345. *Unsaturated Lactones and Related Substances. Part V.* Dihydro-β-ketomuconic Acid and Carboxy-lactones of the Protoanemonin Type.*

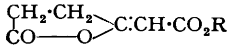
By Ulli Eisner, J. A. Elvidge, and R. P. Linstead.

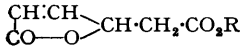
The investigation of the chemistry of unsaturated lactonic acids of potential biological activity has been continued.

Fumaric half-ethyl ester half-chloride (made by a very convenient process from maleic anhydride) reacts with ethyl magnesiomalonate to yield ethyl *trans*-β-carbethoxyacrylylmalonate (VII*a*), characterised as the copper enolate. β-Carbomethoxyacrylyl chloride with ethyl and methyl magnesiomalonates similarly affords the triesters (XI) and (VII; R = R′ = Me), which like (VII*a*) give only poor yields of dihydro-β-ketomuconic acid (XV) on hydrolysis, cleavage products (fumaric and malonic acids) predominating. The course of this and related hydrolyses is discussed. Cyclodehydration of (XV) with acetic anhydride–hydrogen bromide affords in very low yield the lactonic acid (III; R = H), converted by diazoethane into the ethyl ester (III; R = Et). The latter arose, as well as γ-dicarbethoxymethylenebutenolide (IV), by pyrolysis of (VII*a*). (IV) is best prepared by cyclisation of ethyl *trans*-β-carboxyacrylylmalonate (XIII), obtained from (VII*a*) with ethanolic potassium hydroxide. The lactone (IV) is comparatively stable to water, and lacks reducing properties, but is readily cleaved to maleic acid and ethyl malonate by aqueous alkali. Hydrogenation affords only the deoxy-acid: no saturated lactone or partial-reduction products were obtained. (IV) is ring-opened to ethyl *trans*-β-anilidoacrylylmalonate (XXIV) by aniline, to (VII*a*) with ethanolic hydrogen chloride, but to the corresponding *cis*-ester (VII*b*) by ethanolic sodium ethoxide, a finding of significance in relation to previous studies in the muconic series.

During the work αβ-dibromo-β′-ketoadipic acid (XVIII) was obtained and cyclised to an unsaturated bromo-lactone (XX).

In preceding papers of this series attention has been directed to those properties of simple unsaturated lactones which indicate the position of the double bond. Thus in Parts III and IV (Eisner, Elvidge, and Linstead, *J.*, 1950, 2223; Elvidge, Linstead, Orkin, Sims, Baer, and Pattison, *ibid.*, p. 2228) the marked differences in the behaviour between the isomeric γ-lactones (I) and (II) on reduction and treatment with certain reagents were discussed. The corresponding doubly-unsaturated γ-lactone system has now been synthesised. This is exemplified by the compounds (III) and (IV), which combine the structural features of both the simpler lactones (I) and (II).


(I.)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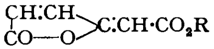
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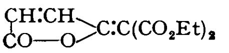
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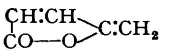
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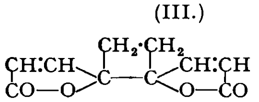
(VI.)

$CO_2R\cdot CH{:}CH\cdot CO\cdot CH(CO_2R')_2$ (VII.)

The lactones (III) and (IV) have an added interest in being derivatives of protoanemonin (V), the γ-lactone of β-acetylacrylic acid. Protoanemonin (for bibliography, see Haynes, *Quart. Reviews*, 1948, **2**, 46) is one of the simplest unsaturated lactones possessed of any marked

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* Part IV, *J.*, 1950, 2228.

antibiotic activity, and operates against a surpisingly wide variety of bacteria. It polymerises quite rapidly, however, mainly to the dimer, anemonin (VI), which has only a feeble antibacterial action. A few other compounds containing the protoanemonin system are known, *e.g.*, the halogen-substituted analogues prepared by Karrer and his co-workers (*Helv. Chim. Acta*, 1947, **30**, 859; 1949, **32**, 1019, 1028), and methylenephthalide and its derivatives.

The ready preparation of γ-carboxymethylenebutanolide (I; R = H) by the cyclodehydration of β-ketoadipic acid (Eisner, Elvidge, and Linstead, *loc. cit.*) suggested that γ-carboxymethylenebutenolide (III; R = H) might be obtained similarly from the *unsaturated* keto-acid, dihydro-β-ketomuconic acid.

An investigation of the synthesis of this unknown acid was accordingly undertaken first. An obvious route was the reaction of a half-ester half-chloride of fumaric acid with magnesiomalonic ester to give the triester (VII), followed by hydrolysis and mono-decarboxylation. The subsidiary problems which arose are conveniently considered under the following headings.

