

Cyclic Compounds from Acetopyruvic Esters

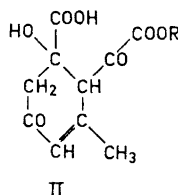
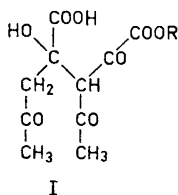
Part IV. Revision of Previous Results

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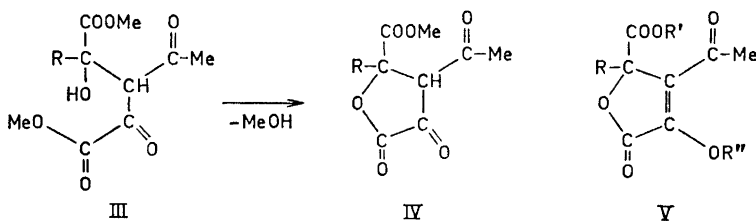
A new scheme for the condensation of acetopyruvic esters is proposed. According to this the condensation product (methyl 2-acetonyl-3-acetyl-4-hydroxy-5-oxo-dihydro-2H-furan-2-carboxylate) contains an unsaturated γ -lactone ring to which an enolic hydroxyl group is bound. A τ value of about 4 in PMR indicates that there is no hydrogen bonding, although a carbonyl group is in β -position to the hydroxyl. It is suggested that the reason for this is that the single bond connecting the two double bonds has a transoid conformation. The crystalline hydrogenation product (methyl-2-acetonyl-3-ethyl-4-hydroxy-5-oxo-dihydro-2H-furan-2-carboxylate) contains an ethyl group and is also an enol. The crystalline substance obtained by treatment of the condensation product with methanol and hydrogen chloride (formerly called the HCl-product, now the isoester) is a bicyclic ester (formula XV) which contains a hydrogen-bonded enolic hydroxyl group (4-hydroxy-2,2'-dimethoxy-2,2'-dimethyl-5,5'-dioxo-tetrahydro-2H,2'H,3,4'-bifuryl).

The bimolecular condensation of acetopyruvic esters in an alkaline medium was first described by Claisen.¹ He found that the crystalline condensation product could be titrated as a monobasic acid and therefore meant that one of the ester groups was hydrolyzed during the process. The open-chained formula I which Claisen gave for the condensation product would explain that treatment with barium hydroxide caused the splitting off of oxalic acid and after ring closure the formation of 3-methyl-5-hydroxybenzoic acid.



Berner and Laland² who in 1949 started an investigation of the condensation product verified the observation of Heikel³ that the product contained one molecule of crystal water which could be removed in a vacuum and afterwards was taken up in a moist atmosphere. They concluded therefore that Claisen's formula could not be correct. The presence of the crystal water together with the fact that the condensation product could be resolved optically into components of relatively high rotation led Berner and Laland to assume the cyclic structure II. The condensation product obtained from the methyl ester of acetopyruvic acid is in the following called the *methyl product* (MP), while the corresponding product from the ethyl ester is called the *ethyl product* (EP).

It has been proved (see experimental part) that the two molecules of acetopyruvic esters are linked as in Claisen's formula I. However, the conception that one of the ester groups is hydrolyzed during the condensation process is obviously wrong. It is instead suggested that a γ -lactone ring is established by splitting off alcohol from the primary condensation product III. This would give formula IV for the MP, but the acidic character of the product shows that it must actually consist of one of the two possible enolic forms to which then one molecule of water is bound (in the formulae $R = \text{CH}_3 \cdot \text{CO} \cdot \text{CH}_2 -$).



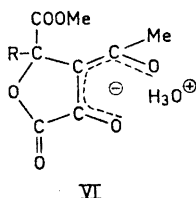
- Va $R' = \text{Me}, R'' = \text{H}$
 Vb $R' = \text{Me}, R'' = \text{Me}$
 Vc $R' = \text{Me}, R'' = \text{Ac}$
 Vd $R' = \text{Et}, R'' = \text{H}$
 Ve $R' = \text{Et}, R'' = \text{Me}$
 Vf $R' = \text{Et}, R'' = \text{Ac}$

In analogy with the acetopyruvic ester in which the enolic hydroxyl is predominantly at the α -position it is reasonable to assume that Va is the correct form (the other enolic form would have the hydroxyl group in the side-chain). Another argument in favour of Va is that it leads to stabilization of the five-membered lactone ring by establishing a double bond in the ring. As a parallel could be mentioned cyclopentane-1,2-dione which is nearly 100 % enolized.

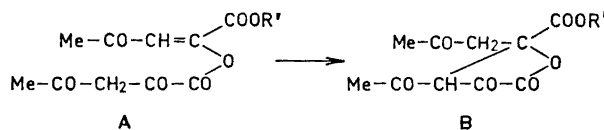
The PMR spectrum of the MP (hydrate form) shows a signal at $\tau = 3.95$ of intensity three protons (mobile proton plus hydrate water), while the anhydrous MP shows $\tau = 3.0$ of intensity one proton. The τ values indicate that there is no hydrogen-bonded enol. The plausible explanation for this is

that the single bond connecting the two double bonds in V has a transoid conformation as indicated in the formula which prevents the establishment of a hydrogen bond.

The molecule of water in the MP seems to be stronger bound than ordinary crystal water, and it is therefore suggested that the MP has the character of a salt in which H_3O^+ forms the cation as demonstrated in formula VI.



