[COMMUNICATION FROM THE DEPARTMENT OF INDUSTRIAL AND CELLULOSE CHEMISTRY, PULP AND PAPER RESEARCH INSTITUTE, McGILL UNIVERSITY]

MECHANISM OF ORGANIC REACTIONS. II. THE "NON-EXISTENCE" OF A MIGRATORY METHYL GROUP IN THE CONVERSION OF GLYCEROL-DI-CHLOROHYDRIN INTO GLYCEROL MONOMETHYL ETHER

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The structure of carbohydrates and polysaccharides rests primarily on the data obtained by preliminary methylation of the material in question, followed by hydrolysis and identification of the resulting methylated product. The assumption has been made throughout that methylation processes are unaccompanied by (a) ring scission or ring shift, or (b) migration of one or more methyl groups during the methylation process.[2]

It has long been recognized that certain groups are particularly prone to migrate as, for example, in the case of acyl groups from oxygen to nitrogen[3] and more recently in connection with the wandering of this same type of group in the synthesis or analysis of glycerol esters.[4]

On the other hand, there are only one or two isolated cases known which appear to indicate the possibility of the migration of a methyl group, the most striking of which is that indicated in the conversion of glycerol-α,α'-di-chlorohydrin into the α-monomethyl ether of glycerol, as reported by Gilchrist and Purves.[5] These authors found that glycerol-α,α'-di-chlorohydrin (prepared by the action of hydrochloric acid on epichlorohydrin)[6] on methylation and subsequent hydrolysis yielded glycerol-α-monomethyl-ether and not the β-isomer as was to be expected. In other words, either a wandering of a methyl group had occurred, or the α,α'-di-chlorohydrin used was impure. No experimental details are given as to the actual method of isolating the glycerol-α,α'-di-chlorohydrin used by them.

They suggested the possibility of an impure starting material, although the homogeneous character and identity of the glycerol-α,α'-di-chloro-

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[2] Haworth, "Constitution of Sugars," London, **1929**, p. 55.

[3] Raiford and co-workers, THIS JOURNAL, **46**, 430, 2246, 2305 (1924).

[4] For a review see Part I of this series, *ibid.*, **51**, 1601 (1929); Fairbourne and Cowdrey (Ref. 12).

[5] Gilchrist and Purves, *J. Chem. Soc.*, **127**, 2738 (1925). For a review of such migrations compare *J. Chem. Soc.*, 129 (1929).

[6] Smith, *Z. physik. Chem.*, **92**, 717 (1918).

hydrin thus prepared had been emphasized by Smith.[6] Furthermore, the experiments of Conant and Quayle,[7] who prepared the *p*-nitrobenzoate from Smith's product in excellent yield, appeared to disprove this idea, since this was found to have properties markedly different from those of the isomeric derivative prepared from glycerol-α,α'-di-chlorohydrin. In view of this, the evidence offered by Gilchrist and Purves[5] appeared to be so unsatisfactory that considering the importance of the subject it seemed highly desirable to repeat their work taking the greatest possible precautions to utilize materials only after their identity had been definitely established.

It has been found that when pure glycerol-α,α'-di-chlorohydrin is methylated, then converted into the acetate, and the latter hydrolyzed, the expected glycerol-β-methyl ether is obtained, there being no evidence whatever of any abnormality in the reaction implying a migration of the methyl group.

The glycerol-α,α'-di-chlorohydrin employed boiled constantly at 174–175° and on methylation with silver oxide and methyl iodide yielded a dichloroglycerol methyl ether from which the unchanged glycerol-di-chlorohydrin was readily removed by washing with hot water. This α,α'-dichloroglycerol-β-methyl ether boiled constantly at 156–159° and so far as could be judged from its physical properties represented a homogeneous chemical substance.

This material on heating with an aqueous alcoholic solution of potassium acetate under pressure was converted into the corresponding acetate. The latter on hydrolysis with a 3% aqueous alcoholic solution of hydrochloric acid[8] yielded a glycerol-monomethyl ether (b. p. 123–125° (13 mm.); $d_4^{17} = 1.1321$); yield, 33%. The identity of this was established not only by its sharp boiling point and density on the one hand[9] but also by its conversion into *p*-nitrobenzylidene-glycerol-β-methyl ether and into the corresponding di-phenyl carbamate on the other.[9]

This synthesis has been repeated several times using glycerol-α,α'-di-chlorohydrin from various sources[10] and it was found that in all other cases the material used was an impure product consisting of a mixture of the isomeric glycerol-α,α'- and α,β-di-chlorohydrins.

It has been shown by Fairbourne and Foster[11] and more recently by Fairbourne and Cowdrey[12] that the structures assigned to many β-substituted monoglycerides are of doubtful value. The latter investigators have prepared a number of "α,β-" disubstituted glycerols from the corre-

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[7] Conant and Quayle, THIS JOURNAL, **45**, 2771 (1923).

[8] Gilchrist and Purves used alkali as the saponifying agent.

[9] Hibbert, Whelen and Carter, THIS JOURNAL, **51**, 302 (1929).

