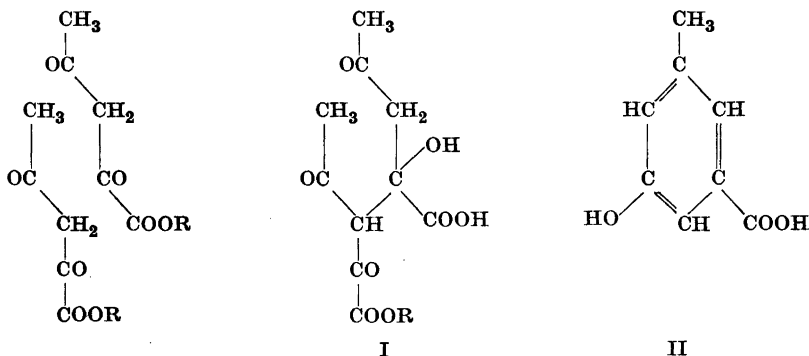


## The Formation of Cyclic Compounds from Acetylpyruvic Esters

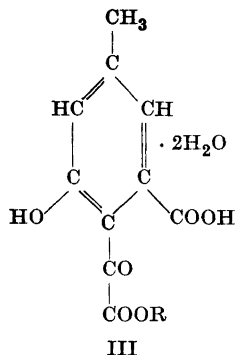
ENDRE BERNER and SØREN LALAND

*Universitetets Kjemiske Institutt, Blindern — Oslo, Norway*

An intermolecular condensation of esters of acetylpyruvic acid was first described by Claisen<sup>1</sup>. On mixing the sodium compound of ethyl acetylpyruvate with glacial acetic acid and subsequently adding diluted sulphuric acid Claisen obtained a crystalline condensation product  $C_{12}H_{16}O_8$  with m. p. 90—91°. The condensation product could be titrated as a monobasic acid, the titrated solution turning strongly yellow on the addition of an excess of alkali. When the product was heated with aqueous barium hydroxide oxalic acid and ethanol were split off and 3-methyl-5-hydroxybenzoic acid was formed. From these data Claisen concluded that the condensation product had the aliphatic structure I which is written so as to indicate the transformation into the aromatic acid II:



Claisen also found that the condensation took place in the same manner when the methyl ester of acetylpyruvic acid was used instead of the ethyl ester.



Heikel<sup>2, 3</sup>, who had previously studied the condensation of acetylacetone in the presence of alkali into an aromatic compound, drew the conclusion that even the primary condensation product of the acetylpyruvic ester was an aromatic compound to which he assigned the structure III. In order to account for the composition found by analysis the compound should contain two molecules of water of crystallisation. He found, however, that the product on drying in a vacuum gave off one molecule of water only which was taken up again in a moist atmosphere. Heikel also discussed the possibility that the condensation product could have an aliphatic

structure differing from the one postulated by Claisen only in the reversed positions of the free and the alkylated carboxyl group. He would then explain the loss of water on drying as being due to the formation of a lactone.

In connection with another investigation the present authors obtained the condensation product of the ethyl ester of acetylpyruvic acid, and finding it to be subject to several interesting reactions and transformations took up the question of its constitution. We have also investigated the analogous condensation product of the methyl ester of acetylpyruvic acid. The condensation product of the ethyl ester is shortly called the *ethyl product* and that of the methyl ester the *methyl product*.

We soon arrived at the conclusion that neither the formula of Claisen nor any of the two formulae put forward by Heikel could explain satisfactorily the experimental data. This will be evident from the following four points.

1. The ethyl product which is a monoethyl ester of a dibasic acid contains one molecule of crystal water. This is in accordance with Heikel's drying experiments which we have verified. It has further been checked by the fact that the ethyl product, more correctly written  $\text{C}_{12}\text{H}_{14}\text{O}_7 \cdot \text{H}_2\text{O}$ , by treatment with diazomethane gave an ethyl methyl ester  $\text{C}_{12}\text{H}_{16}\text{O}_7$  identical with the ester obtained when the anhydrous ethyl product reacted with diazomethane.

2. The ethyl product could be resolved into optically active components of high specific rotation (about  $83^\circ$ ). The aromatic formula of Heikel is decisively excluded by this fact, but also the open-chained formula of Claisen and that of Heikel may be excluded for the reason that an aliphatic compound would hardly give such a high specific rotation.

3. The ethyl product gave a di-2,4-dinitrophenylhydrazone. From the aromatic formula one should expect a mono-hydrazone to be formed, and from the open-chained formulae tri-hydrazones.

4. By catalytic hydrogenation the methyl product took up two molecules of hydrogen giving a compound  $C_{11}H_{16}O_7$ , which did not contain water of crystallisation and which gave a mono-2,4-dinitrophenylhydrazone. On sublimation in a vacuum the hydrogenated product lost one molecule of water forming a lactone which on dissolving in alkali again took up water.

Other points which must be considered before postulating a new structural formula for the condensation product are:

5. The easy formation of 3-methyl-5-hydroxybenzoic acid in addition to the oxalic acid.

6. The yellow colouring of the solution of the condensation product caused by an excess of alkali. On acidification of the yellow solution shortly after the addition of the alkali most of the condensation product could be recovered unchanged. Even the fully alkylated substance obtained by treatment of the condensation product with diazomethane produced a yellow colour in alkaline medium, and it gave on prolonged treatment with diazomethane in the presence of methanol a yellow syrup, being evidently the methylated enol-form.

