STUDIES ON THE BROMINATION OF TETRA-ETHYL DICARBOXYGLUTACONATE AND REMARKS ON THE CONSTITUTION OF THE GLUTACONIC ACIDS.

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In the last two years the author published some papers dealing with studies on the derivatives of glutaconic acid.(1) The first experiment was the bromination of tetraethyl dicarboxyglutaconate, the object of which was, in the first place, to obtain tetraethyl α, β-dibromodicarboxyglutarate; and this theme was given by Prof. K. Matsubara. Since the expected result was not obtained, it was given up without further investigations, and another compound with a similar constitution, diethyl dicyanoglutaconate, was taken as the substance to be subjected to the action of bromine. What the so-called diethyl dicyanoglutaconate is, and how it is acted on by bromine, were already described in details.(2) In the meantime it seemed that some important results might be brought out by tracing the reaction between bromine and tetraethyl dicarboxyglutaconate. Experiments have been newly repeated, with the results described in the following pages.

Action of Bromine on Tetraethyl Dicarboxyglutaconate. When bromine was added to the ester in the proportion of $2\,Br : C_{15}H_{22}C_8$, and the mixture was well stirred, the colour of bromine almost disappeared after a moment and hydrogen bromide was generated at the same time. The reaction mass was diluted with ether, shaken with aqueous alkali, washed with water, dried, and evaporated in vacuo. An oily substance remained; but hydrogen bromide was again genarated.

The elimination of hydrogen bromide was completed through the following treatment. An ethereal solution of pyridine in an amount equimolecular to the ester was added to such of the reaction product of bromine and tetraethyl dicarboxyglutaconate. After standing for a night the ethereal solution was freed from pyridine hydrobromide by washing it with water, and further it was washed successively with dilute sulphuric acid, dilute alkali, and water. The solution was dehydrated and evaporated in vacuo over concentrated sulphuric acid, when a colourless oil was obtained which splitted off hydrogen bromide no more. 0.1858 And 0.1780 gr. of the substance gave respectively 0.0876 and 0.0843 gr. of AgBr. (Found: Br = 20.06; 20.15. $C_{15}H_{21}O_8Br$ requires Br = 19.54.%) In one experiment 29.8 gr. of the product was obtained from 24.2 gr. of $C_{15}H_{22}O_8$ and 11.7 gr. of bromine,

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(1) This journal, **2** (1927), 26; 236; 278; 305; **3** (1928), 102.

(2) This journal, **2** (1927), 26.

the theoretical yield calculated from the following equations being 30 gr. It is shown by these numbers that the product was formed according to the following equations:

$$C_{15}H_{22}O_8 + 2\,Br = C_{15}H_{22}O_8Br_2,$$
$$C_{15}H_{22}O_8Br_2 = C_{15}H_{21}O_8Br + HBr,$$
$$HBr + C_5H_5N = C_5H_5N.HBr.$$

The reaction resulted as if a substitution took place, but really it consisted of two processes of addition of 2 Br and elimination of HBr, because the calculated amount of bromine was consumed at once, and the elimination of hydrogen bromide was not complete unless the product was treatad with pyridine.

The intermediate product formed by addition of 2 Br to $C_{15}H_{22}O_8$, has, of course, the formula $C_{15}H_{22}O_8Br_2$ and the following constitution:

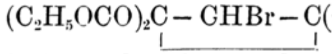
$$(C_2H_5OCO)_2CBr-CHBr-CH(COOC_2H_5)_2.$$

This addition product splits off a molecule of hydrogen bromide, and this dissociation is complete in the presence of pyridine which fixes the hydrogen bromide.

Hydrogen bromide may possibly be splitted in three ways, and the produced bromo-ester may have one of the following formulae:

$$\text{(I)}\quad (C_2H_5OCO)_2CBr-CH = C\,(COOC_2H_5)_2,$$
$$\text{(II)}\quad (C_2H_5OCO)_2C = CBr-CH\,(COOC_2H_5)_2,$$

(III)



$$\text{(III)}\quad (C_2H_5OCO)_2C-CHBr-C(COOC_2H_5)_2.$$

It is impossible for such a three-carbon ring as shown by formula (III) to be formed by elimination of hydrogen bromide, and this formula is excluded, if the result of saponification of the bromo-ester is further taken into account. The bromo-ester possesses no acid hydrogen, for it does not dissolve in alkali, and formula (II) is also improbable. The following experiment settles the question, indicating that the bromo-ester is most reasonably represented by formula (I).

