

## 233. A New Synthesis with Maleic Anhydride.

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An addition was found to take place even at ordinary temperature between one mol. of acetylacetone and two mols. of maleic anhydride. It is suggested that the maleic anhydride first formed double molecules by a substitution addition, and that in a second stage the acetylacetone was added to the double molecules. By treatment with concentrated sulphuric acid the adduct lost water, giving a derivative of isocoumaranone which could be degraded to *p*-xylenol. The adduct and the dehydrated product showed, when treated with weak alkali, an interesting colour phenomenon caused by enolising processes. Maleic anhydride was found to react in a similar way with ethyl acetoacetate.

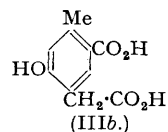
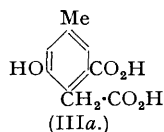
A  $\beta$ -DIKETONE is generally more or less enolised, and in some cases there is evidence of the existence even of dienols which would contain two accumulated double bonds. In the case of the simplest  $\beta$ -diketone, acetylacetone (I), it may be assumed that a dienol (II) could also exist. Such a dienol ought to react with maleic



(I.)



(II.)



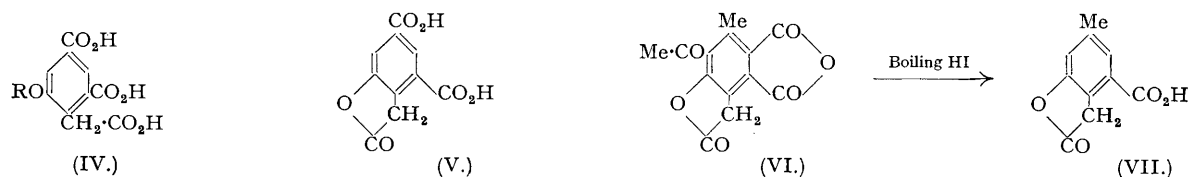
anhydride or other dienophilic compounds. In order to test this assumption, a mixture of acetylacetone and maleic anhydride was heated at 110—115° for two hours. It was apparent that a reaction had taken place for, on being kept for some time, the mixture deposited crystals of a new compound. It was found later that the

reaction took place even at room temperature, though very slowly, and for practical purposes a temperature of 70—80° was found the most suitable.

Assuming the reaction to be an addition of one mol. of maleic anhydride to one mol. of acetylacetone, a compound  $C_9H_{10}O_5$  should have been formed. Analysis of the new compound showed, however, the remarkable result that addition had taken place between one mol. of acetylacetone and two mols. of maleic anhydride, the *adduct* having the molecular formula  $C_{13}H_{12}O_8$  (VIII). The adduct was both a lactone and an acid anhydride, and it readily combined with one mol. of water, giving a crystalline *substance*,  $C_{13}H_{14}O_9$ . For total neutralisation the adduct required 3 equivs. of alkali. A solution of the adduct in ethyl acetate did not add on bromine. In a freshly prepared aqueous solution, however, addition of bromine took place. This solution also gave a red-violet colour with ferric chloride. By catalytic hydrogenation four atoms of hydrogen were taken up. The adduct was easily oxidised by potassium permanganate.

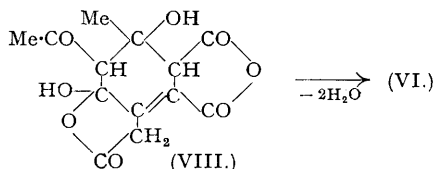
Before discussing the constitution of the adduct (VIII) and the manner of its formation, it is necessary to consider some of the degradation products. By treatment of the adduct with concentrated sulphuric acid two mols. of water were split off, an aromatic compound  $C_{13}H_8O_6$  (VI) being obtained. This was both an acid anhydride and a lactone. As will be shown it can, however, be regarded as a derivative of coumaran or, better, of *isocoumaranone*.

When the dehydrated adduct (VI) was boiled for some hours with concentrated hydriodic acid in the presence of red phosphorus no reduction took place, but one mol. of acetic acid and one mol. of carbon dioxide were split off, a colourless, crystalline substance  $C_{10}H_8O_4$  (VII) being formed. This substance was also a lactone and contained one free carboxyl group. The corresponding hydroxy-dicarboxylic acid,  $C_{10}H_{10}O_5$ , was obtained by acidifying the alkaline solution. It gave by methylation with methyl sulphate a compound containing three methoxyl groups, two of which could be removed by hydrolysis. The total decarboxylation of the acid, achieved by heating the sodium or calcium salt with calcium hydroxide, led to *p*-xylenol. The acid may therefore be either *5-hydroxy-3-carboxy-p-tolueneacetic acid* (IIIa) or the 2-carboxy-isomer (IIIb); no other structure is possible, because the parent substance (VI) is an acid anhydride and therefore must be derived from an acid having two adjacent carboxyl groups. In order to decide between (IIIa) and (IIIb) the following reactions were carried out. By oxidation of the *methyl ether* of (IIIa) with potassium permanganate the nuclear methyl group was converted into a carboxyl group, and a methoxy-tricarboxylic acid (IV, R = Me) was formed. When the corresponding hydroxy-tricarboxylic acid (IV, R = H), obtained by treatment with hydriodic acid, was sublimed in a high vacuum it lost only one mol. of water, yielding the lactonic *isocoumaranone-4 : 6-dicarboxylic acid*,  $C_{10}H_6O_6$  (V). From this it is evident that the compound  $C_{10}H_{10}O_5$  must have the formula (IIIa); for if formula (IIIb) had been correct, two molecules of water should have been lost during the sublimation, giving  $C_{10}H_4O_5$ , which would also have contained an acid anhydridic ring.



