90°. A small sample, recrystallized from acetone, gave only a minute quantity of white nodules[38] melting at 190–191°. The purification of the remaining product was effected by extraction with benzene, in which this high-melting impurity was found to be relatively insoluble. The extract, upon dilution with petroleum ether to the point of cloudiness at 0°, gave on long standing at −15° almost colorless crystals melting indefinitely between 84 and 90°. By further recrystallizations from ethyl acetate–petroleum ether at −15°, 5 g. of straw-colored needles melting at 90–91° was eventually obtained. This compound, 1,2-benzylidene glycerol-3-*p*-nitrobenzoate (2-phenyl-1,3-dioxolane-4-carbinol-*p*-nitrobenzoate), is apparently not recorded in the literature. The solubilities of this compound are similar to those of its isomer.

Anal. Calcd. for $C_{17}H_{15}O_6N$: N, 4.25. Found (Micro-Dumas): 4.28, 4.42.

Acid Hydrolysis of the Isomeric Benzylidene Glycerol *p*-Nitrobenzoates.—One g. of each of the isomers was dissolved in 10 cc. of ethyl alcohol, then diluted with an equal volume of water to which 0.5 g. of concd. hydrochloric acid had been added. The milky solution was allowed to simmer in an open Erlenmeyer flask for twenty minutes, during which time benzaldehyde was continually evolved. The solution was then evaporated almost to dryness under reduced pressure, neutralized exactly with 10% potassium hydroxide and the evaporation carried to dryness under 10-mm. pressure. The sirupy residue was separated from inorganic salts by extraction with 20 cc. of ethyl acetate, the solution after filtration diluted with petroleum ether to the point of cloudiness at 0° and then further cooled to −15°. Unless considerable care was exercised, the compound, despite its m. p. of 107°, tended to come out as an oil even at −15°. After a seeding crystal had once been obtained, beautiful crystals melting at 106.5° could be grown readily. In each case, the product proved to be identical with a sample of glycerol α-*p*-nitrobenzoate prepared from acetone-glycerol-*p*-nitrobenzoate following the procedure given by Fischer.[24a] A mixed melting-point determination of all three melted at 106–106.5°. Since in both cases an α-derivative resulted, a migration of the β-acyl group during the hydrolysis of 1,3-benzylidene glycerol-2-*p*-nitrobenzoate is indicated.

The various *p-bromo*benzoates were prepared by methods exactly analogous to those just described for the *p-nitro*benzoates. These compounds all possessed a considerable tendency to separate from solvents as oils until seeding crystals had been prepared, when beautifully crystalline, colorless

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[37] This indicated that the original distilled compound contained at least 12% of the isomeric 1,3-benzylidene glycerol held in solution. This same impracticability of completely separating the two isomers by distillation was noted in previous preparations[13c] of their methyl ethers.

[38] This compound is probably *p*-nitrobenzoic anhydride, although the possibility of the formation of glycerol tri-*p*-nitrobenzoate (m. p. 192°) from traces of glycerol in the distilled original compound is not excluded.

compounds could usually be obtained, all of which are apparently new derivatives.

1,3-Benzylidene-glycerol-2-*p*-bromobenzoate (2-phenyl-5-*m*-dioxanol-*p*-bromobenzoate) was prepared from 2 g. of 1,3-benzylidene glycerol and a pyridine solution of 2.5 g. of *p*-bromobenzoyl chloride, in 80% yield. Recrystallization from 20 cc. of warm ethyl acetate gave colorless needles melting at 146°, soluble in chloroform, ether, benzene; insoluble in petroleum ether, ligroin, alcohol and water.

Anal. Subs., 9.150, 9.798: AgBr, 4.763, 5.166. Calcd. for $C_{17}H_{15}O_4Br$: Br, 22.01. Found: 22.15, 22.44.

1,2-Benzylidene-glycerol-3-*p*-bromobenzoate (2-phenyl-1,3-dioxolane-4-carbinol-*p*-bromobenzoate), isomeric with the above, was prepared from 1.7 g. of the impure, liquid 1,2-benzylidene glycerol and a pyridine solution of 2 g. of *p*-bromobenzoyl chloride. As expected, the product was contaminated with its higher-melting isomer. Successive recrystallizations from (a) hot methyl alcohol and (b) ethyl acetate–petroleum ether (1:2) finally yielded large, colorless crystals melting at 72°, which had a peculiar, greasy consistency when cut. These were soluble in most organic solvents except cold alcohol, petroleum ether and ligroin; insoluble in water.