In the above scheme for the condensation process it is supposed that the initial step consists of a nucleophilic attack of an ester anion with the negative charge localized at the β -carbon atom on the α -carbonyl group in another ester molecule. Alternatively a nucleophilic reaction could be visualized in which an ester anion with the charge on the oxygen attacks the carboxyalkyl group of another ester molecule leading to the primary product A. The secondary step could then consist of an intramolecular cyclization in a Michael manner and would lead to B which is identical with formula IV above.



a) *Acidity and spectra of the condensation product.* The MP is a fairly strong acid. A 0.01 M solution in water has pH 2.2 (EP same value) as compared with 2.0 and 3.4 for 0.01 N solutions of hydrochloric and acetic acids, respectively. As expected the MP could be titrated as a monobasic acid and was recovered unchanged on acidifying the titrated solution.

The PMR spectrum of the MP in deuterated chloroform (details in Table 1) shows a frequency of the active hydrogen at about $\tau=3.97$ (for EP about 4.0). This ought to fit with the special structure of the hydrate given in formula VI. Another characteristic feature of the spectrum is the AB system due to the methylene group with a coupling constant of about 18 cps. A similar system is often realized when a methylene group is bound to an asymmetric carbon atom. As an example a coupling constant of the same magnitude was found in the case of citramalic acid and its ester.

Table 1.^a

Formula V	$\text{CH}_3-\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}_2-$	$\text{CH}_3-\overset{\text{O}}{\parallel}{\text{C}}-\overset{\text{O}}{\parallel}{\text{C}}=$	$\begin{array}{c} \text{H}_B \\ \diagdown \text{C} \diagup \\ \text{H}_A \end{array}$	$-\text{COOR}'$	$-\text{OR}''$
Va	τ 7.83 (3H) Singl.	τ 7.47 (3H) Singl.	τ 6.68; 6.29 Two doubl. AB 17.9	τ 6.24 (3H) Singl.	τ 3.97 (3H) ^b Singl.
Vb	τ 7.87 (3H) Singl.	τ 7.53 (3H) Singl.	τ 6.65; 6.40 Two doubl. AB 18.0	τ 6.25 (3H) Singl.	τ 5.61 (3H) Singl.
Vc	τ 7.83 (3H) Singl.	τ 7.52 (3H) Singl.	τ 6.66; 6.37 Two doubl. AB 17.2	τ 6.23 (3H) Singl.	τ 7.58 (3H) Singl.
Vd	τ 7.79 (3H) Singl.	τ 7.45 (3H) Singl.	τ 6.64; 6.27 Two doubl. AB 17.8	τ 8.72 (3H) Tripl. 5.74 (2H) Quart. 7.5	τ 4.04 (3H) ^b Singl.
Ve	τ 7.86 (3H) Singl.	τ 7.52 (3H) Singl.	τ 6.66; 6.42 Two doubl. AB 17.8	τ 8.74 (3H) Tripl. 5.79 (2H) Quart. 7.1	τ 5.61 (3H) Singl.
Vf	τ 7.84 (3H) Singl.	τ 7.53 (3H) Singl.	τ 6.67; 6.39 Two doubl. AB 17.5	τ 8.76 (3H) Tripl. 5.78 (2H) Quart. 7.2	τ 7.59 (3H) Singl.

^a Chemical shifts (τ) are given in ppm, coupling constants (J) in cps.

^b Signals include enolic protons and protons from hydrate water.

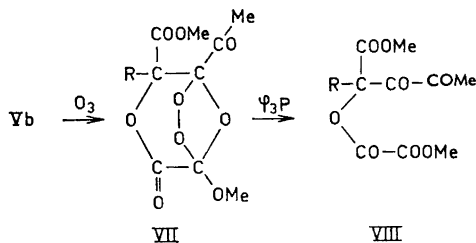
The UV spectra of the MP as well as of the EP in ethanol were strongly dependent upon the presence of water. MP from which the hydrate water had been removed as far as possible in a vacuum when dissolved in anhydrous ethanol showed λ_{max} 274 $m\mu$ ($\epsilon=10\ 300$) and only a weak shoulder at about 320 $m\mu$ ($\epsilon=3000$). By gradually adding water the maximum at 274 $m\mu$ diminished and the absorption at 320 increased, and after 15 % water had been added only the absorption at λ_{max} 320 $m\mu$ ($\epsilon=12\ 300$) remained. The same

change in the UV spectrum took place by adding one equivalent of alkali to the solution in ethanol.

The maximum at $274\text{ m}\mu$ is obviously due to the conjugated system in the un-dissociated enol-form and the maximum at $320\text{ m}\mu$ to the enolate ion. This bathochromic shift is commonly known as the phenol-phenolate shift. About the same change of absorption took place in the case of methyl aceto-pyruvate. The ester dissolved in ethanol had $\lambda_{\text{max}} 292\text{ m}\mu$ ($\epsilon=7400$) and after adding one equivalent of alkali $\lambda_{\text{max}} 315\text{ m}\mu$ ($\epsilon=9000$). A similar behaviour was shown by other enols as described below.

The methyl ether of MP (MPMe) prepared by means of diazomethane showed $\lambda_{\text{max}} 277\text{ m}\mu$ ($\epsilon=10\,260$) and no absorption at longer wave-lengths. This would agree well with a structure of the methyl ether Vb. Further the PMR spectrum of MPMe (see Table 1) was very similar to that of the MP with the only exception that instead of the hydroxyl group the presence of an enolic methoxyl was shown at $\tau=5.61$.