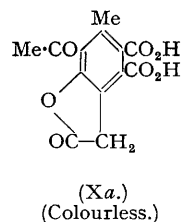
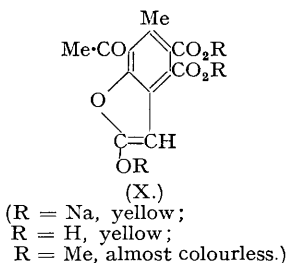
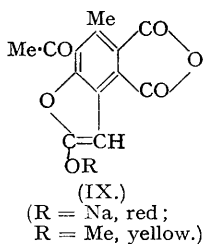
The compound  $C_{10}H_8O_4$ , obtained by the action of hydriodic acid on the dehydrated adduct, must be *6-methylisocoumaranone-4-carboxylic acid* (VII), and accordingly the dehydrated adduct must be the *anhydride of 7-acetyl-6-methylisocoumaranone-4 : 5-dicarboxylic acid* (VI). The formation of acetic acid during the boiling with hydriodic acid was remarkable, because the acetyl group is attached directly to the benzene nucleus. It must, however, have been due to the fact that the nucleus was fully substituted. There can be no doubt that (VI) was a methyl ketone, for it gave iodoform on treatment with an alkaline solution of iodine.

The adduct itself is formulated as (VIII) on the basis of its relationship to (VI) and the fact that it is formed from 1 mol. of acetylacetone and 2 mols. of maleic anhydride. The formula (VIII) does not show hydrogen bonds which undoubtedly exist between each of the two hydroxyl groups and the nearest carbonyl group.



The anhydride (VI) dissolved rapidly in aqueous sodium carbonate giving a blood-red solution which in a few minutes turned yellow. With sodium hydroxide the same dark red colour appeared, but in this case it turned yellow immediately. It is suggested that the action of the alkali in the first instance results in an enolisation only at the group  $\cdot CH_2 \cdot CO \cdot$ , giving a soluble enolate (IX, R = Na) the colour of which is ascribed to the 7 double bonds, all of which take part in a crossed conjugated system. The intensity of the colour of the primarily-formed enolate must be due to the fact that two of the carbonyl groups in the conjugated system form

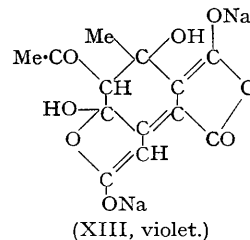
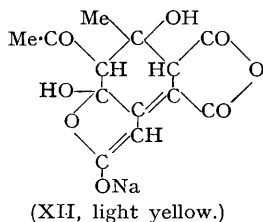
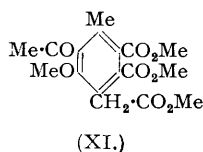
part of a heterocyclic ring for, when this ring was opened by the continued action of alkali, the colour brightened and became yellow (X, R = Na).



The red enolate still contained the acid anhydride ring, for, if the red solution was acidified, a colourless substance separated which was identical with the original dehydrated compound. If, however, the solution was acidified only after it had become yellow, the colour of the solution turned lighter yellow, but no precipitation took place. When this solution was left for some time excellent crystals of a bright yellow substance were formed. This substance (X, R = H) had m. p. 160° and the composition  $C_{13}H_{10}O_7$  and was obviously the free enolic form corresponding to the yellow enolate (X, R = Na); its aqueous solution showed the characteristic reaction of enols (a red-violet colour with ferric chloride), and it added bromine. It could generally be recrystallised unchanged from water. Once, however, during the crystallisation it changed into an isomeric, colourless substance, m. p. 176°, evidently the corresponding lactonic form (Xa). Subsequently it was found that the aqueous solution contained the two isomerides in equilibrium. On heating the solution the equilibrium was displaced in the direction of the enolic form, as shown by a deepening of the yellow colour. On cooling, the colour again became faintly yellow. From the aqueous solution the yellow or the colourless isomeride could be obtained by inoculation with one or the other. Both isomerides were reconverted into (VI) by concentrated sulphuric acid.

From the formula of the dehydrated adduct (VI) it would appear that no reaction should take place with diazomethane. The substance did, however, react, giving an intensely yellow crystalline substance, sparingly soluble in ether. The reaction with diazomethane must therefore be induced by an enolisation just as in the action of sodium carbonate, and the yellow substance must be the methyl ether (IX, R = Me) corresponding to the blood-red sodium salt. The presence of the double bond developed by the enolisation could not be proved directly in this methyl ether, but, as soon as the acid anhydride ring was opened, the unsaturated character of the compound became evident. The opening of the ring was achieved by boiling with methanol. By subsequent treatment with diazomethane, the dimethyl ester of the methyl ether (X, R = Me) was formed. This ester was practically colourless, with only a tinge of yellow. In the molten state, however, it had a marked yellow colour. In conformity with the structure (X, R = Me) the ester added two atoms of hydrogen on catalytic hydrogenation. It rapidly took up two atoms of bromine, with loss of 1 mol. of hydrogen bromide, so the resulting product had the composition  $C_{16}H_{15}O_7.Br$ . Apparently it is the hydrogen atom in the CH group which has thus been replaced by bromine, but this has not yet been verified.