Anal. Subs., 9.087, 8.920: AgBr, 4.695, 4.571. Calcd. for $C_{17}H_{15}O_4Br$: Br, 22.01. Found: 21.99, 21.81.

Acetone-glycerol-α-*p*-bromobenzoate (2,2-dimethyl-1,3-dioxolane-4-carbinol-*p*-bromobenzoate) was prepared from 2.5 g. of acetone-glycerol and 4.2 g. of *p*-bromobenzoyl chloride in pyridine solution. The colorless oil remaining after evaporation of the solvent from the chloroform solution of the reaction product was heated to 100° for a few minutes under 0.5 mm. to remove the last traces of solvent. After standing at 18° for three days, two small crystals had formed. Subsequent recrystallization from warm petroleum ether of the solid mass obtained with the aid of these seeding crystals yielded small, colorless needles melting at 39–40°, soluble in most organic solvents except cold petroleum ether and low-boiling ligroin, and very prone to separate as an oil during crystallization; yield, 70%.

Anal. Subs., 8.551, 8.792: AgBr, 5.06 6,5.228. Calcd. for $C_{13}H_{15}O_4Br$: Br, 25.36. Found: 25.21, 25.30.

Acid hydrolysis of small samples of each of the three compounds last described was carried out in exactly the same manner as with the corresponding *p*-nitrobenzoates, and yielded three identical specimens of glycerol-α-*p*-bromobenzoate, as shown by a mixed-melting point of 68–69°. Since an α-derivative resulted in each case, a migration of a β-acyl group is again indicated during the hydrolysis of 1,3-benzylidene-glycerol-2-*p*-bromobenzoate.

Glycerol-α-*p*-bromobenzoate, apparently not hitherto described in the literature, was obtained on recrystallization from warm benzene as small clusters of transparent needles, m. p. 70°. Crystallization is only induced with difficulty, most readily by scratching a small sample of the oily form immersed in petroleum ether. It is soluble in most organic solvents except cold ether, benzene, petroleum ether and ligroin; insoluble in water.

Anal. Subs., 8.994, 8.435: AgBr, 5.983, 5.701. Calcd. for $C_{10}H_{11}O_4Br$: Br, 29.02. Found: 28.31, 28.77.

Preparation of Glycerol-α,α′-ditrityl-β-methyl Ether. XV.—Fifty g. of glycerol-α,α′-ditrityl ether, XIV, prepared by the method of Helferich and Sieber[28] (m. p.

175–176°; yield, 86%) was dissolved in a mixture of 80 cc. of benzene and 50 g. of methyl iodide and methylated in the usual manner by the slow addition, with constant stirring, of 40 g. of dry silver oxide during a period of three hours, during which the temperature was raised to 50°. The heating and stirring were continued for a further period of eight hours. The reaction mixture was filtered with suction and to the filtrate were added two warm benzene extractions of the silver oxide–silver chloride residue. The total filtrate was then evaporated under reduced pressure to a volume of 75 cc. and on cooling 38 g. of a white amorphous powder separated. Further evaporation and cooling of the mother liquor gave 11.7 g. of the same material. Recrystallization from hot ethyl acetate yielded large, colorless crystals of glycerol-α,α'-ditrityl-β-methyl ether, melting sharply at 158.5°. This compound, soluble in ethyl acetate, benzene, chloroform and ethylene bromide, insoluble in ether, ligroin and water, has not been previously described in the literature; yield, 49.7 g. (97%).