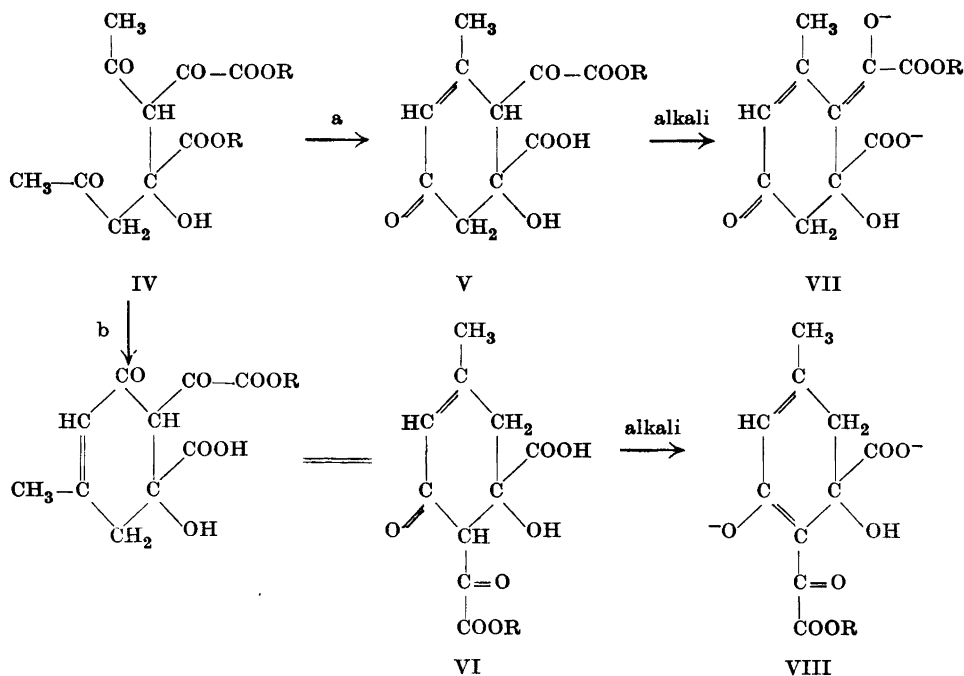
7. The methyl product gave a positive iodoform reaction with alkaline iodine solution.

8. a) The hydrogenated methyl product gave a negative iodoform reaction.

b) It could be dissolved in one equivalent of alkali without coloration, but the solution turned yellow with an excess of alkali. On acidifying the colour disappeared and the unchanged hydrogenated product was easily recovered.

9. The hydrogenated condensation product could be transformed into two substances  $C_{10}H_{10}O_5$  and  $C_8H_{12}O_3$  together with oxalic acid. This point will be discussed in detail below.

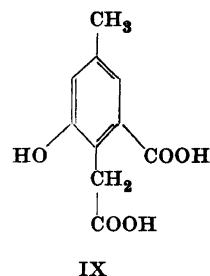
The fact mentioned in point 2 would suggest that the ethyl product (as also the methyl product) must be a cyclic compound. The initial stage of the condensation leads most probably to an open-chain compound (IV). On further reaction in the weak alkaline medium the formation of a six-membered homocyclic ring takes place, during which process one molecule of water is split off. At the same time one of the ester groups is hydrolysed. The second stage of the condensation can be assumed to follow either of the two routes a and b leading to the two formulae V and VI. As the condensation product does not give carbon dioxide by oxidation with hydrogen peroxide it is most likely not a free  $\alpha$ -ketoacid, and the carboxylic acid group bound directly to the ring must therefore be the free one. Both the formulae V and VI are in accordance with the experimental data set forth under points 1, 2, 3, 4, 5, 7 and 8 a. In order to decide between them it is necessary to consider also the points 6 and 9.



The yellow colouring of the condensation product or its methylated derivative mentioned in point 6 must be due to the formation of an enol-form. Formula V would give rise to an enol-form with the structure VII, whilst formula VI would give an enol-form with structure VIII. In the latter case there is also the possibility that the mobile hydrogen atom could migrate to the carbonyl in the side-chain. The arrangement of the double bonds in formula VII could be regarded as a semi-quinoid grouping and would probably represent a better chromophore than the system of conjugated double bonds in formula VIII. This might accordingly indicate that the condensation product has the structure given in formula V. In this connection it is noteworthy that compounds obtained by diene syntheses using *p*-benzoquinone as the dienophilic component contain a similar semi-quinoid grouping and that they are yellow in colour. See for example the recent results of Lora-Tamayo and Leon<sup>4</sup>. It must however be admitted that the experimental fact from point 6 can not alone be decisive in the question and therefore the facts from point 9 must be taken into account.

Assuming provisionally formula V for the ethyl product ( $R = C_2H_5$ ) the hydrogenated product has been assigned formula X (see p. 341). By the hydrogenation, two molecules of hydrogen are added, and as the hydrogenated

product forms a monohydrazone one molecule of hydrogen is taken up by the double bond and the other by one of the carbonyl groups. When the hydrogenated product was sublimed in a vacuum a lactone was obtained. From the formula V it will be seen that this result can be explained equally well in terms of the reduction of either one of the carbonyl groups. On the other hand the facts mentioned below concerning the degradation of the hydrogenated product can be explained in the simplest way by assuming that the carbonyl group in the side-chain is reduced to a secondary alcohol group as indicated in formula X.



On heating with aqueous barium hydroxide the hydrogenated product X was transformed into three substances: a) an aromatic compound  $C_{10}H_{10}O_5$ , b) a hydroaromatic compound  $C_8H_{12}O_3$  and c) oxalic acid. Starting with one mole of X a little more than half a mole of oxalic acid could be isolated.

The compound  $C_{10}H_{10}O_5$  is isomeric with the 5-hydroxy-3-carboxy-p-tolueneacetic acid (IX) previously described by one of us<sup>5</sup>. In some respects the new compound showed a great resemblance to the substance IX. Both compounds could be titrated as dibasic acids, and they gave with diazomethane, dimethyl esters. On treatment with dimethyl sulphate and alkali the phenolic hydroxyl group also was methylated giving trimethoxy compounds. When these were hydrolysed with alkali the corresponding methyl ethers of the free acids were obtained. The methyl ether of IX (m. p.  $206^\circ$ ) could be degraded by oxidation. By using potassium permanganate the nuclear methyl group only was oxidised to a carboxyl group. When the product from this oxidation was treated with dilute nitric acid the side-chain was oxidised, resulting in the formation of methoxybenzene-2,3,5-tricarboxylic acid (l. c.). Recently we have found that the methyl ether (m. p.  $206^\circ$ ) by direct oxidation with nitric acid gave 4-methyl-6-methoxy-phthalic acid which had the same m. p. ( $200^\circ$ ) as given for this substance in the literature. On the other hand we have not succeeded in degrading by oxidation either the new compound  $C_{10}H_{10}O_5$  or its methyl ether. When oxidation did occur, complete destruction of the substance took place. It is evident therefore that the arrangement of the substituents in the new substance gives rise to marked steric hindrance. This is obvious also from the fact that it has not been possible to obtain a benzylidene derivative by treatment with benzaldehyde. Another outstanding difference between the two isomers lies in the fact that the old one (IX) easily gives a lactone, while the new one does not give one.