When bromine was added to tetraethyl α-methyldicarboxyglutaconate $(C_2H_5OCO)_2C(CH_3)-CH=C(COOC_2H_5)_2$, in which the acid hydrogen is replaced by a methyl group, a part of bromine combined with the ester after a short time, the colour fading to some extent, but never completely even if the bromine was used in an amount much smaller than two atoms to one molecule of the ester, while the elimination of hydrogen bromide was not detected. This observation ascertained the existence of equilibrium in the following reversible reaction:

$$C_{16}H_{24}O_8 + 2\,Br \rightleftarrows C_{16}H_{24}O_8Br_2$$

In the ethereal solution this reaction is fixed. Thus, when the reaction mixture was dissolved in ether, shaken with an aqueous solution of sodium sulphite, washed with water, dried and evaporated in vacuo, the remaining colourless oil soon spitted bromine and became red. The addition of bromine to tetraethyl dicarboxyglutaconate is nearly complete, causing the elimination of hydrogen bromide, and that to a limited extent, while the action of bromine on tetraethyl α-methyldicarboxyglutaconate can proceed only incompletely, the elimination of hydrogen bromide being impossible here. In both cases the saturated compounds formed by the addition of bromine is in equilibrium with unsaturated compounds, in the former case the unsaturated bromo-ester $C_{15}H_{21}O_8Br$ being produced by a secondary change of the saturated addition product, while in the latter a part of the original uusaturated ester being left intact. This difference must be attributed to the presence of the acid hydrogen in the one, and the absence in the other. In other words, when hydrogen bromide is splitted from the saturated dibromo-ester, the acid hydrogen takes part in the formation of hydrogen bromide. Therefore, the unsaturated bromo-ester $C_{15}H_{21}C_8Br$ misses the acid hydrogen and must be the compound represented by fomula (I) which should be called tetraethyl α-bromodicarboxyglutaconate. The bromine atom remaining in the bromo-ester is situated in the γ-position of the original ester, tetraethyl dicarboxyglutaconate, but it may be designated as the α-substituent in comformity to the subsequent arrangement of the propylene nucleus, in which the single and the double bonds exchange their positions during the addition of bromine and elimination of hydrogen bromide.

A substance with the same composition and constitution as the above bromo-ester has been already known and obtained by the interaction of bromine and the sodium or cupric derivative of tetraethyl dicarboxyglutaconate.⑴ Recently F. Faltis and J. Pirsch⑵ obtained tetraethyl allene-tetracarboxylate by the action of silver oxide on this bromo-ester.

Hydrolysis of Tetraethyl α-Bromo-dicarboxyglutaconate. The bromo-ester, formed by the elimination of hydrogen bromide from the addition product of bromine to tetraethyl dicarboxyglutaconate, was hydrolysed by boiling with hydrochloric acid. The product was obtained in various grade of purities according to the conditions of saponification. It has been found that a large quantity of alcohol must be present in order to get the product in a state free from resinous coloured contamination, the presence of alcohol accelerating the reaction at the same time. The following proportion gave a good result. The mixture of the bromo-ester 25 gr., alcohol 70 gr., concentrated hydrochloric acid 100 gr., and water 30 gr, is boiled for 3 or 4 hours with a reflux condenser, and the solution is evaporated on the water bath. When the solution is evaporated to a small volume, a further amount of

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(1) Guthzeit and Hartmann, *J. prakt. Chem.*, [2] **81** (1910), 350; F. Faltis and Carla Ruiz de Roxas, *Monatsh.*, **42** (1922), 459.

(2) *Ber.*, **60** (1927), 1621.

concentrated hydrochloric acid is added, the solution is evaporated to dryness, and the crystalline mass is dehydrated in a desiccator over concentrated sulphuric acid and soda-lime. In one experiment 24.6 gr. of the bromo-ester gave 9.3 gr. of the crude product in brownish crystals. If the saponification proceeded according to the equation :

$$(C_2H_5OCO)_2CBr-CH=C(COOC_2H_5)_2 + 4\,H_2O$$
$$HOOC-CHBr-CH=CH-COOH + 4\,C_2H_5OH + 2\,CO_2,$$

the above quantity of the bromo-ester must yield 12.6 gr. of the product. This result suggested some unexpected change. In fact it was found that the saponification product was no longer a compound of bromine, but it contained chlorine. This crystalline compound was purified by repeated recrystallization from a little amount of water until it showed a nearly constant melting point 155°. In order to make the recrystallization most effective, it was necessary to remove entirely the mother liquor each time. The mother liquor was well drained off by sucking the crystals in a Gooch crucible with a filter paper fitted at the bottom, and pouring pure benzene on the crystals, the sucking being continued. After the last recrystallization the crystals were well dried over sulphuric acid. It is colourless, easily soluble in water, alcohol, acetic acid, acetone, and ether, but difficultly soluble in benzene and chloroform. It is readily oxidized by the alkaline permanganate solution and is found to be an unsaturated acid. 0,3498 Gr. of the substance gave 0.4662 gr. of CO_2 and 0.0954 gr. of H_2O; 0.2134 gr. of the substance gave 0.2840 gr. of CO_2 and 0.0574 gr. of H_2O; 0.2374 gr. of the substance gave 0.2042 gr. of AgCl. (Found: C=36.36, 36.31; H=3.05, 3.01; Cl=21.28. $C_5H_5O_4Cl$ requires C=36.47; H=3.06; Cl=21.56%.) It is doubtlessly a chloroglutaconic acid.