Hydrolysis of Glycerol-α,α'-ditrityl-β-methyl Ether, XV, to Glycerol-β-methyl Ether.—Forty-three g. of glycerol-α,α'-ditrityl-β-methyl ether was dissolved in 100 cc. of an 80% solution of glacial acetic acid in benzene and cooled to 0°. Slow addition of 30 cc. of a cold, saturated solution of hydrogen bromide in glacial acetic acid caused immediate precipitation of trityl bromide, which was filtered off and sucked as dry as possible. The filtrate was neutralized with dry potassium carbonate and heated under reduced pressure to remove the bulk of the benzene and the water formed in the neutralization. The extremely bulky, frothy suspension of potassium acetate was extracted three times with a total of 150 cc. of acetone, which was then dried over calcium chloride and evaporated to a volume of 25 cc., resulting in the deposition of 3.5 g. of triphenylcarbinol (formed by hydrolysis of trityl bromide). After filtration, the acetone solution of the glycerol β-methyl ether was distilled under reduced pressure. The acetone readily evaporated and as the bath temperature was gradually raised to 150°, 1.5 g. of a colorless liquid was collected between 118–140° at 13 mm., leaving a residue of 1.5 g. of solid triphenylcarbinol in the flask. The wide range of temperature (glycerol-β-methyl ether has a b. p. of 123° at 13 mm.) is explained by the fact that considerable superheating was necessary to distil the ether from the unavoidable residue of solid triphenylcarbinol; yield, 19%.[39] For the positive identification[29] of the distillate, a portion was condensed with *p*-nitrobenzaldehyde and yielded 0.9 g. of 1,3-*p*-nitrobenzylidene glycerol-2-methyl ether (2-*p*-nitrophenyl-5-*m*-dioxanol methyl ether), m. p. 138°, with no trace of the isomeric α-ether derivative.

Summary

1. A review of the literature shows that the β-acyl group in glycerol derivatives readily undergoes migration to the α-position.
2. The mechanism of such migration is apparently that first proposed by E. Fischer, namely, the intermediate formation of an unstable cyclic acetal. Three methods are suggested for the synthesis of the latter product.
3. There does not appear to be any reliable evidence in the literature indicating the migration of a methyl or other alkyl group, in the case of glycerol and other alkyl ethers.
4. Experimental evidence is given proving that in the hydrolysis of various β-acyl derivatives of glycerol cyclic acetals, a migration of the acyl

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[39] This experiment is being repeated in an effort to perfect a more satisfactory procedure for the isolation of the glycerol β-methyl ether from the strongly acid hydrolysis mixture.

radical from the β- to the α-position takes place, giving as final product an α-glycerol ester.

5. The data submitted provide further convincing evidence as to the unreliability of deductions relating to the structure of glycerol, carbohydrates and polysaccharides based on conclusions drawn from experiments on the hydrolysis of their acyl derivatives.

MONTREAL, CANADA

NEW BOOKS

The Origins and the Growth of Chemical Science. BY J. E. MARSH, M.A., F.R.S., Fellow of Merton College. John Murray, 50A Albemarle Street, London, W. 1, England, 1929. x + 161 pp. Illustrated. 12.5 × 19 cm. Price, 5 shillings, net.

The history of chemistry, from the point of view of the author of this small but compact and well-filled book, is not a mere record of events. The events must be interpreted, correlated, put in order—for history itself is also a science and its data, however interesting they may be in themselves as data, still submit to a scientific treatment. Marsh interprets the history of chemistry as the history of two principal ideas—of the idea of salt formation, first clearly articulate with Boyle and even now presenting problems and influencing research, and of the idea of the fixation of gases, with the early work on which the names of Black, Priestley, Cavendish, Scheele and Lavoisier are associated.

In his preface Marsh says that "there was no science of Chemistry before the seventeenth century, but the art of Chemistry had progressed through long ages," etc. His first chapter is devoted to the "fire theories" of the ancient philosophers and of the alchemists and phlogistonists. Now it seems to the reviewer that, where we have theories, there we have data interpreted—and have science. Primitive chemical theories were chemical theories after all, not wilfully fantastic perversions of thought. We wish to know how they came to be and the reasons which led to their abandonment. Marsh points out that the phlogiston doctrine, which was the last stand of the ancient fire theory, was put forward in 1702 but "did not attract much attention from chemists in Stahl's lifetime or for some forty years after his death in 1734. The theory was then taken up by Priestley, by Scheele and by Cavendish, to explain the nature of the gases which they discovered." But the quantitative phenomena connected with the fixation of gases showed its inadequacy and created the necessity for the interpretations of Lavoisier.

The book contains a number of things such, for example, as the mention of Higgins's suggestions in 1789 relative to multiple proportions, which show that the author has a scholarly knowledge of his subject. One chapter details briefly the essential facts about the discovery of each of the