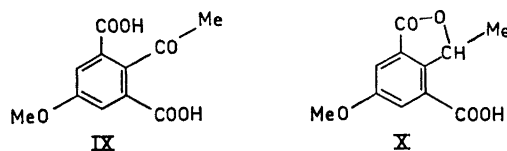
Ozonation of MPMe (MW=270) in either chloroform, ethanol, or methanol gave a crystalline peroxidic compound (m.p. $68-69^\circ\text{C}$) which decomposed rapidly by standing at room temperature. Mass spectrometry gave a small molecular ion peak at 318 corresponding to an ozonide being formed. This indicates that the double bond in MPMe is located in the lactone ring and not in the side-chain. In the latter case one would expect different products when ozonizing in chloroform or alcohols. According to the Criegee mechanism for ozonation⁴ ozonides are normally not formed in protic solvents. But when the double bond is located in a five-membered ring ozonides have been formed with acetic acid as solvent.⁵ PMR of the present ozonide (VII) showed four methyl peaks as did also the product (VIII) from reduction of VII with triphenylphosphine.⁶



b) *Optically active components.* By means of strychnine the EP had previously² been resolved into components of relatively high rotation. This has been verified and it has been found that also the MP, if not as easily, could be resolved. The specific rotation in ethanol of the components of both products were of the same magnitude ($90-100^\circ$). It increased on dilution especially with water, and decreased somewhat on heating the solution due to racemization.

A levorotatory component of the EP with the specific rotation -99.2° on treatment with diazomethane gave a methyl ether with specific rotation -92.7° .

c) *Degradation of the MP.* As already mentioned Claisen found that the condensation product on treatment with barium hydroxide split off oxalic acid and gave 3-methyl-5-hydroxybenzoic acid, $C_8H_8O_3$. It has now been found that only about 50 % of the condensation product were degraded in this way. The rest underwent a cyclization in such a way that all ten directly linked carbon atoms in the product were retained. The new degradation product is, in accordance with what could be expected from structure V, 2-acetyl-5-hydroxyisophthalic acid and was conveniently isolated as the methyl ether IX.



The carbonyl group in IX is sterically hindered and no hydrazone or semicarbazone could be obtained. The carbonyl group was, however, easily reduced with sodium amalgam giving the corresponding secondary alcohol which immediately lost water to give the phthalide derivative X.

d) *Hydrogenation of the MP.* By catalytic hydrogenation of the MP about two mole hydrogen were taken up resulting in the formation of about equal quantities of two products: a crystalline substance slightly soluble in cold water, and a yellowish syrup which was easily soluble in water. They are designated HMPA and HMPB, respectively.

The HMPA, $C_{11}H_{14}O_6$, could be recrystallized from rather concentrated solutions in water. From dilute solutions a hydrate $C_{11}H_{14}O_6 \cdot H_2O$ generally separated which easily lost the crystal water in a desiccator. A 0.01 M solution had pH 3.90. On titration it required one equivalent of alkali and was recovered unchanged on adding mineral acid. It gave monoderivatives with dinitrophenylhydrazine, semicarbazide, and hydroxylamine. It was acetylated to a monoacetyl derivative and on treatment with diazomethane gave a methyl ether $C_{12}H_{16}O_6$.

Extensive reduction as described in the experimental part led to the isolation of β -ethylglutaric acid. This proved that the linking of the two molecules acetoacetic ester took place between the methylene group in the one and the α -carbonyl in the other. It was at first thought that the ethyl group was formed during the reduction process, but the PMR spectrum showed decisively that an ethyl group was present in the HMPA itself. Also the PMR spectra of the methyl ether and the acetyl derivatives confirmed the presence of the ethyl group. As seen in Table 2 these spectra contained a similar AB system as in the MP.

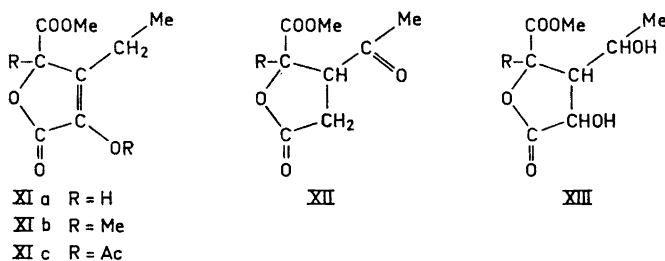
Table 2.^a

Formula XI	CH_3-CH_2-	$\text{CH}_3-\text{CO}-$	$\text{CH}_3-\text{CH}_2-\overset{\text{I}}{\text{C}}=$	$\begin{array}{c} \text{H}_A \\ \diagup \\ \text{C} \\ \diagdown \\ \text{H}_B \end{array}$	$-\text{COOMe}$	OR'
XIa τ J	8.84 (3H) Tripl. 7.5	7.80 (3H) Singl. 7.5	7.66 (2H) Quart. 7.5	7.13; 6.49 Two doubl. AB 17.5	6.21 (3H) Singl.	3.28 (1H) Singl. (broad)
XIb τ J	8.89 (3H) Tripl. 7.5	7.82 (3H) Singl. 7.5	7.52 (2H) Quart. 7.5	7.19; 6.51 Two doubl. AB 17.5	6.22 (3H) Singl.	6.01 (3H) Singl.
XIc τ J	8.88 (3H) Tripl. 7.8	7.75 (3H) Singl. 7.8	7.62 (2H) Quart. 7.8	7.07; 6.45 Two doubl. AB 17.4	6.18 (3H) Singl.	7.53 (3H) Singl.

^a Chemical shifts (τ) are given in ppm, couplings constants (J) in cps.