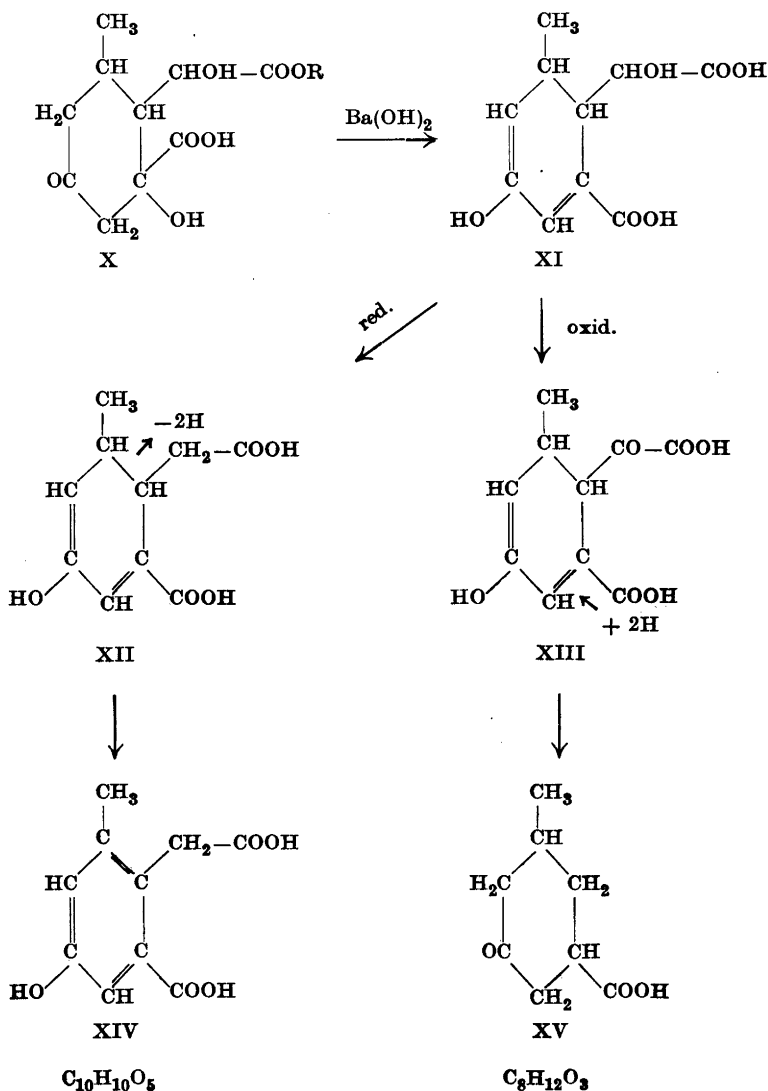
In agreement with formula IX the methyl ether of that substance on treatment with acetic anhydride gives an acid anhydride which dissolves in alkali

with the production of a yellow colour. It has previously been found by W. Dieckmann<sup>6</sup> that the anhydride of homophthalic acid owing to enolisation gives an intense yellow coloration with alkali. On the other hand the new isomeric acid does not give any intramolecular anhydride. Heating the acid itself with acetic anhydride results in the acetylation of the hydroxyl group, and when the methyl ether of the acid is used a mixed anhydride with acetic acid is formed. The fact that no intramolecular anhydride is obtained must be due to the steric hindrance mentioned above. The only reasonable explanation of the experimental data must therefore be that the new compound  $C_{10}H_{10}O_5$  is 5-hydroxy-3-carboxy-*o*-tolueneacetic acid (XIV). This is also in accordance with the fact that the acid on treatment with dilute nitric acid gives a dinitro-compound in which the hydroxyl group is so strongly activated that the substance can be titrated as a tribasic acid and that it gives a trimethoxy derivative with diazomethane. It should be added that if the original condensation product had the formula VI given above this would have led to a compound identical with IX.

The compound  $C_8H_{12}O_3$  is evidently a methylcyclohexanone-carboxylic acid. It forms a monomethyl ester and gives both a 2,4-dinitrophenylhydrazone and a semicarbazone. As the original condensation product can so easily be transformed into the 3-methyl-5-hydroxybenzoic acid the compound  $C_8H_{12}O_3$  is most probably a 3-methylcyclohexanone-5-carboxylic acid (XV). Following the procedure of Meldrum and Perkin jun.,<sup>7</sup> the 3-methyl-5-hydroxybenzoic acid by hydrogenation and subsequent oxidation has been transformed into a liquid mixture of stereoisomeric forms of 3-methylcyclohexanone-5-carboxylic acid. On treatment of this with 2,4-dinitrophenylhydrazone a mixture of two crystalline hydrazones was obtained which could be separated by fractional crystallisation. One of the hydrazones had the same m. p. as the hydrazone of  $C_8H_{12}O_3$  and showed no depression when mixed with the latter. In accordance with the structural formula XV our methylcyclohexanone-carboxylic acid gave a dibenzylidene derivative.

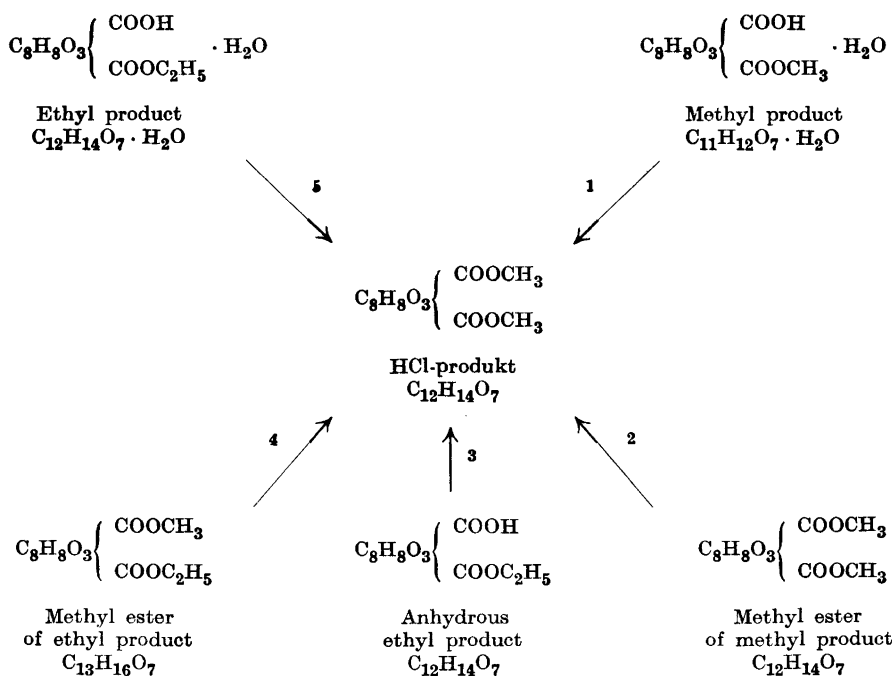
The following scheme explains the transformation of the hydrogenated product X into the compounds just described. On heating with aqueous barium hydroxide the ester group in X is hydrolysed, and at the same time one molecule of water is split off thereby forming a double bond in the ring. Through enolisation a second double bond is established in the ring, and the first intermediate product XI may therefore be regarded as a derivative of dihydrobenzene. Consequently it shows great reactivity, and the assumption can now be made that two kinds of reactions take place. By the first of these reactions pairs of molecules XI react in such a way that the side-chain  $-CHOH-COOH$  in one molecule is reduced to  $-CH_2-COOH$  whilst in the