Another ester,  $C_{17}H_{20}O_8$ , was obtained by methylating (VI) directly with methyl sulphate in alkaline solution. Under these conditions both the lactonic and the anhydride ring were opened, and the resulting product contained four methoxyl groups. It must be the fully methylated ester (XI), and accordingly it showed no unsaturated character.



The same ester was also obtained from the yellow substance (X, R = H) and the isomeric, colourless substance (Xa). Both these substances gave with diazomethane the same dimethoxy-compound which reacted readily with methanol. By treatment of the product of the latter reaction with diazomethane (XI) was formed. As (X, R = H) is probably an enol, this result was unexpected, and is being further examined.

A special interest is attached to the colour phenomenon accompanying the dissolution of the adduct in weak alkali. The pulverised adduct dissolved rapidly in dilute sodium carbonate solution, giving at first a faintly yellow solution. In the course of  $\frac{1}{4}$  minute or more, depending on the concentration of the sodium carbonate, the solution gradually became violet, this colour deepening in 20—30 mins. and then diminishing slowly during several days. The violet solution became dirty yellow when acidified, and immediately turned violet again when sodium carbonate was added. On the basis of the formula (VIII) for the adduct, these changes may be

interpreted in the following way. The dissolution is caused by enolisation. At first a mono-enolate (XII) is formed, which in solution is light yellow. Gradually a second enolisation sets in, resulting in the formation of the violet dienolate (XIII), which contains a system of crossed conjugated double bonds and so is strongly coloured. When mineral acid is added to the violet solution, the corresponding dirty yellow dienol is liberated.

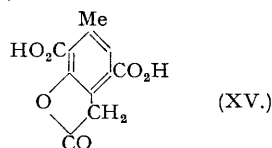
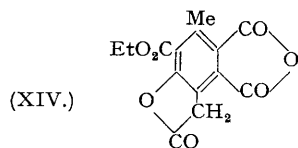
As the second step of the enolisation proceeds more slowly than the first, the process can be carried through in two stages. On shaking the finely pulverised adduct with a small quantity of dilute sodium carbonate, the mono-enolate is rapidly formed, but, as there is not sufficient alkali for the second stage, the solution remains light yellow (with perhaps a tinge of violet). Only after more sodium carbonate has been added to the yellow solution, from which the excess of adduct has been filtered off, does the solution gradually turn violet. Obviously only a small part of the adduct undergoes enolisation. In the greater part both the rings are most certainly opened by the action of the alkali.

The existence of the enolic forms was proved by means of the ferric chloride reaction. A few seconds after the sodium carbonate had been added, the colour of the solution still being only light yellow, the solution was acidified and ferric chloride added. A light red-violet colour indicated the presence of an enol. After treatment of the violet solution of the dienolate in the same way, a deeper red-violet colour appeared. It was also established that the formation of the enolic forms depended upon the existence of the acid anhydride ring, since the hydrated adduct did not give any colour with alkali or with ferric chloride.

The fact that the adduct reacts with diazomethane, although it contains no free carboxyl group, may obviously be due to its ability to pass into enolic forms. When the finely pulverised adduct was added to an ethereal solution of diazomethane, a slow reaction took place by which about one quarter of the adduct was converted into a crystalline substance (A), sparingly soluble in ether, while the remainder (B) dissolved completely during the reaction. The substance (A) had the composition  $C_{15}H_{16}O_8$  and contained two methoxyl groups. It may be the dimethyl ether corresponding to the violet enolate (XIII), but this is not yet proved. At present it can only be stated that (A) reacted with methanol and then with diazomethane, giving a *tri-methoxy*-compound  $C_{18}H_{20}O_9$ , m. p.  $146^\circ$ , most probably the trimethyl ester of the acid arising from the adduct when both the anhydride and the lactonic ring were opened. The remainder (B) also reacted first with methanol and then with diazomethane. In this way a mixture of a colourless, crystalline substance and a dark orange-coloured, viscous liquid was obtained. The former (m. p.  $109^\circ$  after recrystallisation from methanol) also contained three methoxyl groups. It had, however, the composition  $C_{17}H_{22}O_9$  and must therefore be a *homologue* of the above ester, m. p.  $146^\circ$ . This noteworthy result, *viz.*, that the action of diazomethane leads to the introduction of a methyl group which cannot be split off by the Zeisel-Fanto reaction, will be studied further. The orange-coloured liquid will also be examined more closely.

Ethyl acetoacetate also reacted with maleic anhydride in the same way as acetylacetone. The crystalline *adduct*,  $C_{14}H_{14}O_9$  (VIII, but with  $CO_2Et$  for  $COMe$ ), behaved like that obtained from acetylacetone, apart from the fact that on hydrogenation it absorbed only two atoms of hydrogen. For instance, it lost 2 mols. of water by treatment with sulphuric acid, resulting in formation of an aromatic compound, which dissolved in aqueous sodium carbonate with the same blood-red colour as the acetylacetone adduct, and from which similar derivatives could be prepared. These derivatives are analogous to those obtained from acetylacetone, but have a carbethoxy- instead of an acetyl group, and this difference accounts for the absorption of two hydrogen atoms less.