Hitherto only one chloroglutaconic acid has been known, and that is β-chloroglutaconic acid melting at 129°⁽¹⁾. Now another chloroglutaconic acid melting at 155° has been obtained. These two kinds of acids are subjected to the similar treatment at the last process of preparation, that is, saponification with hydrochloric acid, and it is supposed that they are not geometrical isomers to each other. Hence the chloroglutaconic acid, the constitution of which is now under discussion, must be one of the following isomers :

(IV) α-chloroglutaconic acid, $HOOC-CHCl-CH=CH-COOH$;
(V) γ-chloroglutaconic acid, $HOOC-CH_2-CH=CCl-COOH$.

Now it must be considered how the bromine atom in the bromo-ester $C_{15}H_{21}O_8Br$ is replaced by a chlorine atom during its saponification giving the chloroglutaconic acid. This is well understood if it is supposed that the

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(1) Burton, Pechmann, *Ber.*, **20** (1907), 147; Inyold, Nickolis, *J. Chem. Soc.*, **121** (1922), 1638.

addition of hydrogen chloride and at the same time the elimination of hydrogen bromide take place. It is natural to consider that, if addition is easy to take place, then the inverse reaction may be also easily realised. Thus if the compound with bromine is less stable than that with chlorine in the saponifying medium where the concentration of hydrogen chloride is much greater than that of hydrogen bromide even after the replacement of the halogens has been finished, it is not surprising that the addition of hydrogen chloride and the elimination of hydrogen bromide take place simultaneously.

In whatever manner addition and elimination may take place, a compound of the type (V) can not be formed. Hence the chloroglutaconic acid in question must have formula (IV). Now, after the constitution of the saponification product has been determined in this way, the mechanism of the formation of the chloro-acid from the bromo-ester can be explained to some extent as follows:

$$>CBr-CH=C< \xrightarrow{+HCl} >CBr-CH_2-CCl< \xrightarrow{-HBr} >C=CH-CCl<$$

It is probable that hydrogen chloride adds in such a manner that enables the chlorine atom to take the position the most remote from the bromine atom. The above reaction may occur probably in every stage of the saponification.

The tetraethyl α-bromodicarboxyglutaconate prepared by Faltis' method was saponified by the same procedure, and the product was recrystallised from water several times. 0.2024 Gr. of the substance gave 0.2708 gr. of CO_2 and 0.0556 gr. of H_2O; 0.2064 gr. of the substance gave 0.1724 gr. of AgCl. (Found: $C=36.50$; $H=3.07$; $Cl=20.66$. $C_5H_5O_4Cl$ requires $C=36.47$;, $H=3.06$; $Cl=21.56\%$.) The quantity of the substance was too small to be purified to a constant melting point, but the substance melted at 154°, and the mixture of this specimen and the α-chloroglutaconic acid described in the preceding pages melted at 154°, which showed the identity of the two specimens.

By the studies described in this paper it has been found that in the derivative of glutaconic acid addition and simultaneous elimination can easily take place, and the most stable compound in the condition is obtained as the final product, without destroying the structure of the propylene chain. If the substance which adds to a glutaconic derivative is the same as that is eliminated from the intermediate saturated compound, this transformation will not be detected by analysis of the final product; but it is possible that the final product differs from the substance not yet subjected to this transformation; in other words, the movement of the double union is possible. For instance, if a glutaconic derivative containing no halogen is hydrolysed with hydrochloric acid, hydrogen chloride may add to the unsaturated bond in such a manner that hydrogen will take the γ-position, chlorine the β-position, according to the usual rule of addition to an unsaturated acid, and then the chlorine may be splitted with α-hydrogen in the following manner:

$$\mathrm{HOOC{\cdot}CR{:}CR'{\cdot}CHR''{\cdot}COOH + HCl \rightarrow HOOC{\cdot}CHR{\cdot}CR'Cl{\cdot}CHR''{\cdot}COOH}$$
$$\rightarrow \mathrm{HOOC{\cdot}CHR{\cdot}CR'{:}CR''{\cdot}COOH + HCl.}$$

This must be borne in mind when one carries out an experiment such as the saponification of the derivatives of glutaconic acid by means of hydrochloric acid. It is not meant that such a transformation can take place only in the derivatives of glutaconic acid, but that it is possible at least in this class of organic compounds. In one experiment of saponifying the bromo-ester, hydrochloric acid was replaced by sulphuric acid. and the product was examined. After removing the sulphuric acid by adding the calculated amount of barium carbonate, the solution was filtered from barium sulphate and evaporated on the water bath. On concentrating it the white fume of hydrogen bromide was evolved. The product, after recrystallisation from water, was found to contain nearly no halogen. Thus, in the saponification with sulphuric acid the reaction is also so complicated that the constitution of the product can be difficultly deduced from that of the starting substance.