other molecule it is oxidised to  $-\text{CO}-\text{COOH}$  giving the substances XII and XIII respectively. By the second reaction substance XII gives off two atoms of hydrogen which are taken up by substance XIII. Substance XII is thereby transformed into the aromatic compound XIV, while substance XIII owing to the simultaneous splitting off of oxalic acid gives the hydroaromatic compound XV. As will be seen this scheme also explains the formation of approximately half a molecule of oxalic acid from each molecule of the hydrogenated product.



From the preceding experimental data it would appear most probably that the methyl and the ethyl product have the structure V ( $R = CH_3$  and  $C_2H_5$  respectively).

We now turn to some remarkable transformations which take place when the methyl or ethyl product or the corresponding esters, obtained by means of diazomethane, are treated with anhydrous methanol containing hydrogen chloride. In an attempt to esterify the free carboxylic group in the methyl product with methanolic hydrogen chloride a substance was obtained which was different from the dimethyl ester prepared by means of diazomethane. The new substance which is shortly designated the *HCl-product* contained two methoxyl groups as expected, and it was found to be isomeric with the ester prepared by means of diazomethane. Quite unexpectedly however it could still be titrated as a monobasic acid, and an excess of alkali produced a yellow coloration of the solution. The following scheme shows the alternative substances from which the same HCl-product can be obtained by treatment with methanolic hydrogen chloride.



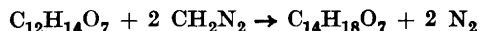
As will be seen the transformations include in some cases an esterification, in some an alcoholic exchange of ethyl with methyl also, and in all cases an intermolecular rearrangement. In transformation 2 the rearrangement is the



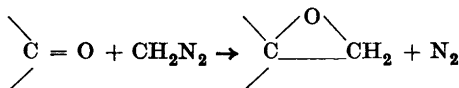
only process. It should be added that when ethanol was used instead of methanol an analogous HCl-product containing two carboxethyl groups was obtained.

A closer examination of the HCl-product gave the following results. On heating with aqueous barium hydroxide the HCl-product was decomposed into oxalic acid and the same methyl-hydroxybenzoic acid as obtained from the original condensation product. The acid group could not be a carboxyl group since the HCl-product was recovered unchanged even after boiling for one hour with thionyl chloride. Neither could a salt be obtained with bases such as strychnine. The HCl-product gave a di-2,4-dinitrophenylhydrazone. As the product could be prepared also from the methyl ester of the methyl product it must certainly contain two methylated carboxyl groups. Of the seven oxygen atoms four will thus belong to the two ester groups and two to the carbonyl groups. The one remaining oxygen atom must therefore belong to a hydroxyl group which is accordingly responsible for the acid character.

When the HCl-product was treated with diazomethane a reaction took place according to the equation:

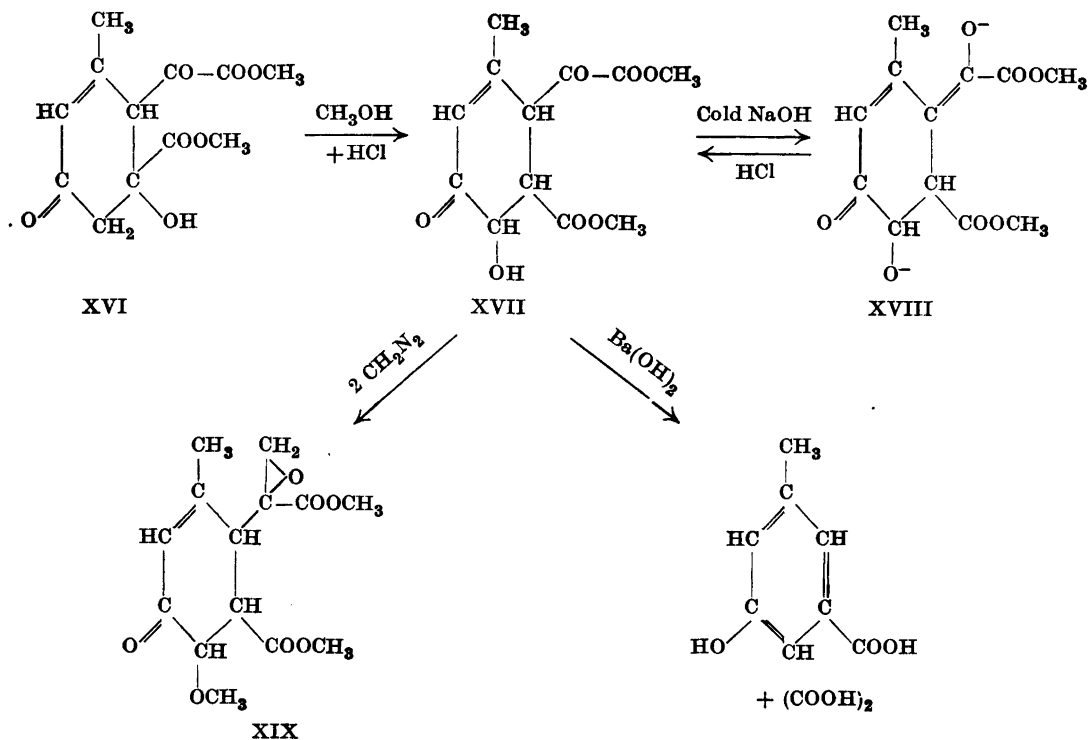


Consequently one would expect the new substance to contain four methoxyl groups. However by the Zeisel-Fanto determination three methoxyl groups only were found. A methylene group must therefore have been taken up in such a form that it is not split off as methyl iodide on boiling with hydroiodic acid. From the literature it is known that diazomethane can react with ketones forming ethylene oxides or homologous ketones<sup>8</sup>. Since the HCl-product as mentioned was a diketone it could be assumed that one of the ketone groups had reacted in a similar way. This seems to be the case when the product from the treatment with diazomethane gave only a mono-2,4-dinitrophenylhydrazone. Most probably one of the keto-groups has reacted with diazomethane in the following way:



The substance  $\text{C}_{14}\text{H}_{18}\text{O}_7$  did not give a yellow coloration with alkali, and on heating with aqueous barium hydroxide it did not give rise to any oxalic acid.