[10] European supply houses.

[11] Fairbourne and Foster, *J. Chem. Soc.*, **128**, 3148 (1926).

[12] Fairbourne and Cowdrey, *ibid.*, 129 (1929).

sponding chlorohydrins and found them to be identical with their supposedly "α,α'-" isomerides. It is thus evident that conclusions drawn from results obtained by employing chlorohydrins for such syntheses must be regarded with grave suspicions in so far as they relate to questions of structure. Moreover, it is to be observed from the results of these investigators that migration often takes place when the hydroxyl group of the di-chlorohydrin is esterified by conversion into an acyl group followed by subsequent substitution of the halogen.

In the present investigation it is shown that a primary replacement of the hydrogen in the hydroxyl group of the glycerol di-chlorohydrin by an alkyl radical does not involve any migration during the subsequent hydrolysis and thus indicates that acyl groups are directly concerned. An earlier hypothesis put forward by Gabriel and Ohle[13] suggested that many of these conversions may be due to the formation of propylene oxide through loss of hydrogen chloride either during the reaction, or previously, with the production of an impure starting material, but as pointed out by Fairbourne and Cowdrey,[12] this in any event is evidently only applicable to specific cases.

In the writers' opinion the question of migration is intimately associated with the presence in the β-position of an acyl radical containing a reactive carbonyl group.

Under these conditions, as first pointed out by Fischer,[14] there exists the possibility of the ready formation of an unstable, intermediate, cyclic ester (Fischer's ortho-ester), which in undergoing spontaneous decomposition permits of a transfer of the acyl group in question.

The four cases reported in the literature involving a migration from the α- to the β-positions of either an alkyl or an acyl radical would seem to call for a reinvestigation in the light of the present results.

It is evident from the above, that conclusions with regard to structure based on the interconversion of glycerol halohydrins into monomethyl ethers may be accepted as involving no migration of the methyl group.

Experimental

Preparation of Glycerol-α,α'-di-chlorohydrin.—One hundred grams of epichlorohydrin (b. p. 117°) was treated with approximately 125 cc. of concentrated hydrochloric acid. The latter was added in small quantities, the mixture being shaken and cooled throughout the addition. After standing for several hours at room temperature, the reaction product separated into two layers. The mixture was neutralized by washing with sodium bicarbonate solution, at which stage the lower layer was separated, dried over anhydrous sodium sulfate, filtered and fractionated, yielding 110 g. of glycerol-α,α'-di-chlorohydrin boiling sharply at 174–175°.

Methylation of Glycerol-α,α'-di-chlorohydrin.—Fifty grams of glycerol-α,α'-dichlorohydrin was methylated in the usual manner, using 100 g. of silver oxide and 125 g.

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[13] Gabriel and Ohle, *Ber.*, **50**, 804 (1917).

[14] Fischer, *ibid.*, **53**, 1621 (1920).

of methyl iodide. The reaction mixture was extracted three times with ether, the ether removed and the remaining product freed from unchanged α,α'-glycerol-dichlorohydrin by shaking vigorously several times with hot water. After drying with anhydrous sodium sulfate, careful fractionation yielded 21.4 g. of glycerol-α,α'-di-chlorohydrin-β-methyl ether, b. p. 157–159°; $n_D^{17} = 1.4550$.

Anal. Subs., 4.988 mg.: CO_2, 6.072 mg.; H_2O, 2.548 mg. Calcd. for $C_4H_8OCl_2$: C, 33.56; H, 5.56. Found: C, 33.20; H, 5.71.

Hydrolysis of Glycerol-α,α'-di-chlorohydrin-β-methyl Ether.—The method used for replacement of the two chlorine atoms by hydroxyl groups was essentially that used by Gilchrist and Purves,[5] but was modified to the extent that the hydrolysis of the di-acetate was carried out in acid instead of alkaline solution, as it had been previously shown[16] that the presence of dilute mineral acids has no influence on the methyl group.

Twenty and four-tenths grams of glycerol-α,α'-di-chlorohydrin-β-methyl ether was heated in a sealed tube with 29 g. of crystalline potassium acetate, dissolved in 50 cc. of 75% aqueous ethyl alcohol, for sixteen hours at 115–130°. The potassium chloride formed was removed by filtration and the filtrate containing the di-acetate refluxed for one hour with 100 cc. of 75% ethyl alcohol containing 3% of hydrochloric acid. The reaction mixture was neutralized with lead carbonate, the solution filtered and concentrated to a small volume. At this point considerable solid material separated out on cooling; this was removed by filtration. The filtrate was further concentrated and then fractionated under reduced pressure, yielding a clear colorless liquid, b. p. 110° (4 mm.), which on redistillation yielded pure glycerol-β-methyl ether, b. p. 123–125° (13 mm.);[15] $d_4^{17} = 1.1321$; $n_D^{17} = 1.4485$; yield, 5.2 g., equal to 33% calculated on the glycerol-α,α'-di-chlorohydrin-β-methyl ether employed. The product was further identified by conversion into the *p*-nitrobenzylidene-glycerol-β-methyl ether[9] (m. p. 106°) as well as into the di-phenyl carbamate, m. p. 101°. Mixed melting point determinations of these compounds with known samples showed no lowering of the melting point. A mixed melting point of the di-phenyl carbamate, as obtained above, with a known sample of the di-phenyl carbamate of glycerol-α-methyl ether (m. p. 118°) melted indefinitely at 90°.