When the dehydrated adduct (XIV) from ethyl acetoacetate was boiled with hydriodic acid, it gave a mixture of  $C_{10}H_8O_4$  (VII), obtained from acetylacetone, and a substance  $C_{11}H_8O_6$  (XV), which, on prolonged boiling with hydriodic acid, gave (VII). The substance (XV) contained one carboxyl group more than (VII) and represented the primary product of the decarboxylation. As (XV) did not give an acid anhydride, the two carboxyl groups in the benzene nucleus could not be adjacent and consequently must be situated as shown in (XV).

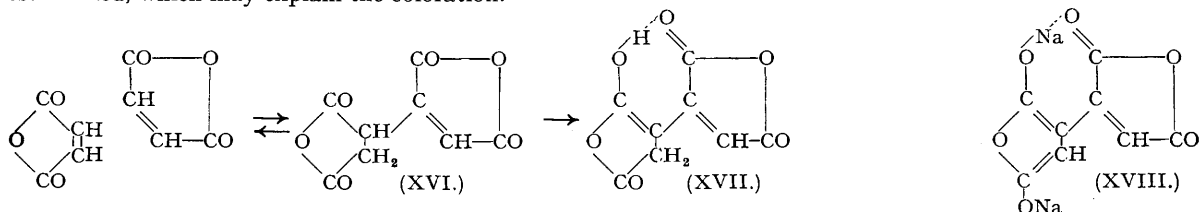


It remains to be explained how one molecule of acetylacetone (or ethyl acetoacetate) can react with two molecules of maleic anhydride to give an adduct with the constitution given above. From the formula (VIII) it is clear that a carboxyl group of one of the maleic anhydride molecules has been directly involved in the formation of the six-membered ring. This suggested that the first step in the reaction was a linking together of the two anhydride molecules to a double molecule (XVI). In this double molecule enolisation will take place, resulting in formation of a pair of conjugated double bonds (XVII). In the second stage of the reaction the enolic form of acetylacetone serves as a dienophilic component and is added to the double molecule of maleic anhydride.

A chance observation apparently justifying the suggestion of a primary formation of a double molecule of the maleic anhydride is that when dilute alkali was added to a solution of maleic anhydride in acetylacetone a light red to brown colour appeared for a shorter or longer time according to the conditions of the experiment. It made no difference if the anhydride was first dissolved in anhydrous methanol and the acetylacetone then added. If, however, the anhydride was dissolved in water before the acetylacetone was added, alkali produced

no colour. Ethyl acetoacetate behaved in the same way as acetylacetone, and it was even found that solutions of maleic anhydride in some other organic liquids gave a light red colour when alkali was added, although these liquids did not react with maleic anhydride under the same conditions as acetylacetone or ethyl acetoacetate. As examples of such liquids can be mentioned the esters of methyl- and dimethyl-acetoacetic acid, ethyl malonate, ethyl methylmalonate, and the esters of methanetricarboxylic acid.

These observations are interpreted in the following way. When maleic anhydride is dissolved in such liquids, molecules of the anhydride will react in pairs by means of a so-called substituting addition, resulting in the formation of double molecules of the type (XVI). It is suggested that the monomeric and the dimeric form of the maleic anhydride are interconvertible, and that an equilibrium exists containing only very little of the latter. In the double molecule enolisation will take place, giving an enol which is stabilised through the building up of a chelate structure as indicated in (XVII). When alkali is added, a further enolisation takes place in the double molecule, giving the dienolate (XVIII). In this a system of crossed conjugated double bonds is established, which may explain the coloration.



This explanation of the reaction of maleic anhydride with acetylacetone (or ethyl acetoacetate) must be regarded as a working hypothesis, and further investigations will be necessary in order to prove its correctness. The author has, however, found it appropriate to publish his results at this stage.

#### EXPERIMENTAL.

(Temperatures are uncorrected.)

**Acetylacetone and Maleic Anhydride.**—A lightly closed vessel containing acetylacetone (50 g.; 0.5 mol.) and maleic anhydride (98 g.; 1 mol.) was placed in an oven at 75°. After two weeks a compact and hard crystal cake had been formed. As the cake was very difficult to remove, it was more convenient to inoculate the solution a few days after the heating had started with crystals of the adduct and then stir it from time to time with a glass rod. In this way a paste of small crystals and a brown mother liquor were obtained. It was diluted with ethyl acetate (or ether) and filtered and the crystals were washed with the same solvent until colourless. Yield, 60–70%.

The reaction proceeded even at room temperature, although very slowly: a solution of maleic anhydride (19.6 g.) in acetylacetone (10 g.) in a closed vessel began to deposit crystals in about 40 days, and after 1½ years 18 g. of the adduct (62% of the theoretical) had been formed.