The formula XVII which from these experimental facts has been postulated for the HCl-product will be found in the scheme below. In the same scheme the isomerisation of the methyl ester of the methyl product XVI has



been demonstrated, and as will be seen this isomerisation involves only the migration of the hydroxyl group from the meta to the para position in regard to the nuclear methyl group. Formula XVIII represents the structure responsible for the yellow colouring in alkaline solution. Formula XIX represents the substance  $\text{C}_{14}\text{H}_{18}\text{O}_7$ , and it is in accordance with the fact that this substance does not give oxalic acid or a yellow coloration with alkali.

Finally it should be mentioned that we have not been able to give a satisfactory explanation of the yellow coloration appearing when an excess of alkali is added to the hydrogenated product X.

## EXPERIMENTAL PART

### Condensation of ethyl acetylpyruvate

To ethyl acetylpyruvate (15.8 g) was added a solution of sodium acetate (6.8 g) in water (30 ml), and the mixture left at room temperature over night. Next day the ester had dissolved and the rather dark-coloured solution was acidified with 50 per cent sulphuric acid. The crystalline ethyl product which then separated (9 g = 70 per cent yield) was recrystallised from water and dried in the air to constant weight; m. p. 80–91°.

Owing to the yellow coloration produced with excess of alkali the titrations had to be carried out very carefully. About 200 mg of the substance were dissolved in 15 ml ethanol and 0.1 *N* sodium hydroxide added drop by drop.

0.233 and 0.204 g required 8.20 and 7.24 ml 0.1 *N* NaOH

$C_{12}H_{14}O_7 \cdot H_2O$	Calc.	C 50.00	H 5.55	$C_2H_5O$	15.65	<i>M</i> 288.3
	Found	49.74, 49.56	5.50, 5.63		15.25, 15.57	284, 282

The finely powdered ethyl product dispersed in a thin layer on a watch glass was dried at room temperature in a vacuum above phosphorous pentoxide. The substance first deliquesced and then crystallised. In two days 568 mg lost 33.5 mg water, calc. for one mole water 35.5 mg. The watch glass with the substance was then placed in a moist atmosphere and in the course of one day the weight increased with 33.5 mg. The analysis showed that the substance had regained the same composition as the original ethyl product.

#### Ethyl product and aqueous barium hydroxide

The ethyl product (1 g) was heated on the water-bath with barium oxide (1.5 g) and water (20 ml) for half an hour. The barium oxalate which separated was filtered off and the oxalic acid identified in the usual way. The filtrate was evaporated to a small volume and acidified with hydrochloric acid. The 3-methyl-5-hydroxybenzoic acid which separated was purified by sublimation in a vacuum; m. p. 207° (decomposition).

$C_8H_8O_3$	Calc.	C 63.15	H 5.26
	Found	62.88, 62.94	5.11, 5.11

#### Methyl ester of ethyl product

Powdered ethyl product (15 g) was mixed with ether (50 ml) and an ethereal solution of diazomethane added until the yellow colour remained. After evaporation of the ether the ester was recrystallised twice from ethanol. Yield 12 g; m. p. 58–59°.

$C_{13}H_{16}O_7$ (284.3)	Calc.	C 54.93	H 5.63
	Found	54.73, 54.67	5.90, 6.00

#### Alkoxy determination after Zeisel-Fanto:

0.1630 and 0.1927 g subst. gave 0.2645 and 0.3152 g AgI. Calc. for one ethoxyl and one methoxyl group 0.2692 and 0.3180 g AgI.

#### Cryoscopic measurements in benzene:

0.4435 g subst.,	19.67 g benzene,	$\Delta$ 0.425°	<i>M</i> 272
0.7755 »	»	19.67 »	» 0.73° » 277

#### Anhydrous ethyl product and diazomethane

The ethyl product was dried as described above. It was then powdered again and dried for two days more. The completely dried powder was added to an ethereal solution of diazomethane which had been dried first with potassium hydroxide and then by placing

it for some hours above metallic sodium. After removing the ether the ester was recrystallised from ethanol. The m. p. 58–59° was not altered after mixing with ester prepared from the ethyl product containing crystal water.

$C_{13}H_{16}O_7$	Calc. C 54.93	H 5.63
	Found † 54.61, 55.31	† 5.54, 5.29

#### Optical resolution of ethyl product

a) In water: Ethyl product (2 g) and strychnine (2.34 g) were dissolved by heating in water (100 ml), and the solution filtered. After two days the strychnine salt which had separated was filtered off and recrystallised from water (40 ml). Yield 1.5 g. The salt was dissolved in 40 per cent sulphuric acid, and the ethyl product extracted with ether. After drying with sodium sulphate and removal of the ether 0.5 g ethyl product remained; m. p. 80–90°.

$$[\alpha]_D^{20} = -83.3^\circ \quad (\alpha -7.82^\circ, c 9.38 \text{ in ethanol, 1 dm tube}).$$

b) In acetone: Ethyl product (2 g) and strychnine (2.34 g) were dissolved in acetone (40 ml). The strychnine salt crystallised much more slowly from acetone than from water. After two days 1.12 g salt had separated and the ethyl product (0.42 g) isolated as above; m. p. 81–92°.

$$[\alpha]_D^{20} = -82.7^\circ \quad (\alpha -7.75^\circ, c 9.38 \text{ in ethanol, 1 dm tube}).$$

The isolation of the dextro-form was performed in the following way. The aqueous mother-liquor from the salt of the levo-acid was left for one week in an open beaker when some more strychnine salt separated. Having removed this the filtrate was concentrated in a vacuum desiccator to half volume. After acidifying with sulphuric acid 0.73 g of the dextro-acid was isolated by extraction with ether; m. p. 81–91°.

$$[\alpha]_D^{20} = +58.6^\circ \quad (\alpha +5.50^\circ, c 9.38 \text{ in ethanol, 1 dm tube}).$$

No attempts were made to obtain the optically pure dextro-form.