The presence of the ethyl group was further shown by isolating propionic acid as one of the oxidation products of the HMPA. It has also been found⁷ that the degradation product $\text{C}_{10}\text{H}_{10}\text{O}_5$ described by Berner and Laland² contains an ethyl group.*

The addition of two moles hydrogen with an intermittent loss of water would lead to the substances XIa and XII and the addition of hydrogen alone to XIII ($\text{R}=\text{CH}_3\cdot\text{CO}\cdot\text{CH}_2-$).



* Note added in proof: The structure of the methyl ether of the hydrogenated product HMPA (XIb) has now been confirmed by X-ray crystallography performed by F. Mo and B. K. Sivertsen, Institute of X-ray Crystallography, The Technical University of Norway, 7034-Trondheim NTH, Norway. A report on this will be presented at the "VIII International Congress of Crystallography", Stony Brook, New York, in August 1969.

It is obvious that XIa represents the crystalline fraction. The PMR spectrum shows a mobile proton at $\tau=3.3$, a normal value for an enol not engaged in hydrogen bonding. The UV spectrum in ethanol had λ_{\max} 241 $m\mu$ ($\epsilon=11\ 400$); after adding alkali another maximum appeared at 281 $m\mu$ ($\epsilon=5800$). The corresponding methyl ether had only one maximum at 239 $m\mu$ ($\epsilon=8200$).

The other fraction HMPB may contain the substances XII and XIII but none of them have so far been isolated. However, after treatment of the syrup with *p*-nitrobenzoylchloride a substance was isolated (m.p. 162°) having a composition not far from that calculated for a diester of XIII.

The degradation of the HMPA by treatment with barium hydroxide leading to the three substances $C_{10}H_{10}O_5$, $C_8H_{12}O_3$, and oxalic acid² is easily explained by the new formula XIa and therefore not dealt with in detail here.

On hydrogenating the optically active components of MP and EP the corresponding active hydrogenated products were isolated. During the hydrogenation the sign of the rotation was not changed but the specific rotation increased considerably, *viz.* from about 90° to about 250°.

e) *The isomethylester derived from MP and from EP.* On treatment of MP or EP with methanol containing hydrogen chloride Berner and Laland² isolated the same substance $C_{12}H_{14}O_7$ which was isomeric with the methyl ether of MP. It was then called the HCl-product but is now called the isoester (IMP). The two isomeric substances gave on degradation with barium hydroxide the same products as obtained from the MP itself. The isoester differed, however, in its properties considerably from the methyl ether. Thus it could be titrated as a monovalent acid and it gave with one molecule diazomethane a crystalline enol ether.

On catalytic hydrogenation the isoester added only one mole hydrogen. Degradation of the hydrogenated isoester was carried out by Bernatek⁸ who found that nearly one mole oxalic acid was split off, and that a dihydrobenzene derivative $C_8H_{10}O_3$ was formed which on dehydrogenation gave the same methylhydroxybenzoic acid as obtained from the MP.

The degradation has now been carried out under such mild conditions that a cyclization was prevented (see next paragraph). The result was the isolation of α -propyl- γ -methylbutyrolactone proving decisively that the condensation products of acetyruvic esters contain an open skeleton of carbon atoms.

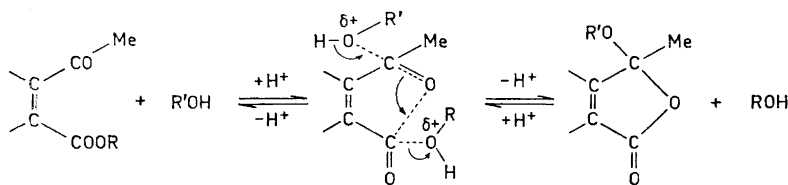
The elucidation of the structure of the isoester was based mainly on the results of the spectrometric investigations. The UV spectrum in anhydrous ethanol had a strong maximum at 288 $m\mu$ ($\epsilon=12\ 500$) and a weak one at 352 $m\mu$ ($\epsilon=2150$). After adding one equivalent alkali the absorption at 288 $m\mu$ had decreased ($\epsilon=6000$) and that at 352 $m\mu$ (obviously due to the enolate ion) increased ($\epsilon=8600$). Decisive was the PMR spectrum which showed the presence of one mobile proton (at $\tau=-0.65$ which could be hydrogen-bonded enol), one olefinic proton, two tertiary methyl groups, and two tertiary methoxyl groups (see Table 3). An extensive rearrangement must therefore have taken place during the formation of the isoester. It should be mentioned that also the methyl ethers of the condensation products were converted into the isoester on treatment with methanol containing hydrogen chloride (or sulphuric acid).

Table 3.^a

Formula XIV	$\text{CH}_3-\overset{\text{H}}{\underset{\text{H}}{\text{C}}}-$	$\text{CH}_3\text{O}-\overset{\text{H}}{\underset{\text{H}}{\text{C}}}-$	$-\overset{\text{H}}{\text{C}}=\overset{\text{H}}{\text{C}}-$	OR
XIVa τ	8.27; 8.20 (3H) Two singl.	6.82, 6.65 (3H) Two singl.	2.95 (1H) Singl.	-0.65 (1H) Singl. (broad)
XIVb τ	8.29, 8.26 (3H) Two singl.	6.71; 6.73 (3H) Two singl.	2.59 (1H) Singl.	5.83 (3H) Singl.
XIVc τ	8.30 (6H) Singl.	6.71 (6H) Singl.	2.60 (1H) Singl.	7.65 (3H) Singl.