For most purposes the crude, washed product was pure enough. Purification was effected by powdering, and digestion with hot ethyl acetate. For analysis it was recrystallised from ethyl acetate; m. p. 180° (decomp.) (Found: C, 52.55; H, 4.2. C<sub>13</sub>H<sub>10</sub>O<sub>8</sub> requires C, 52.7; H, 4.1%). The adduct (VIII) could not be titrated directly, because of the violet colour which occurred when dilute alkali was added. An excess of 0.2N-sodium hydroxide was therefore rapidly added; after the substance had dissolved completely phenolphthalein was added, and the excess of alkali titrated (Found: *M*, as a tribasic acid, 297.8. C<sub>13</sub>H<sub>12</sub>O<sub>8</sub> requires *M*, 296.2). 5 G. in anhydrous methanol (50 c.c.) with platinum oxide (0.2 g.) absorbed 778 c.c. of hydrogen in the course of two days (Calc. for 4 atoms of hydrogen: 757 c.c.).

The adduct was practically insoluble in ether, benzene, carbon disulphide, and chloroform, but dissolved in hot acetone. The solution in ethyl acetate did not add bromine. When the adduct was boiled with water it slowly dissolved. A freshly prepared aqueous solution evidently contained an enolic form, since it gave a red-violet colour with ferric chloride, and added bromine. The solution was also coloured light violet by the addition of alkali. When, however, the aqueous solution had been heated for some time on the water-bath, practically no coloration occurred either with alkali or with ferric chloride and very little bromine was added. This was due to the opening of the acid anhydride ring, and the fully hydrated adduct gave no reactions for enols. A crystalline *monohydrate* was prepared by evaporating a solution of the adduct in alkali to which sulphuric acid had been added; after recrystallisation from water it had m. p. 194° (becoming violet at about 175°) (Found: C, 49.55; H, 4.55; *M*, by titration as a tribasic acid, 315.4. C<sub>13</sub>H<sub>14</sub>O<sub>9</sub> requires C, 49.7; H, 4.5%; *M*, 314.2).

The alkaline solution of the adduct was easily oxidised by potassium permanganate, but no definite oxidation product could be isolated.

**Acetylacetone Adduct and Diazomethane.**—To an ethereal solution of diazomethane, prepared from nitrosomethylurethane, finely pulverised adduct (8 g.) was added in small portions. A slow reaction started, and in a short time crystals separated. The reaction was promoted by shaking and stirring with a glass rod, and finally the whole was left overnight in an ice-chest. After being separated, washed with ether, and dried in a vacuum, the insoluble *product* (2 g.) had m. p. 148–150° [Found: OMe, 19.2. C<sub>13</sub>H<sub>10</sub>O<sub>8</sub>(OMe)<sub>2</sub> requires OMe, 19.15%].

This solid reaction product dissolved completely when shaken for 3 days with methanol at room temperature. Usually, however, the reaction was carried out by heating for 2 hours on the water-bath. The solution in methanol reacted vigorously with diazomethane. By evaporation of the solution a crystalline product (2.1 g.) was obtained, which by recrystallisation from methanol gave short prismatic crystals, m. p. 146°. Sometimes the recrystallisation would give fine needles with practically the same m. p. This was obviously a labile, dimorphic form, for if the mother-liquor with the crystals was left for some time the fine needles disappeared, and the prismatic crystals were formed. The needles or the prismatic crystals could also be obtained at will from the same solution by inoculating it with one form or the other [Found: C, 54.15; H, 5.75; OMe, 26.6. C<sub>13</sub>H<sub>11</sub>O<sub>8</sub>(OMe)<sub>3</sub> requires C, 53.95; H, 5.65; OMe, 26.15%].

The ethereal mother-liquor from the compound of m. p. 148–150° gave on evaporation a yellow syrup, the colour being intensified when the syrup was heated with 50 c.c. of methanol on the water-bath for 3 hours. After addition of excess of diazomethane and evaporation of the solvent, an orange syrup was left from which 2.35 g. of a colourless, crystalline *substance* separated. Recrystallised from ethanol, it had m. p. 109° [Found: C, 55.2; H, 6.0; OMe, 25.05. C<sub>14</sub>H<sub>13</sub>O<sub>8</sub>(OMe)<sub>3</sub> requires C, 55.15; H, 6.0; OMe, 25.15%].

That part of the orange syrup which did not crystallise has not yet been examined more closely.

*Dehydration of the Acetylacetonone Adduct.*—The adduct (20 g.) was dissolved in concentrated sulphuric acid (90 c.c.), the temperature being kept below 40°. After  $\frac{1}{2}$  hour the clear, yellowish solution was poured slowly into ice-water, with vigorous stirring. The dehydrated product (VI) separated as a fine, amorphous powder which, after the suspension had been stirred for  $\frac{1}{2}$  hour, was collected, washed, and dried in a vacuum. It was thus obtained as a white, light powder (14.7 g.) which could be used directly for most reactions; for analysis it was crystallised from methylal, ethyl acetate, or toluene; needles, m. p. 217—218° (Found: C, 59.9; H, 3.15; *M*, by titration as a tribasic acid, 263.8.  $C_{13}H_8O_6$  requires C, 60.0; H, 3.1%; *M*, 260.2). It was insoluble in water at room temperature, but dissolved slowly on boiling, giving a faintly yellow solution, which was coloured red-violet by ferric chloride; it also added bromine. From this aqueous solution the substances (X) could be obtained. In cold methanol and ethanol substance (VI) was slightly soluble, giving yellow to yellow-red solutions from which it could not be recovered by evaporation. In acetone it dissolved with a yellow-red colour and crystallised unchanged on evaporation. In pyridine it dissolved easily with a dark red colour; on addition of acetic anhydride to this solution, the colour became dark brown but no acetylation product could be isolated.