#### Condensation of methyl acetylpyruvate

The necessary methyl acetylpyruvate was most conveniently prepared by adding first ethyl oxalate (256 g) and then acetone (100 g) to anhydrous methanol (1200 ml) in which sodium (40 g) had been dissolved. Simultaneously with the condensation an alcoholysis took place, and the sodium salt of the methyl acetylpyruvate separated in the course of a day. This salt is much more easily filtered than the sodium salt of the ethyl ester. It was stirred up with ice-water and sufficient 40 per cent sulphuric acid added. The solid methyl acetylpyruvate (161 g = 67 per cent of theory) after filtration and washing with water was then sufficiently pure for our needs.

The intermolecular condensation of the methyl acetylpyruvate in the presence of sodium acetate was carried out as described for the ethyl ester. It could also be per-

formed without first isolating the methyl acetylpyruvate. In this case an equivalent quantity of acetic acid was added to the sodium salt of the methyl acetylpyruvate directly after filtration. The methyl product after recrystallisation from water had m. p. 68–75°.

0.181 and 0.161 g subst. required 6.83 and 6.04 ml 0.1 *N* NaOH  
 $C_{11}H_{12}O_7 \cdot H_2O$  Calc. C 48.50      H 5.12       $CH_3O$  11.31      *M* 274.2  
 Found    » 48.22, 48.40    » 5.29, 5.20      » 11.34, 11.21    » 265, 267

The methyl product gave a strongly positive iodoform test.

#### Methyl ester of methyl product

The methyl product was treated with diazomethane as described for the ethyl product. After recrystallisation three times from ethanol the methyl ester of the methyl product had m. p. 74–75°.

$C_{12}H_{14}O_7$  Calc. C 53.33      H 5.18       $CH_3O$  22.97  
 Found    » 53.67, 53.47    » 5.18, 5.00      » 22.80

When sodium ethylate was added to a solution of the methyl ester of the methyl product in ethanol the solution became intensely yellow in colour. To a solution of the methyl ester in anhydrous ether containing about 10 per cent methanol an ethereal solution of diazomethane was added and the whole left over night at room temperature. After the solvent had been evaporated under reduced pressure a yellow syrup remained which did not crystallise.

Preparation of the hydrazone: The ester was dissolved in methanol and heated for a few minutes with a sufficient quantity of 2,4-dinitrophenylhydrazine dissolved in 2 *N* hydrochloric acid. Next day an orange-yellow substance had separated which could be recrystallised by dissolving in glacial acetic acid and cautiously adding water; m. p. 212°. The substance was according to the analysis a dihydrate of the dihydrazone.

$C_{24}H_{22}O_{13}N_8 \cdot 2H_2O$  Calc. N 16.81,      Found N 16.54, 16.65

#### Hydrogenation of methyl product

A solution of methyl product (10 g) in methanol (50 ml) to which platinum oxide (0.6 g) had been added took up 1280 ml hydrogen (1190 mm Hg) in 24 hours; calc. for 2 mole hydrogen 1220 ml. After filtering the methanol was evaporated on the water-bath and the hydrogenated product recrystallised from water. Yield 5 g; 164–165° (decomp.).

26.31 and 21.40 mg subst. required 1.054 and 0.833 ml 0.1 *N* NaOH  
 $C_{11}H_{16}O_7$  Calc. C 50.77      H 6.15       $CH_3O$  11.90      *M* 260.2  
 Found    » 50.78, 50.89    » 6.39, 6.15      » 11.52    » 250, 257

The hydrogenated methyl product could be sublimated in a vacuum, losing at the same time one molecule of water and giving a product with m. p. 162–163°.

0.1133 and 0.1286 g subst. required 4.75 and 5.30 ml 0.1 *N* NaOH  
 $C_{11}H_{14}O_6$  Calc. C 54.51      H 5.78       $CH_3O$  12.81    *M* 242.2  
 Found    » 54.68, 54.75    » 5.67, 5.69    » 12.80    » 239, 243

The product from the sublimation, which was a lactone, was dissolved in sodium hydroxide and the solution acidified. The substance which then separated was identical with the hydrogenated methyl product. *M. p.* 164–165°.

Found C 51.05, 51.28      H 6.39, 6.10

A mono-2,4-dinitrophenylhydrazone of the hydrogenated product was prepared in the usual way. The orange-yellow hydrazone was recrystallised from ethanol; *m. p.* 186–187°.

$C_{17}H_{20}O_{10}N_4$  Calc. N 12.73      Found N 12.69, 12.97

#### Degradation of hydrogenated product

The hydrogenated product (12.5 g) was heated with barium oxide (16.4 g) and water (250 ml) for half an hour on a water-bath. The colour of the solution which was at first intensely yellow changed to orange and finally became rather dark. During the heating a salt separated which was found to be barium oxalate. It was dissolved in dilute hydrochloric acid and again precipitated by adding ammonia until *pH* 6. The dry salt then weighed 6.82 g which is 59 per cent of the amount (10.82) calculated on the assumption that one mole of oxalic acid had been split off from each mole of the hydrogenated product. The oxalic acid was isolated by extracting the solution of the barium salt in hydrochloric acid with ether. From the ethereal solution a crystalline substance was obtained which had *m. p.* 101° and gave a crystalline precipitate with calcium ions.

The filtrate from the barium oxalate was acidified with hydrochloric acid and extracted five times with 200 ml portions of benzene. Evaporation of the combined and dried extracts gave 3.4 g of a crystalline substance. This on recrystallising twice from benzene gave colourless needles with *m. p.* 94–95°. The substance was a mono-basic acid.

94.0 and 82.1 mg subst. required 6.04 and 5.35 ml 0.1 *N* NaOH  
 $C_8H_{12}O_3$  Calc. C 61.55      H 7.69      *M* 156.2  
 Found    » 61.63, 61.58    » 7.72, 7.56    » 156, 153

Molecular weight by ebulliometric method:

0.1808 g subst. in 8.18 g ether,  $\Delta$  0.33° *M* 141

The solution which had been extracted with benzene was now extracted five times with ether in 300 ml portions. After drying with sodium sulphate the ether was distilled off. A crystalline substance (3.5 g) remained which possessed a fatty acid odour. It was recrystallised from water containing a few per cent of hydrochloric acid and was then obtained in glossy shells without any smell; *m. p.* 268° (decomp.). The substance was a dibasic acid.