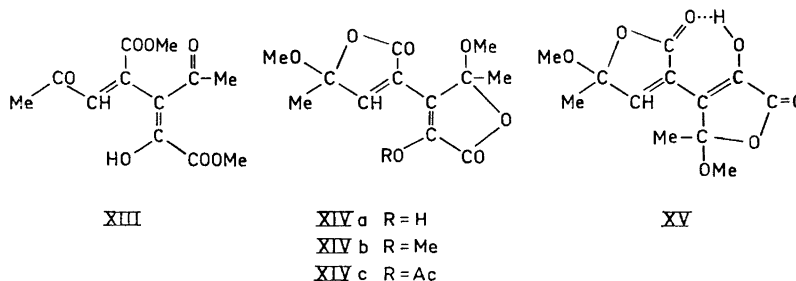
^a Chemical shifts (τ) are given in ppm.

The final solution of the problem depended on experience gained by esterification of certain γ -ketoacids. The free ketoacids as well as their open esters on treatment with an alcohol and mineral acid were turned nearly completely into cyclic esters. This acid-catalyzed transformation could be formulated by the following scheme:



The experiments show that the equilibria are completely displaced to the right.

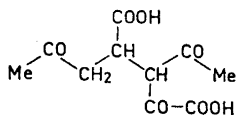
When the MP (Va) is treated with methanol and mineral acid the lactone ring is opened and one mole of water is split off. The bis- γ -ketoester thus



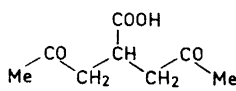
formed (XIII) stabilizes itself according to what has been said above as the bis-cyclic ester XIVa. As the PMR spectrum shows the presence of a hydrogen-bonded enol the formula of the isoester is written as XV.

The isoester contains two asymmetric carbon atoms and it was found that an optical resolution was possible, but no attempts were made to prepare the pure components.

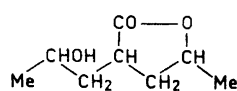
f) *Degradation of the hydrogenated isoester.* The hydrogenated isoester was a crystalline, very hygroscopic substance⁸ which rapidly deliquesced in a moist atmosphere whereby a hydrolysis of the methoxyl groups set in. After complete hydrolysis under very mild conditions the triketo-dicarboxylic acid XVI was obtained as a thick oil. It was oxidised with hydrogen peroxide to the crystalline diketocarboxylic acid XVII characterised by its bishydrazone. Catalytic hydrogenation of XVII led to another crystalline substance XVIII which on reduction with hydrogen iodide and red phosphorus gave α -propyl- γ -methylbutyrolactone identified by its boiling point and its hydrazone of known melting point.



XVI



XVII



XVIII

EXPERIMENTAL PART

General. PMR-spectra were recorded on a Varian A 60 A Spectrometer, using deuteriochloroform as solvent with TMS as internal standard.

UV-spectra were recorded on a Perkin-Elmer Spectrophotometer Model 137 UV.

Melting points are not corrected. Several experiments of interest for the present paper have been described earlier in this series²⁻⁴ and are not or only shortly mentioned.

Preparation of the MP. The best way of preparing the pure MP was by first preparing pure methyl acetopyruvate and shake this with a solution of sodium acetate.² Recrystallizations from hot aqueous solutions should be avoided. Instead the MP was dissolved in a small quantity of ethanol (or methanol) and cold water added. M.p. 76°.

By titration the MP required one equivalent of alkali for neutralization. By adding more alkali the solution became intensely yellow but no oxalic acid was split off. After adding mineral acid more than 80 % of the MP was recovered by extraction with ether as an oil which on grinding with a few drops of water crystallized. M.p. 75°.

Acetyl derivative. To a solution of MP (1 g) in acetic anhydride (10 ml) two drops of conc. sulphuric acid were added. After 30 min the rather dark solution was shaken with ice-water and extracted with ether. A yellow oil (0.9 g) was obtained which crystallized. Recrystallized from ethanol it was colourless, m.p. 71°. (Found: C 52.30; H 4.99. Calc. for C₁₃H₁₄O₆: C 52.35; H 4.73).

Optical resolution of EP and MP. The resolution of the EP by means of strychnine has been carried out earlier.² By repeating the experiment the rotation of the levo-form was found to be $[\alpha]_D^{20} = -89.2^\circ$ ($c = 4.67$ in abs. ethanol), the rotation being somewhat greater in aqueous ethanol. By recrystallization from hot water a partial racemization took place. The methyl ether prepared by means of diazomethane had $[\alpha]_D^{20} = -97.5^\circ$ ($c = 4.05$ in methanol) and did not racemize on recrystallization. In another experiment the levorotatory EP had $[\alpha]_D^{20} = -99.2^\circ$ ($c = 0.186$ in ethanol). The dextro-form isolated from the mother liquor had $[\alpha]_D^{20} = +71.7^\circ$ ($c = 0.126$ in ethanol).

The resolution of the MP met with difficulties, but in the end crystals were obtained by using acetone as a solvent. Seeding with these crystals resolution was carried out as by the EP. The levo-form had $[\alpha]_D^{20} = -88.9^\circ$ ($c = 0.177$ in ethanol) and the dextro-form $[\alpha]_D^{20} = +55.0^\circ$ ($c = 0.146$ in ethanol).

Degradation of the MP. To a solution of $\text{Ba}(\text{OH})_2 \cdot 8\text{aq}$ (44 g) in water (400 ml) MP (20 g) was added under stirring and the strongly yellow-coloured solution heated one hour on the steam-bath. The barium oxalate which had separated was purified by dissolving in hydrochloric acid and renewed precipitation; it weighed 9.7 g or 54.7 % of theory.