*Action of Alkali on (VI).*—The colour reactions of this substance have been described on p. 1053. The compound (X, R = H), prepared as there described and recrystallised from water, had m. p. 160° (Found: C, 56.15; H, 3.95; *M*, by titration as a tribasic acid, 284.6.  $C_{13}H_{10}O_7$  requires C, 56.1; H, 3.6%; *M*, 278.2). The isomeric compound (Xa) had m. p. 176° (Found: C, 56.1; H, 3.7%; *M*, 278.3).

Both these substances gave with diazomethane the same colourless, crystalline dimethoxy-derivative, slightly soluble in ether, m. p. 148—150° [Found: C, 58.95; H, 4.6; OMe, 20.35.  $C_{13}H_8O_5(OMe)_2$  requires C, 58.8; H, 4.6; OMe, 20.25%]. When shaken for 3 days at room temperature with methanol, it dissolved, and on evaporation of the solvent in a vacuum desiccator over concentrated sulphuric acid, a colourless syrup was obtained; in the course of some weeks this turned into a solid mass, identical with the original substance, m. p. 148—150°, the methanol evidently having reacted and been removed again. However, if diazomethane was added to the solution in methanol, a vigorous reaction took place, resulting in the formation of the fully methylated substance (XI). The same product could also be obtained by methylating the dehydrated adduct directly with methyl sulphate in the presence of alkali. It was purified by crystallisation, first from dilute ethanol and then from light petroleum; m. p. 74° [Found: C, 57.85; H, 5.65; OMe, 35.05.  $C_{13}H_8O_4(OMe)_4$  requires C, 57.95; H, 5.7; OMe, 35.25%].

*Action of Diazomethane on (VI).*—The finely powdered substance (2 g.) was added in portions to excess of a vigorously stirred ethereal solution of diazomethane. A slow reaction set in and soon the intensely yellow substance (IX, R = Me) began to separate. The mixture was left overnight, and the compound separated and washed with ether; 1.6 g. were obtained, and a little more was got from the mother-liquor. Recrystallised from benzene, it had m. p. 198° [Found: C, 61.1; H, 3.9; OMe, 10.95.  $C_{13}H_8O_5(OMe)$  requires C, 61.3; H, 3.7; OMe, 11.3%]. Its solution in benzene did not react with bromine. In boiling methanol the substance was slightly soluble and crystallised rapidly on cooling. If left for a day or two in the mother-liquor, the crystals dissolved, and the yellow colour disappeared, obviously owing to the opening of the acid anhydride ring. Such a solution added bromine. For purpose of further methylation the substance (IX, R = Me) (4 g.) was refluxed for 6 hours with anhydrous methanol (150 c.c.). The bulk of the methanol was distilled off, and after the syrupy residue had been diluted with ether, an ethereal solution of diazomethane was added. When the lively reaction had terminated, the solution was evaporated to dryness in a vacuum desiccator, leaving a crystalline mass; after being washed with cold methanol, this (3.55 g.) was recrystallised from methanol and obtained as nearly colourless crystals, m. p. 137° to a yellow liquid. This substance was obviously methyl 7-acetyl-2-methoxy-6-methyl-benzofuran-4 : 5-dicarboxylate (X, R = Me) [Found: C, 60.0; H, 5.1; OMe, 29.0.  $C_{13}H_7O_4(OMe)_3$  requires C, 60.0; H, 5.05; OMe, 29.05%]. On catalytic hydrogenation this ester readily absorbed hydrogen.

Dissolved in carbon tetrachloride, (X, R = Me) reacted with bromine, evolving hydrogen bromide. Evaporation of the solvent in a vacuum desiccator over paraffin-vaseline afforded a syrupy bromo-compound, which was heated for an hour at 80° (Found: Br, 19.7.  $C_{16}H_{15}O_7Br$  requires Br, 20.0%).

*Action of Hydriodic Acid on (VI).*—The compound (VI) (10 g.) was heated for 7 hours with hydriodic acid (*d* 1.7; 120 c.c.) to which some red phosphorus had been added. Carbon dioxide and acetic acid were evolved, and a crystalline substance gradually separated. Next day the product was separated and washed with cold water. It was then dissolved in ether, in which it was only slightly soluble, the solution shaken with aqueous sodium thiosulphate and with water, and dried ( $Na_2SO_4$ ). After the ether had been distilled off, the residue (5.5 g.) was crystallised from ethanol forming 6-methyl-isocoumaranone-4-carboxylic acid (VII), m. p. 249° (Found: C, 62.6; H, 4.2; *M*, by titration as a dibasic acid, 191.7.  $C_{10}H_8O_4$  requires C, 62.5; H, 4.2%; *M*, 192.2). It contained one free carboxyl group and reacted with diazomethane giving a crystalline methyl ester which, recrystallised from ethanol, had m. p. 164° (Found: C, 64.1; H, 4.85; OMe, 14.9.  $C_{11}H_{10}O_4$  requires C, 64.05; H, 4.9; OMe, 15.05%).