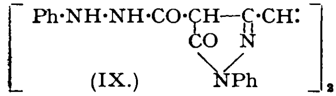
(a) β-*Carbalkoxyacrylyl Chlorides.*—The half-methyl ester half-chloride of fumaric acid (β-carbomethoxyacrylyl chloride) has been prepared from fumaryl chloride and methanol (Lutz, *J. Amer. Chem. Soc.*, 1930, **52**, 3423), but the product is difficult to separate and purify because of its tendency to co-distil with the unchanged dichloride and with the diester which is also formed. A preparation from methyl fumarate, involving hydrolysis to methyl hydrogen fumarate and reaction of the latter with thionyl chloride (Erlenmeyer and Schoenauer, *Helv. Chim. Acta*, 1937, **20**, 1008), proved very tedious and, on a reasonably large scale, virtually unworkable because of the conditions of extreme dilution necessary for half-hydrolysis of the ester (Waren and Grose, *J. Amer. Chem. Soc.*, 1912, **34**, 1600; Erlenmeyer and Schoenauer, *loc. cit.*) and the labour of isolating and drying the product. Moreover, the β-carbomethoxyacrylyl chloride which was eventually obtained by this process was not pure. The main product, m. p. 54°, from the reaction with ethyl magnesiomalonate was contaminated with methyl fumarate, which was difficult to remove, and a very sparingly soluble substance, m. p. 117°, was also present.

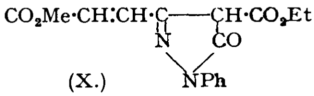
Attention was then turned to a possible shorter route which might have led to desirable *cis*-material. Maleic half-ester was allowed to react with thionyl chloride under conditions analogous to those for the corresponding succinic acid derivatives (Riegel and Lilienfeld, *J. Amer. Chem. Soc.*, 1945, **67**, 1273), but fractional distillation failed to afford any sharp separation of the products. A portion of the first runnings reacted with *p*-aminobenzenesulphonamide to yield the half " sulphanilamide " of ethyl fumarate, and a later fraction gave a chlorine-containing derivative, $C_{12}H_{15}O_5N_2ClS$, which obviously differed from both the known half-sulphanilamide half-ethyl esters of maleic and fumaric acids (Bergmann and Schapiro, *J. Org. Chem.*, 1942, **7**, 419). The formation from maleic half-ester and thionyl chloride of a hydrogen chloride addition product (mixed chlorosuccinic half-ester chlorides), as well as fumaric half-ester chloride, which is indicated by these results, contrasts strongly with the straightforward formation of the latter from fumaric half-ester and thionyl chloride. Maleic half-ester half-chlorides have not been reported hitherto, though maleyl chloride (which has a cyclic structure) can be prepared in small quantities (Ott, *Annalen*, 1912, **392**, 245; van Dorp and van Dorp, *Rec. Trav. chim.*, 1906, **25**, 96; Anschütz and Wirtz, *Ber.*, 1885, **18**, 1947).

Eventually a reproducible and highly convenient method for β-carbethoxyacrylyl chloride was devised. When maleic anhydride was dissolved in 1 mol. of hot ethanol and a small quantity of thionyl chloride then added, ethyl hydrogen fumarate was readily obtained in good yield, and from it with thionyl chloride pure β-carbethoxyacrylyl chloride was easily prepared.

Repetition of this procedure with methanol gave a somewhat different result. The product from the first stage was mainly methyl fumarate, mixed with some methyl hydrogen fumarate and fumaric acid. Nevertheless, the half-ester could readily be separated in a pure state, though only in 16% overall yield. In spite of this the method was considerably more rapid and convenient, especially on a large scale, than the half-hydrolysis of methyl fumarate. Subsequent treatment of the half-ester with thionyl chloride afforded pure β-carbomethoxyacrylyl chloride in high yield.

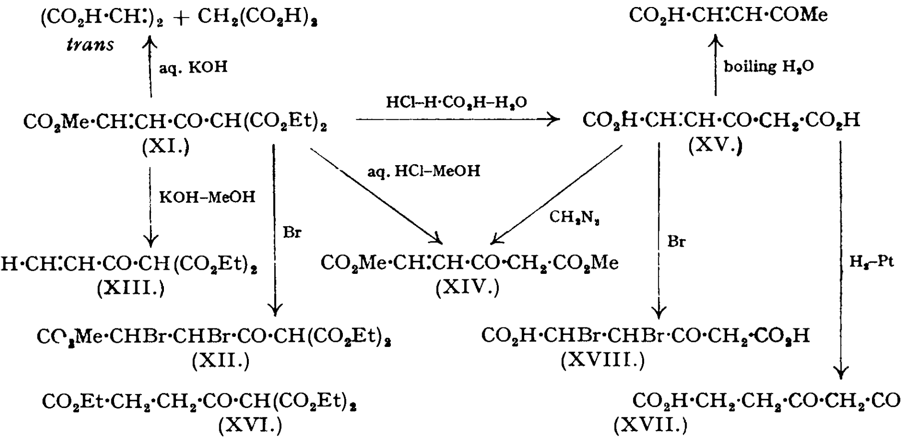
$[(CO_2Et)_2CH{\cdot}CO{\cdot}CH{:}]_2$
(VIII.)