The filtrate from the oxalate was acidified by adding 50 ml 5 N HCl when it became strongly violet-coloured. The colour faded on the subsequent concentration to about 200 ml. Next day a crystalline substance (4.4 g) had separated which was identified as 3-methyl-5-hydroxybenzoic acid, m.p. 211° . By extracting the filtrate twice with 500 ml ether a yellowish substance (7 g) was obtained which was methylated with dimethyl sulphate (15 ml) and strong alkali. After saponifying the ester groups by boiling the alkaline solution and subsequent acidifying, a brown oil (6.7 g) was extracted with ether. After some time the oil had crystallized and was then dissolved in hot water. On cooling 1.6 g of the methyl ether of the 3-methyl-5-hydroxybenzoic acid had separated, m.p. and mixed m.p. 132° . The mother liquor on concentration gave hard crystals (3.9 g) which after crystallizations from water and ethyl acetate had m.p. 182° . 44.6 mg substance required 4.02 ml N/5 NaOH. (Found: C 55.35; H 4.06; CH_3O 12.98; $M = 236$. Calc. for $\text{C}_{11}\text{H}_{10}\text{O}_6$: C 55.46; H 4.23; CH_3O 13.02; $M = 238.2$).

This substance, obviously 2-acetyl-5-methoxyisophthalic acid (IX), was reduced in the following way. A solution of IX (1 g) in water (40 ml) was neutralized with alkali and pieces of 4 % sodium amalgam added. The solution was shaken continuously at room temperature and small portions of dilute sulphuric acid added from time to time. After 15 min the reduction was discontinued by pouring from the amalgam and adding a surplus of sulphuric acid. The phthalide derivative X (0.21 g) which separated was recrystallized several times from water, m.p. 217° . 136.1 mg substance required 3.07 ml N/5 NaOH. (Found: C 59.43; H 4.63; CH_3O 14.10; $M = 221$. Calc. for $\text{C}_{11}\text{H}_{10}\text{O}_5$: C 59.46; H 4.54; CH_3O 13.97; $M = 222.2$).

Hydrogenation of the MP. A solution of MP (20 g) in anhydrous methanol (150 ml) to which had been added platinum oxide (1 g) was shaken with hydrogen at atmospheric pressure and room temperature. During 24 h 3875 ml (22° , 760 mm) hydrogen had been taken up, equal to 3464 ml under normal conditions. Calculated for two mole H_2 3450 ml.

The filtrate from the catalyst was concentrated in a vacuum desiccator above calcium chloride when about 8 g of a beautiful crystalline substance separated: HMPA (XI). The filtrate on concentration gave a little more of the crystals but mainly about 8 g of an oily substance (HMPB) which was easily soluble in water and may contain the substances XII and XIII (see paragraph d).

HMPA after recrystallization from a concentrated solution in water had m.p. $164-165^\circ$. 99.8 mg substance required 2.04 ml N/5 NaOH. (Found: C 54.51; H 5.94; $M = 245$. Calc. for $\text{C}_{11}\text{H}_{14}\text{O}_6$: C 54.51; H 5.78; $M = 242.2$).

On crystallization from a dilute aqueous solution needles were obtained having the same m.p. (Found: C 51.02; H 6.62. Calc. for $\text{C}_{11}\text{H}_{14}\text{O}_6 \cdot \text{H}_2\text{O}$: C 50.77; H 6.15). The hydrate on being kept in a vacuum desiccator above sulphuric acid lost 6.33 % in weight, calculated 6.57 %.

Derivatives of the hydrogenated MP. A monoderivative with 2,4-dinitrophenylhydrazine has been described before.²

Semicarbazone: To a mixture of 1 g semicarbazide hydrochloride and 1 g potassium acetate in water and a little ethanol 1 g of HMPA was added and the solution heated on the water-bath until all had dissolved. The semicarbazone, which separated on standing was filtered, washed with water and ethanol and finally boiled several times with ethanol, m.p. $196-198^\circ$. (Found: C 48.08; H 5.87; N 14.11. Calc. for $\text{C}_{12}\text{H}_{17}\text{O}_6\text{N}_3$: C 48.16; H 5.73; N 14.06).

An oxime was prepared according to the method of Schmidt.⁹ To a solution of HMPA (2 g) in methanol (40 ml) a mixture of 1 g hydroxylamine hydrochloride and 1.6 g barium carbonate was added and the solution refluxed for 5 h. The filtrate from undissolved barium carbonate was concentrated at room temperature in a vacuum desiccator. The remaining oil (2.4 g) crystallized on grinding. The oxime after recrystallizations first from water and then from chloroform-petrol ether had m.p. 138–139°. (Found: C 51.23; H 5.97; N 5.21. Calc. for $C_{11}H_{15}O_4N$: C 51.36; H 5.88; N 5.45).

Acetylation: To a solution of 1 g HMPA in 10 ml acetic anhydride two drops of concentrated sulphuric acid were added. No colour appeared. After 20 min the solution was poured into ice-water and the acetylated product extracted with ether. It was obtained as an oil which crystallized spontaneously. Recrystallized from ethanol, m.p. 78°. (Found: C 54.96; H 5.80. Calc. for $C_{13}H_{16}O_7$: C 54.93; H 5.67).

Methylation: Pulverized HMPA (3 g) was added in portions to an ethereal solution of diazomethane. After completion of the reaction the solvent was evaporated in a vacuum. The crystalline residue after recrystallizations from ethanol had m.p. 67°, yield 1.8 g. (Found: C 56.39; H 6.15; CH_3O 23.63. Calc. for $C_{12}H_{16}O_6$: C 56.29; H 6.29; CH_3O 24.22).