When the acid (VII) was dissolved in 0.2*N*-aqueous sodium carbonate, the lactone ring was not opened, and the acid was reprecipitated immediately on addition of mineral acid, but when it was dissolved in sodium hydroxide solution, it gave a yellow solution with green fluorescence. The colour and the fluorescence disappeared quickly and the solution became only slightly coloured. On addition of hydrochloric acid to this solution, scratching afforded 5-hydroxy-3-carboxy-*p*-tolueneacetic acid (IIIa) (Found: C, 57.1; H, 4.8.  $C_{10}H_{10}O_6$  requires C, 57.15; H, 4.8%) as a white, crystalline powder; this had the same m. p. 249° as the lactone, presumably because it lost water during the heating. It could be crystallised from water.

On treatment with diazomethane, the acid (IIIa) was converted into its dimethyl ester, the hydroxyl group being unaffected; recrystallised from dilute ethanol, this cleared at 88° but had no sharp m. p. [Found: C, 60.65; H, 5.95; OMe, 25.6.  $C_{10}H_8O_3(OMe)_2$  requires C, 60.9; H, 5.9; OMe, 26.05%]. This ester had a tendency to split off one molecule of methanol, giving the ester of the lactonic form (VII); e.g., distillation in a high vacuum afforded a mixture of this lactonic form with unchanged dimethyl ester. Also during an abortive attempt at catalytic hydrogenation of the dimethyl ester dissolved in methanol, the lactonic ester, m. p. 164°, was obtained on evaporation.

The complete methylation of (IIIa) was achieved by shaking its alkaline solution with an excess of sodium hydroxide and methyl sulphate. The product, methyl 3-carbomethoxy-5-methoxy-*p*-tolueneacetate, separated as an oil which solidified on cooling; crystallised from dilute ethanol, it had m. p. 82° [Found: OMe, 36.5.  $C_{10}H_7O_2(OMe)_3$  requires OMe, 36.9%]. When this was boiled with aqueous sodium hydroxide, it afforded the methoxy-acid; crystallised several times from dilute ethanol, this had m. p. 206° [Found: C, 58.7; H, 5.45; OMe, 13.75.  $C_{10}H_9O_4(OMe)$  requires C, 58.9; H, 5.4; OMe, 13.85%].

*Decarboxylation of (IIIa).*—The acid (IIIa) (16.5 g.) was converted into the sodium salt, mixed with twice its weight of calcium hydroxide and some sand, and in three portions heated electrically in a glass tube connected with a receiver which was cooled in a mixture of ice and hydrochloric acid. The distillate (6.5 g.) consisted of a dark oil which partly crystallised. On redistillation, the main fraction (4.3 g.) boiled at 203—210° and had a phenolic odour. After being kept in an ice-chest, the crystalline part was filtered off, pressed on porous porcelain, and twice crystallised from petrol; it had m. p. 75.5°, and in admixture with *p*-xylenol (m. p. 76°), it had m. p. 76° (Found: C, 78.4; H, 8.35. Calc. for  $C_8H_{10}O$ : C, 78.65; H, 8.25%). Its oxalate, prepared by Bischoff and von Hedenström's method (*Ber.*, 1902, 35, 3443),

had m. p. 110° (lit. 111°), and no *m*-xylenyl oxalate could be isolated from either the solid or the liquid part of the distillate.

*Oxidation of 3-Carboxy-5-methoxy-p-tolueneacetic Acid.*—To a solution of the acid (5 g.) in 25 c.c. of 2*N*-sodium hydroxide and 200 c.c. of water, 5% aqueous potassium permanganate was added slowly, with vigorous stirring, the temperature gradually rising to ca. 80°. When 130 c.c. had been added, the manganese dioxide was filtered off, and the clear solution evaporated on the water-bath to about 100 c.c. Addition of 15 c.c. of 5*N*-sulphuric acid precipitated 4 g. of a fine white powder. It was crystallised several times from water in which it was sparingly soluble at room temperature; in most cases it formed small, clear prisms, m. p. 242°, but occasionally it separated as a labile, dimorphic form in fine needles [Found: C, 52.3; H, 4.15; OMe, 12.1; *M*, by titration as tribasic acid, 255.8. C<sub>10</sub>H<sub>8</sub>O<sub>6</sub>(OMe) requires C, 51.95; H, 3.95; OMe, 12.2%; *M*, 254.2]. This 2-methoxy-4 : 6-dicarboxyphenylacetic acid (IV, R = Me), on methylation by means of diazomethane, gave a trimethyl ester which, purified by crystallisation once from dilute ethanol and twice from petrol, had m. p. 94° [Found: C, 57.2; H, 5.5; OMe, 41.6. C<sub>10</sub>H<sub>4</sub>O<sub>3</sub>(OMe)<sub>4</sub> requires C, 56.75; H, 5.45; OMe, 41.9%].

Demethylation of (IV, R = Me) was achieved by boiling it with 20 times its weight of hydriodic acid (*d* 1.7) in presence of a little red phosphorus. On cooling, crystals separated which, when crystallised from water, dried, and sublimed in a high vacuum, afforded by loss of 1H<sub>2</sub>O isocoumaranone-4 : 6-dicarboxylic acid (V) which had no definite m. p. (Found: C, 54.3; H, 2.65. C<sub>10</sub>H<sub>6</sub>O<sub>6</sub> requires C, 54.05; H, 2.7%).