(IX.)


(X.)

(b) *Dihydro-*β*-ketomuconic Acid, Precursors, and Derivatives.*—The by-product, m. p. **117°**, from the reaction (mentioned above) of slightly impure β-carbomethoxyacrylyl chloride **with** ethyl magnesiomalonate was identified as the tetraethyl ester (VIII) (*trans*-1 : 1 : 6 : 6-tetracarbethoxyhex-3-ene-2 : 5-dione) by its synthesis from fumaryl chloride and 2 mols. of the malonate, and was further characterised by condensation with phenylhydrazine (of which 4 mols. reacted) to yield the high-melting derivative (IX).

The main product, m. p. 54°, from the β-carbomethoxyacrylyl chloride reaction was the expected triester (XI) (ethyl *trans*-β-carbomethoxyacrylylmalonate), which yielded a normal phenylpyrazolone derivative (X). The constitution of the ester as (XI) was confirmed by its behaviour under a variety of reaction conditions, summarised in the accompanying scheme. Cold aqueous potassium hydroxide gave a mixture of fumaric and malonic acids. With bromine, a dibromo-adduct (XII) was formed. Cold methanolic potassium hydroxide afforded the mono-acid (XIII) (ethyl *trans*-β-carboxyacrylylmalonate), and methanolic hydrogen chloride ontaining water gave the dimethyl ester (XIV), also prepared from dihydro-β-ketomuconic cid (XV) (below) and diazomethane.



Meanwhile, the possibility of hydrolysing the triester (XI) to dihydro-β-ketomuconic acid (XV) was examined. In the analogous case of the saturated compounds (Eisner, Elvidge, and Linstead, *loc. cit.*), the triester (XVI) had been smoothly hydrolysed and monodecarboxylated to the ketodicarboxylic acid (XVII) by cold concentrated hydrochloric acid. Acid hydrolysis of the new unsaturated triester (XI), however, was very difficult because of its insolubility and the relative ease of fission of the molecule to fumaric and malonic fragments. Hydrolysis of (XI) with alkali was therefore tried under conditions additional to those already described. With barium hydroxide (cf. Hunsdiecker and Hunsdiecker, *Ber.*, 1942, **75**, 291) and methanolic lithium hydroxide, only mixtures of fumaric and malonic acids resulted, together with a little partially hydrolysed ester (XIII) in the last case.

However, in acetic or formic acid solution containing water and saturated with hydrogen chloride, hydrolysis of the triester (XI) proceeded slowly, and during 2—6 days a white solid separated, which was a mixture of fumaric and dihydro-β-ketomuconic acids. The proportions, as well as the total yield, varied widely in a series of experiments. From such mixtures, provided its proportion was not too high, fumaric acid could be extracted with boiling acetone to leave in small quantity dihydro-β-ketomuconic acid (*trans*-3-ketobut-1-ene-1 : 4-dicarboxylic acid) (XV), obtained as a micro-crystalline powder, m. p. 164°, which gave a deep purple with ferric chloride, and was sparingly soluble in most organic solvents. The constitution (XV) was proved by decarboxylation of the acid in boiling water to β-acetylacrylic acid, and hydrogenation to β-ketoadipic acid (XVII) which was further characterised by conversion into lævulic acid semicarbazone. The yield of β-ketoadipic acid was low (20%) and the oil which accompanied it could not be characterised. This result is analogous to the behaviour of oxalo-crotonic and -sorbic esters on catalytic reduction (Borsche and Manteuffel, *Ber.*, 1932, **65**, 868). It was verified that β-ketoadipic acid was not reduced under the conditions employed.

With bromine in acetic acid, (XV) afforded the dibromo-adduct (XVIII). An attempt to obtain the latter by hydrolysis of the dibromo-triester (XII) with hydrobromic acid was unsuccessful, the ester being recovered unchanged. This resistance of the dibromo-triester (XII) to hydrolysis contrasts with the ease of hydrolysis of its dihydro-analogue (XVI), and may well be due to its insolubility. Both dibromo-compounds (XII) and (XVIII) were crystalline and had every appearance of being single racemates. Indeed, this was to be expected from theoretical considerations, which indicate that each compound has purely an *erythro*-spatial arrangement of the bromine substituents, having resulted from a *trans*-addition to a double bond about which the configuration is *trans* (see literature summary by Raphael, *J.*, 1949, S 44).