The methylated product gave a mono-2,4-dinitrophenylhydrazone crystallizing in yellow needles from ethanol, m.p. 177–178°. (Found: C 49.77; H 4.73; N 12.64. Calc. for $C_{18}H_{20}O_9N_4$: C 49.55; H 4.62; N 12.83).

Reduction of the hydrogenated MP. In a wide-necked bottle HMPA (5.2 g) was dissolved in 30 ml ethanol and 40 ml water, and 4 % sodium amalgam which had quickly been washed with water was added. In order to promote the reduction the bottle was shaken continuously and the temperature gradually raised to 40°. The milieu was kept as neutral as possible by adding from time to time small amounts of hydrochloric acid and controlling the reaction on pH-paper. When samples did not give yellow colour with alkali the reduction was considered as finished, which generally took about 3 h. To the solution decanted from the amalgam 10 ml of 5 N hydrochloric acid were added and the solution concentrated to about 20 ml. Sodium chloride separated and was filtered off and washed with a little acid. By extraction twice with 350 ml ether a thick oil was obtained which after drying in a vacuum desiccator above sulphuric acid weighed 3.2 g. It was titrated by adding an excess of alkali and retitrating with hydrochloric acid. The found equivalent weight 106 corresponds to M 212; calc. for $C_{10}H_4O_5$: M 214.

A part of the above reduction product (1.8 g) was heated with 15 ml hydroiodic acid (d 1.7) and 0.5 g red phosphorus in a bomb tube for 8 h to a temperature of 180–190°. On dilution with 40 ml water a small amount of an oil appeared on the surface and was removed by distilling off a little of the solution. Extracting the rest of the solution twice with ether gave 0.85 g of an oil which crystallized spontaneously. After recrystallization from benzene; m.p. 73°, the m.p. being the same after mixing with an authentic sample of β -ethylglutaric acid. 45.2 mg substance required 2.81 ml N/5 NaOH. (Found: C 52.41; H 7.40; M=161. Calc. for $C_7H_{12}O_4$: C 52.49; H 7.56; M=160.1).

Oxidation of the hydrogenated MP. If an ethyl group were present bound to a carbon atom propionic acid should be found among the oxidation products. It could be determined by oxidation to oxalic acid according to McNair.¹⁰ The HMPA (2.42 g) was dissolved in 150 ml water and 10 ml N NaOH added. A 5 % solution of potassium permanganate was added drop by drop and the temperature allowed to rise and held at 50°. After adding 220 ml the oxidation had practically stopped. The filtrate from MnO_2 was concentrated on the steambath and 20 ml 5 N sulphuric acid added causing a lively effervescence. The volatile acids were now distilled off, eventually after adding more water, and the distillate neutralized with 71.5 ml N/5 NaOH.

One half of the neutralized distillate was evaporated to dryness, the residue dissolved in 80 ml water containing 18 g sodium carbonate. After adding 130 ml 5 % potassium permanganate the solution was heated 3½ h in a boiling water-bath. Excess of permanganate was reduced by adding 50 ml ethanol. The filtrate from MnO_2 was acidified with acetic acid and an aqueous solution of calcium acetate added. After being kept warm over night the calcium oxalate was filtered, washed and dried. It weighed 0.32 g or 35 % of theory.

For comparison 0.220 g propionic acid after the same treatment gave 0.30 g calcium oxalate, showing that 68 % of the propionic acid had been oxidized to oxalic acid. As a control 0.240 g acetic acid on oxidation under the same conditions gave only 0.042 g calcium oxalate or 7.3 % of theory.

Hydrogenation of optically active EP and MP. A sample of optically active EP with the specific rotation -89.5° was dissolved in 25 ml anhydrous methanol and platinum oxide (0.1 g) added. The hydrogenation was completed in 5 h after which the filtered solution was evaporated in a vacuum. The residue was partly crystalline. By washing with methanol 0.2 g remained undissolved; it had the rotation $[\alpha]_D^{20} = -234^\circ$ ($\alpha_D = -9.43^\circ$, $c = 2.02$ in ethanol, 2 dm).

The filtrate from the 0.2 g was evaporated and the remaining substance recrystallized from water, m.p. 117° , $[\alpha]_D^{20} = -254^\circ$ ($\alpha_D = -10.78^\circ$, $c = 2.12$ in ethanol, 2 dm).

In the same way a sample of MP with specific rotation -88.9° gave a hydrogenated product with m.p. 143° and $[\alpha]_D^{20} = -258^\circ$ ($\alpha_D = -3.77^\circ$, $c = 1.46$ in ethanol, 1 dm).

The PMR spectrum of the active hydrogenated MP was identical with that of the inactive.

The isomethyl ester (IMP). The isoester (formerly the HCl-product) was originally prepared by dissolving the MP in methanol containing hydrogen chloride (1.1 N). It was later found by Bernatek (private communication) that it was even more simple to dissolve the MP in methanol and add some conc. hydrochloric acid. Also the use of conc. sulphuric acid gave the same result. The isoester was recrystallized from ethyl acetate, m.p. 156° .

Acetylation: A mixture of pulverized isoester (5 g), 20 ml acetic anhydride, and one drop of conc. sulphuric acid was shaken for some hours when a yellow solution was formed. On pouring into ice-water an oil separated which rapidly crystallized (3.3 g). After recrystallization from methanol-water, m.p. 130° . (Found: C 53.84; H 5.04. Calc. for $C_{14}H_{16}O_8$: C 53.84; H 5.17).