*Further Oxidation of (IV, R = Me) with Nitric Acid.*—To a boiling solution of (IV, R = Me) (3 g.) in 120 c.c. of water, 30 c.c. of nitric acid (*d* 1.4) were added in small portions. The boiling was continued for 2½ hours, and the solution then concentrated on the water-bath to about half its volume. Next day, 1.8 g. of crystals had separated, and another 0.3 g. was obtained by further evaporation of the mother-liquor. After crystallisation from glacial acetic acid, in which it was only slightly soluble, the oxidation product had m. p. 252°; it was 3-methoxybenzene-1 : 2 : 5-tricarboxylic acid [Found: C, 50.0; H, 3.5; OMe, 12.65; *M*, by titration as a tribasic acid, 242.5. C<sub>9</sub>H<sub>6</sub>O<sub>6</sub>(OMe) requires C, 50.0; H, 3.35; OMe, 12.9%; *M*, 240.2].

2-Methoxybenzene-1 : 3 : 5-tricarboxylic acid has m. p. 248° (Ullmann and Brittner, *Ber.*, 1909, 42, 2543), but it was different from the above acid, m. p. 252°, for the trimethyl ester of the latter, after crystallisation from ethanol, had m. p. 144° [Found: OMe, 43.7. C<sub>9</sub>H<sub>2</sub>O<sub>3</sub>(OMe)<sub>4</sub> requires OMe, 43.95%], whereas that of the acid of m. p. 248° has m. p. 86°.

That the tricarboxylic acid contained two adjacent carboxyl groups was evident from the fact that, on sublimation in a high vacuum, it gave an anhydride, m. p. 254° (Found: C, 54.15; H, 2.65. C<sub>10</sub>H<sub>6</sub>O<sub>8</sub> requires C, 54.05; H, 2.7%).

*Ethyl Acetoacetate and Maleic Anhydride.*—The reaction between ethyl acetoacetate and maleic anhydride was carried out under the same conditions as described for acetylacetone, and was slow at room temperature. The adduct, crystallised from either ethyl acetate or methylal-benzene, had m. p. 157° [Found: C, 51.45; H, 4.4; OEt, 13.75; *M*, by titration as a tribasic acid, 328.5. C<sub>13</sub>H<sub>8</sub>O<sub>8</sub>(OEt) requires C, 51.55; H, 4.35; OEt, 13.8%; *M*, 326.3]. This was rather more soluble than its analogue (VIII) in boiling water, but the solution gave only a faintly red-violet coloration with ferric chloride. It gave, however, a violet-coloured solution when treated with aqueous sodium carbonate, and this solution behaved in the same way as the violet solution of the acetylacetone adduct.

By catalytic hydrogenation 3 g. of adduct took up 238 c.c. of hydrogen at N.T.P. (Calc. for 2H : 227 c.c.).

Dehydration of the adduct was carried out as described in the previous case. The dehydrated product, 7-carbethoxy-6-methylisocoumaranone-4 : 5-dicarboxylic anhydride (XIV), crystallised from benzene, had m. p. 180° (Found: C, 57.5; H, 3.65. C<sub>14</sub>H<sub>10</sub>O<sub>7</sub> requires C, 57.95; H, 3.45%); it dissolved in aqueous sodium carbonate with a dark red colour, which in this case more rapidly turned yellow. When it (14 g.) was boiled for 4 hours with 140 c.c. of hydriodic acid (*d* 1.7) and a little red phosphorus, crystals separated on cooling overnight; these were filtered off and treated as on p. 1057. Distillation of the ether afforded 10.5 g. of a crystalline substance, which melted very unsharply at 225–240°. It was recrystallised by dissolving it in ethanol and adding water. The first fraction had m. p. 246°, and the second m. p. 250–270°. On recrystallisation the first fraction had m. p. 249°, and was identical with (VII) described above (Found: C, 62.7; H, 4.2%; *M*, by titration as a dibasic acid, 190.3). Addition of mineral acid to the alkaline solution of this acid precipitated the hydroxy-acid (IIIa) (Found: C, 57.05; H, 4.95%). Both (IIIa) and (VII) showed the relationship described on p. 1053.

The fraction, m. p. 250–270°, was purified first by dissolving it in alkali and reprecipitation with sulphuric acid, and then by crystallisation from dilute ethanol, giving a substance, m. p. 295° (Found: C, 51.9; H, 4.15; *M*, by titration as a tribasic acid, 252.1. C<sub>11</sub>H<sub>10</sub>O<sub>7</sub> requires C, 51.95; H, 3.95%; *M*, 254.2). This substance was 3-hydroxy-2 : 5-dicarboxy-p-tolueneacetic acid, and it was converted by sublimation in a high vacuum into the corresponding 6-methylisocoumaranone-4 : 7-dicarboxylic acid (XV) (Found: C, 56.2; H, 3.55. C<sub>11</sub>H<sub>8</sub>O<sub>6</sub> requires C, 55.95; H, 3.4%).

This investigation was carried out with some interruption during the last six years. The author is indebted to Nansenfondet and to Det Videnskabelige Forskningsfond av 1919 for several grants.

Many of the analyses have been carried out by the assistants Rasmus Alm, Kåre Fossan, and Brynjulv Kløve, to whom the author gives his warm thanks.