This consideration may bring an important consequence upon the theory which has been held on the constitution of the glutacodic acids by certain investigators who have been working in this interesting field of organic chemistry.

Remarks on the Constitution of the Glutaconic Acids. In 1905 J. F. Thorpe(1) found that the α- and γ-positions in the glutaconic acids are the same, for instance, α, β-dimethylglutaconic acid $\mathrm{HOOC-CH(CH_3)-C(CH_3)=CH-COOH}$, and β, γ-dimethylglutaconic acid, $\mathrm{HOOC-CH_2-C(CH_3)=C(CH_3)-COOH}$, are identical. From this fact he gave the glutaconic acid and its derivatives the symmetrical formula, the so-called normal form, and the constitution of glutaconic acid was represented by the formula $\mathrm{HOOC-\underset{|}{CH}-CH_2-\underset{|}{CH}-COOH}$. Since then he and his collaborators have been making many important investigations in this sphere, among which some indicated also the identity of the α- and γ-positions in the glutaconic acids.(2) Feist(3) rejected Thorpe's theory of the normal form, and has been supporting the ordinary formula until the present. Feist held the theory of oscillation in order to explain the existence of only one form of glutaconic acid and the

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(1) *J. Chem. Soc.*, **87** (1905). 1669.

(2) *J. Chem. Soc.*, **89** (1906), 631; **99** (1911), 2187.

(3) *Ann.*, **345** (1906), 117: **370** (1909), 41; **428** (1922), 25.

identity of the α- and γ-positions of this acid, and he has been also making many important studies on the derivatives of this acid. Not only Feist, but also any other chemists, have not suspected the uncertainty involved in the experiments showing the identity of the α- and γ-positions of glutaconic acid, on which the standpoint of Thorpe's theory of the normal form was based. In all of the experiments which were taken as the proofs of the identity of the α- and γ-positions the substituted glutaconic acids were obtained by the saponification process with concentrated hydrochloric acid. Now, the present author has shown that the constitution (the position of the double union) of the product can not be deduced from that of the starting substance in a reaction such as the saponification of the glutaconic derivatives with hydrochloric acid. Thus the imperfection in Thorpe's conclusion is pointed out. If the experiments resulted as if the α- and γ-positions were the same, it must be rather concluded that the migration of the double union took place during the reaction. He recognised the migration of the double union when he dealt with the action of sodium ethylate on the derivatives of the glutaconic ester, and even a rule of migration of the double union was devised.(1) It is unnatural to assume the fixity of the double union in the saponification with hydrochloric acid and to conclude the identity of the α- and γ-positions.

A hypothesis as Thorpe's seems to be no longer necessary in the chemistry of the glutaconic acids, and, therefore, the present author will support the opinion held by Feist, but it seems that his theory of oscillation is also no longer indispensable, for it is now the fact of existence of only one form of glutaconic acid that this theory is to explain, and this fact can be easily understood if it is supposed that only one form is stable.

In the paper on the nitrile-esters of the dicarboxyglutaconic acid,(2) the mechanism of the condensation of an ethoxymethylene compound $C_2H_5OCH=CXY$ with a sodio-methylene compound $CHNaX'Y'$ was explained on the assumption that the theory of the normal form can be applied to the derivatives of dicarboxyglutaconic acid. This explanation must be corrected according to the results of the recent investigations which showed that Thorpe's theory of the normal form had been based on somewhat uncertain evidences. In this paper it is stated only that the explanation must be corrected, and how the mechanism of the above condensation is correctly explained will be published in another paper, for it is necessary further to carry out such experiments as will throw light on the consideration of the reactions of this kind.

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(1) *J. Chem. Soc.*, **101** (1912), 249.
(2) This journal, **2** (1927), 282.

Summary.

By the action of bromine on tetraethyl dicarboxyglutaconate, tetraethyl α-bromodicarboxyglutaconate was obtained as the final product. When the tetraethyl α-bromodicarboxyglutaconate was saponified by means of hydrochloric acid, the product was α-chloroglutaconic acid. According to the result of this investigation, it was concluded that, when one carries out the saponification of a derivative of glutaconic acid, the constitution of the product cannot be deduced from the starting substance. Uncertainty in J. F. Thorpe's theory of the normal form was pointed out.

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