25.53 and 30.20 mg subst. required 2.36 and 2.80 ml 0.1 N NaOH

$C_{10}H_{10}O_5$	Calc.	C 57.14	H 4.76	M 210.2
	Found	» 57.14, 57.20	» 4.70, 4.81	» 216, 216
		5.42 mg subst., 46.7 mg camphor, $\Delta$ 22.8° M 204		

#### Investigation of $C_8H_{12}O_3$

The substance was easily soluble in ether, benzene, chloroform and glacial acetic acid. It was sparingly soluble in cold water but dissolved on heating. The iodoform reaction was negative.

A mono-2,4-dinitrophenylhydrazone was prepared in the usual way. It crystallised from 70 per cent ethanol in yellow needles, m. p. 165–166°.

$C_{14}H_{18}O_7N_4$	Calc.	C 50.00	H 5.36	N 16.82
	Found	» 50.00	» 5.11	» 17.00

Semicarbazone: On mixing 50 mg of the substance with an appropriate quantity of semicarbazide a mono-semicarbazone was immediately formed. It was recrystallised from water. Yield 50 mg, m. p. 200°.

$C_9H_{15}O_3N_3$	Calc.	C 50.70	H 7.03
	Found	» 50.59, 50.59	» 6.91, 6.77

The methyl ester of  $C_8H_{12}O_3$  was prepared by means of diazomethane. The ester was liquid. It gave a semicarbazone which after crystallisation from water had m. p. 162–164°.

$C_{10}H_{17}O_3N_3$	Calc.	C 52.86	H 7.49
	Found	» 52.72, 52.70	» 7.40, 7.42

No oxime could be obtained from  $C_8H_{12}O_3$ .

A dibenzylidene derivative was prepared in the following way. A solution of the substance (1.56 g) and benzaldehyde (2.12 g) in ethanol (10 ml) and 2 N sodium hydroxide (8 ml) was left for two days at room temperature. Addition of 2 N hydrochloric acid (10 ml) caused the separation of a syrup which crystallised when stirred with a glass rod. After recrystallising several times from diluted ethanol the dibenzylidene compound was obtained as light yellow crystals, m. p. 170°.

$C_{22}H_{20}O_8$	Calc.	C 79.49	H 6.07
	Found	» 79.75, 79.60	» 6.32, 6.18

#### Investigation of $C_{10}H_{10}O_5$

The substance did not lose water on sublimation in a vacuum. The sublimated product had m. p. 268° (decomp.) and the composition was unchanged.

$C_{10}H_{10}O_5$	Calc.	C 57.14	H 4.76
	Found	» 57.35, 57.35	» 4.62, 4.71

On heating with acetic anhydride an acetyl derivative was formed which had m. p. 173° and from which the original substance with m. p. 268° could be recovered by treatment with alkali.

The dimethyl ester of  $C_{10}H_{10}O_5$  was prepared by means of diazomethane. Recrystallised from diluted ethanol, m. p. 109–110°.

$C_{12}H_{14}O_5$	Calc.	C 60.50	H 5.88	$CH_3O$ 26.05
	Found	» 60.68, 60.73	» 6.09, 6.15	» 25.80

Nitration: By the oxidation of  $C_{10}H_{10}O_5$  with potassium permanganate no definite oxidation products could be isolated. In an attempt to oxidise with dilute nitric acid (about 20 per cent) it was found that a dinitro compound was formed. The nitration was carried out as follows. The substance (200 mg) was heated for ten minutes on the water-bath with the nitric acid (5 ml). Subsequent extraction with ether gave 90 mg of a crystalline substance. After recrystallisation from hydrochloric acid diluted with one volume of water the nitro compound was obtained in yellow needles; m. p. 225° (decomp.). Unlike the original substance the nitro derivative was easily soluble in cold water. It also dissolved easily in ether, acetone and ethyl acetate, but only slightly in benzene. On titration it required three equivalents of alkali for neutralisation.

	24.48 and 17.38 mg subst. required	2.47 and 1.72 ml 0.1 N NaOH
$C_{10}H_8O_9N_2$	Calc.	C 40.01    H 2.66    N 9.35 $M$ 300.2
	Found	» 39.70    » 2.85    » 9.33, 9.20    » 297, 300

On treatment with diazomethane the dinitro compound was transformed into a trimethoxy derivative which was colourless and had m. p. 86–87°.

$C_{13}H_{14}O_9N_2$	Calc.	C 45.61	H 4.09
	Found	» 45.94, 45.70	» 3.86, 3.90

#### Methyl ether of $C_{10}H_{10}O_5$

On treatment of  $C_{10}H_{10}O_5$  with dimethyl sulphate in the presence of sodium hydroxide the carboxylic groups as well as the phenolic hydroxyl were methylated. The ester was not however isolated, but the ester groups were hydrolysed by boiling with an excess of alkali. The methyl ether was precipitated by acidifying the alkaline solution. Yield about 90 per cent of theory. The methyl ether which could be recrystallised from diluted ethanol was dimorphic, the modifications having m. p. 187° and 215°. Each of the forms could be transformed into the other by dissolving and inoculating the solution with crystals of the other form. The ether was a dibasic acid.

	26.3 mg subst. required	2.28 ml 0.1 N NaOH
$C_{11}H_{12}O_5$	Calc.	C 58.94    H 5.35 $CH_3O$ 13.84 $M$ 224.2
	Found	» 58.56, 58.56    » 5.33, 5.17    » 14.00    » 231

On heating with acetic anhydride the methyl ether formed a mixed acid anhydride with acetic acid. The anhydride which was a liquid reacted with ethanol giving ethyl acetate. After treatment with alkali the unchanged methyl ether could be recovered.



## HCl-Product from ethyl product

The ethyl product (15 g) was dissolved in methanol (110 ml) containing hydrogen chloride (1.1 *N*) and the solution left at room temperature for two days. A substance had then separated in large rhombic crystals. From the mother-liquor more of the same substance was obtained after dilution with water. The HCl-product (9 g) was recrystallised from methanol and had m. p. 156°. It could be titrated as a monobasic acid, and the solution became strongly yellow coloured when an excess of alkali was added. On acidification of the yellow solution a few minutes later, the HCl-product could be recovered unchanged in good yield. It contained two methoxyl groups.