No trace whatever was found of the corresponding isomeric glycerol-α-methyl ether.

Preparation of Glycerol-α,β-di-chlorohydrin-α-methyl Ether.—Twenty-three grams of allyl methyl ether (b. p. 42–43°) in which had been dissolved a small crystal of iodine was treated with a slight excess of chlorine at 0°. The uncombined halogen was removed by bubbling dry air through the reaction mixture, the latter was thoroughly washed by shaking with water, the lower layer separated, dissolved in ether and dried over anhydrous sodium sulfate. Fractionation of this yielded 20.4 g. of glycerol-α,β-di-chlorohydrin-α'-methyl ether, b. p. 153–157°; $n_D^{17} = 1.4489$. During the distillation hydrogen chloride was formed in slight amount due to a small amount of secondary decomposition.

Anal. Subs., 5.471 mg.: CO_2, 6.669 mg.: H_2O, 2.735 mg. Calcd. for $C_4H_8OCl_2$: C, 33.56; H, 5.56. Found: C, 33.25; H, 5.59.

Hydrolysis of Glycerol-α,β-di-chlorohydrin-α-methyl Ether.—The replacement of the chlorine atoms by acetyl groups was a much more difficult operation than in the case of the corresponding glycerol-α,α'-di-chlorohydrin-β-methyl ether. In marked contrast to the behavior of the latter with potassium acetate in aqueous alcoholic solution, it was found that glycerol-α,β-di-chlorohydrin-α'-methyl ether yielded a large amount of unsaturated derivatives, a reaction apparently common to organic products

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[15] Hill, Whelen and Hibbert, THIS JOURNAL, **50**, 2235 (1928).

containing chlorine atoms attached to adjacent carbon atoms. Substitution of sodium formate for potassium acetate led to the same result. It was found, however, that the desired diacetate could be obtained (although in low yields) by heating 20.4 g. of glycerol-α,β-di-chlorohydrin-α′-methyl ether with 29 g. of fused potassium acetate and 30 cc. of glacial acetic acid under pressure at 165° for sixteen hours. The crude reaction product had a dark brown color. It was filtered from the solid material, the filtrate neutralized with solid potassium carbonate, again filtered and the filtrate concentrated under reduced pressure to a small volume. Further filtration and fractionation of the filtrate yielded 4.2 g. of a clear colorless liquid, b. p. 215–225°. Three grams of this material was hydrolyzed by refluxing for one hour with 25 cc. of 75% aqueous ethyl alcohol containing 3% of hydrochloric acid. After neutralization with lead carbonate, filtration and concentration, the residual oil on distillation yielded 1.2 g. of glycerol-α-methyl ether; b. p. 111–112° (13 mm.); $d_4^{17} = 1.1189$; $n_D^{17} = 1.4445$. Its identity as pure glycerol-α-methyl ether was further established by its conversion into the di-phenyl carbamate, m. p. 117° C.[9] A mixed melting point of this material with a known sample showed no lowering, while a mixed melting point with the di-phenyl carbamate of glycerol-β-methyl ether melted indefinitely at 93°.

Summary

1. Glycerol-α,α′-di-chlorohydrin on methylation and conversion of the α,α′-dichloro-β-methyl ether into the acetate, followed by saponification, yields only glycerol-β-methyl-ether.

2. Glycerol-α,β-di-chlorohydrin-α′-methyl ether on conversion into its acetate, followed by saponification, yields only glycerol-α-methyl ether.

3. Previous work in this field, pointing to the probability of the migration of a methyl radical in the conversion of glycerol-α,α′-di-chlorohydrin-β-methyl ether into the acetate and subsequent hydrolysis of the latter is based on the mistaken identity of the resulting product as glycerol-α-methyl ether.

4. The bearing of these results on the methylation of glycerol and carbohydrate derivatives is pointed out and the importance of the pure α- and β-glycerol methyl ethers as "type substances" further confirmed.

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NOTES

The Identification of Ortho-, Meta- and Para-Hydroxybenzoic Acids.—It was found necessary, recently, to isolate, purify and identify small amounts of *o*-, *m*- and *p*-hydroxybenzoic acids.

Lyman and Reid[1] have recommended the *p*-nitrobenzyl esters as suitable compounds by means of which these hydroxy acids can be identified. These investigators converted the acids into their sodium salts and heated these, dissolved in a mixture of water and alcohol, with *p*-nitrobenzyl bromide. We obtained unsatisfactory results by the use of this method since it was found that the esters, as soon as they are formed, react to some extent with *p*-nitrobenzyl bromide to form the *p*-nitrobenzyl

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[1] Lyman and Reid, THIS JOURNAL, **39**, 704 (1917).