Methylation: Berner and Laland² found that the isoester reacted with two moles of diazomethane giving a compound $C_{14}H_{18}O_7$. It has now been found that the reaction can be led so that only one mole diazomethane is taken up. When an ethereal solution of diazomethane was added to a suspension of pulverized isoester (1 g) in ether no reaction took place. Only after adding a little methanol a smooth reaction began. As soon as a light yellow colour appeared the addition was discontinued and the solution evaporated. The crystalline residue (about 1 g) was recrystallized several times from ethanol, m.p. 93° . (Found: C 55.23; H 5.91; CH_3O 33.28. Calc. for $C_{13}H_{16}O_7$: C 54.92; H 5.67; CH_3O 32.75).

Hydrogenation of the isoester. Catalytic hydrogenation of the isoester was carried out as described by Bernatek.³ The reaction product having taken up one mole of hydrogen was a crystalline substance HIMP, m.p. $126-129^\circ$. It was hygroscopic and deliquesced rapidly when placed above a bowlful of water under a bell-jar. In order to complete the hydrolysis already begun the product was dissolved in water, the solution left at room temperature for some days, and then concentrated in a vacuum desiccator above calcium chloride. This procedure was carried out twice and gave a colourless thick oil having the equivalent weight 124; calculated for a methoxyl-free compound $C_{10}H_{12}O_7$, 122 (XVI).

Degradation of the hydrogenated isoester. To a solution of 9.6 g of XVI in 50 ml water 4 ml of 34 % hydrogen peroxide were added. The temperature rose to about 37° and the solution was afterwards heated on the water-bath a couple of hours until evolution of carbon dioxide had ceased. On evaporating the solution in a vacuum desiccator a clear syrup (6.5 g) was obtained which crystallized spontaneously (XVII). After recrystallization from ethyl acetate-petrol ether, m.p. 72° . 93.8 mg required 2.69 ml N/5 NaOH. (Found: C 55.36; H 6.95; M=174. Calc. for $C_8H_{14}O_4$: C 55.80; H 7.03; M=172.2).

The diketocarboxylic acid (XVII) gave a bis-2,4-dinitrophenylhydrazone which after crystallization from glacial acetic acid had m.p. 213° . (Found: C 45.17; H 4.00; N 20.71. Calc. for $C_{20}H_{20}O_{10}N_8$: C 45.11; H 3.79; N 21.05).

In order to verify the presence of a free carboxylic group the hydrazone was esterified by boiling for 3 h a sample (1.15 g) with 50 ml methanol to which 1.5 ml conc. sulphuric acid had been added. Filtering warm a yellow substance (0.95 g) was obtained. Crystallized several times from glacial acetic acid, m.p. 183° . (Found: C 46.14; H 4.26; N 20.44. Calc. for $C_{21}H_{22}O_{10}N_8$: C 46.16; H 4.06; N 20.51).

The diketoacid XVII cyclized easily, especially in the presence of alkali as the following experiment shows. To a solution of 0.2 g of XVII in a little water 20 ml N/5 NaOH were added and the solution heated on the water-bath for half an hour. On adding dinitrophenylhydrazine dissolved in hydrochloric acid a deep red hydrazone was obtained which after repeated crystallizations from anhydrous ethanol had m.p. 219°. (Found: C 50.16; H 4.07; N 16.81. Calc. for $C_{14}H_{14}O_6N_4$: C 50.30; H 4.22; N 16.76).

This hydrazone was identical with the hydrazone (m.p. 222°) of the compound $C_8H_{10}O_3$ obtained by Bernatek⁸ by degradation of the hydrogenated isoester with barium hydroxide. Mixed m.p. 221°.

The first step in the reduction of the diketoacid was conveniently effected, by catalytic hydrogenation. A sample of XVII (1.72 g), 0.3 g platinum oxide and 25 ml glacial acetic acid were shaken for 7 h in a hydrogen atmosphere at room temperature. The consumption of hydrogen (760 mm, 0°) after correction for the catalyst was 435 ml; calc. for two moles H_2 428 ml. The filtrate from the platinum was evaporated in a vacuum desiccator above sodium hydroxide. The crystalline residue (1.5 g) was recrystallized several times from ethyl acetate, m.p. 122° (XVIII). 81.0 mg required 2.57 ml N/5 NaOH. (Found: C 60.78; H 8.84; M=158. Calc. for $C_8H_{14}O_3$: C 60.74; H 8.92; M=158.2).

By the subsequent reduction of XVIII with hydrogen iodide the lactone ring remained unaffected. The lactone XVIII (3.5 g), 30 ml hydrogen iodide (*d* 1.7) and 2 g red phosphorus were refluxed 5 h. A few drops of oil swimming on the surface were removed by distilling off about 10 ml hydrogen iodide. After adding 10 ml fresh hydrogen iodide refluxing was continued for 20 h. The solution was then diluted with water and extracted with ether. On removing the ether a mobile oil (2.2 g) was obtained which distilled at 110°, 10 mm Hg. As the oil contained traces of halogen it was treated a short time with sodium amalgam and again taken up in ether. To the recovered only slightly coloured oil (1.25 g) 95 % hydrazine hydrate (0.5 g) was added and the mixture heated for a short time on the water-bath. The rather viscous oil after standing for some time in a vacuum desiccator crystallized (1.54 g). After recrystallizing several times from ethyl acetate, m.p. 139°. The m.p. of the hydrazide of α -propyl- γ -methylbutyrolactone is given as 138°. ¹¹ (Found: C 53.56; H 10.06; N 15.98. Calc. for $C_8H_{18}O_2N_2$: C 55.14; H 10.41; N 16.08).

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