0.3705 and 0.3090 g subst. required 13.91 and 11.53 ml 0.1 <i>N</i> NaOH					
$C_{12}H_{14}O_7$	Calc.	C 53.33	H 5.18	$CH_3O$ 22.97	<i>M</i> 270.2
	Found	» 53.16, 53.18	» 5.40, 5.41	» 22.45, 22.65	» 266, 268

Molecular weight in acetone:

0.4692, 0.5942 g subst., 5.73, 10.33 g acetone,  $\Delta$  0.50, 0.35° *M* 273,274

The HCl-product dissolved easily in acetone but was only slightly soluble in ether and water.

An identical substance was prepared by treating the anhydrous ethyl product (obtained by drying the hydrate in a vacuum above phosphorous pentoxide) with methanolic hydrogen chloride. M. p. 156°, alone and in admixture.

Found C 53.09, 53.20    H 5.34, 5.15     $CH_3O$  22.72, 22.67

## HCl-Product from other substances

By treatment of the methyl product, the methyl ester of the ethyl product and the methyl ester of the methyl product with 1.1 *N* hydrogen chloride in methanol three substances, A, B and C respectively were obtained. These were all identical with the HCl-product prepared from the ethyl product. M. p. in all cases 156°, alone and in admixture.

$C_{12}H_{14}O_7$	Calc.	C 53.33	H 5.18	$CH_3O$ 22.97
A	Found	» 53.37, 53.20	» 5.24, 5.20	» 22.83, 22.73
B	»	» 53.21, 53.30	» 5.25, 5.20	
C	»	» 53.31, 53.25	» 5.13, 5.15	

## Investigation of the HCl-product

A solution of the HCl-product (1 g) and barium oxide (1.5 g) in water (20 ml) was heated for half an hour on the water-bath. Barium oxalate separate and was filtered off. On acidifying the filtrate an acid was isolated which was found to be identical with the 3-methyl-5-hydroxybenzoic acid obtained from the ethyl product. M. p. 207°, no depression.

$C_8H_8O_3$	Calc.	C 63.15	H 5.26
	Found	» 63.10, 63.16	» 5.30, 5.33

A 2,4-dinitrophenylhydrazone of the HCl-product was prepared in the usual way. The hydrazone was orange-yellow. Recrystallisation could not be satisfactorily accomplished so the raw hydrazone had to be used for analysis.

Monohydrazone	Calc. N 12.40		
Dihydrazone	» » 17.78	Found N	16.45, 16.35

Reaction with diazomethane: Finely powdered HCl-product (5 g) was added to an ethereal solution of diazomethane which was cooled with ice-water. Before all the product had reacted a new crystalline substance began to separate. To complete the reaction the substance was left for 5–6 hours at room temperature with an excess of diazomethane. After distilling off the ether the residue was recrystallised several times from ethanol; colourless needles, m. p. 135–137°.

$C_{14}H_{18}O_7$	Calc. C 56.36	H 6.06	$CH_3O$ 31.21
	Found » 56.46, 56.53	» 5.93, 5.97	» 30.84, 31.02

When alkali was added to a solution of the new substance in ethanol no yellow coloration was produced, and on heating for half an hour with aqueous barium hydroxide no barium oxalate was formed.

A mono-2,4-dinitrophenylhydrazone was prepared in the usual way. After recrystallisation from diluted ethanol the orange-yellow hydrazone had m. p. 172–173°.

$C_{20}H_{22}O_{10}N_4$	Calc. N 11.71	Found N	11.92, 12.11
-------------------------	---------------	---------	--------------

#### Ethyl product with ethanolic hydrogen chloride

The ethyl product (3 g) was dissolved in anhydrous ethanol (22 ml) containing hydrogen chloride (1.1 N). After three days at room temperature 1 g of a crystalline substance had separated which was recrystallised from ethanol. M. p. 122–123°. The substance contained two ethoxyl groups, and it could be titrated as a monobasic acid. Excess of alkali gave a yellow coloration.

	27.4 and 26.5 mg subst. required 0.932 and 0.912 ml 0.1 N NaOH		
$C_{14}H_{18}O_7$	Calc. C 56.36	H 6.06	$C_2H_5O$ 30.22 <i>M</i> 298.3
	Found » 56.37, 56.40	» 5.71, 6.14	» 29.48, 30.26      » 294, 297

An identical substance was obtained by treating the methyl product with ethanolic hydrogen chloride. M. p. 122–123° alone and in admixture.

Found C	56.46, 56.30	H 6.10, 6.00	$C_2H_5O$ 29.93
---------	--------------	--------------	-----------------

On heating this ethyl HCl-product with aqueous barium hydroxide 3-methyl-5-hydroxybenzoic acid and oxalic acid were formed.

## SUMMARY

It has been found that the intermolecular condensation of an ester of acetylpyruvic acid led to a substance with cyclic structure. The condensation product could be resolved into optically active components, it could be esterified by means of diazomethane, and it gave a dihydrazone. By catalytic hydrogenation the condensation product took up two molecules of hydrogen, and on heating with aqueous barium hydroxide the hydrogenated product could be degraded to an aromatic hydroxy-dicarboxylic acid, a hydroaromatic keto-carboxylic acid and oxalic acid. On treatment of the condensation product with methanolic hydrogen chloride an interesting isomerisation took place alongside of the esterification, resulting in the formation of a substance which could be titrated as a monobasic acid.

We are indebted to cand. real. Ingvald Augestad for his assistance in some of the preparations.

## REFERENCES

1. Claisen, L. *Ber.* **22** (1889) 3271.
2. Heikel, A. *Suomen Kemistilehti* **B 8** (1935) 33.
3. Heikel, A. *Suomen Kemistilehti* **B 11** (1938) 5.
4. Lora-Tamayo, M., and Leon, J. L. *J. Chem. Soc.* (1948) 1499.
5. Berner, E. *J. Chem. Soc.* (1946) 1052.
6. Dieckmann, W. *Ber.* **47** (1914) 1432.
7. Meldrum, A. N., and Perkin jun., W. H. *J. Chem. Soc.* **95** (1909) 1889.
8. *Newer methods of preparative organic chemistry.* New York (1948) p. 527.

Received March 14, 1949.