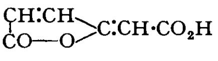
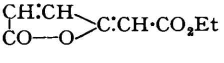
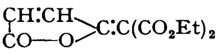
The solid trimethyl and liquid triethyl esters (VII; R = R′ = Me and Et), prepared from the appropriate fumaric half-ester chlorides and magnesiomalonates, were employed, as well as the mono-acid (XIII), in further hydrolysis experiments towards dihydro-β-ketomuconic acid (XV), but these compounds offered no advantage. For example, only 16% yields of (XV) were obtained from the trimethyl ester. Nevertheless, advantages appeared in other directions. Thus the triethyl ester (VII; R = R′ = Et) proved to be much more accessible than the other triesters, and it could be hydrolysed to the mono-acid (XIII) in over 90% yield, a reaction which, incidentally, confirmed its structure.

Hydrolysis of the tetracarboxylic ester (VIII) was also briefly studied, in view of its ready availability. The results were unpromising, although from a trans-esterification reaction with propionic acid, a small quantity of ethyl β-acetylacrylate was separated and identified as the 2 : 4-dinitrophenylhydrazone. No diacetylethylene could be detected in the non-acidic fraction of the reaction product. Apparently the tetracarboxylic ester (VIII) undergoes so-called " acid " cleavage at both ends of the molecule to yield fumaric and malonic entities, and there is only a small degree of mono-fission leading (presumably via dihydro-β-ketomuconate) to acetylacrylate. There appears to be no simple hydrolysis of all the ester groups followed by malonic decarboxylation to give $(CO_2H{\cdot}CH_2{\cdot}CO{\cdot}CH{:})_2$ and thence $CO_2H{\cdot}CH_2{\cdot}CO{\cdot}CH{:}CH{\cdot}COMe$

$$[(CO_2Et)_2CH{\cdot}CO{\cdot}CH{:}CH{\cdot}]_2 \qquad \text{(XIX.)}$$

and diacetylethylene. In this connection it is of interest to note that the higher unsaturated homologue (XIX) seems to undergo *only* " acid " cleavage to muconic acid, at least under the conditions of acid and alkali treatment so far examined, since ketonic material was absent from the hydrolysates (private communication from Dr. B. C. L. Weedon). Thus the various esters studied show a distinct gradation in behaviour on hydrolysis, the tendency to cleavage increasing with growing unsaturation in the series (XVI) (no cleavage), (VII), (VIII), and (XIX) (only cleavage).

Light-absorption characteristics (in dioxan).

Compound.	$\lambda_{max.}$, A.	ε.
$CO_2Me{\cdot}CH{:}CH{\cdot}CO{\cdot}CH(CO_2Me)_2$	3040	15,300
$CO_2H{\cdot}CH{:}CH{\cdot}CO{\cdot}CH(CO_2Et)_2$	2980 3060	12,900 14,200
$CO_2H{\cdot}CH{:}CH{\cdot}CO{\cdot}CH_2{\cdot}CO_2H$	2280 2980	9,160 14,200
 $\begin{matrix}CH{:}CH\\ CO{-}O\end{matrix}{>}C{:}CH{\cdot}CO_2H$	2580 2700 2810	12,200 14,000 16,200
 $\begin{matrix}CBr{:}CH\\ CO{-}O\end{matrix}{>}C{:}CH{\cdot}CO_2H$ (XX.)	2880	19,000
 $\begin{matrix}CH{:}CH\\ CO{-}O\end{matrix}{>}C{:}CH{\cdot}CO_2Et$	2510 2690 2800 2870	7,220 12,900 14,300 12,900
 $\begin{matrix}CH{:}CH\\ CO{-}O\end{matrix}{>}C{:}C(CO_2Et)_2$	2500 2810 2900	9,600 17,300 17,300
$(CO_2Et)_2CH{\cdot}CO{\cdot}CH{:}CH{\cdot}CO{\cdot}CH(CO_2Et)_2$	3400	28,000

None of the unsaturated keto-esters and acids mentioned above formed carbonyl derivatives readily. The esters were strong pseudo-acids, soluble in aqueous sodium hydrogen carbonate, and, like the acids, gave deep colorations with ferric chloride. They showed ultra-violet light absorption characteristics (see Table) in keeping with the enolic forms of the formal keto-structures shown above. Characterisation of the liquid triethyl ester (VII; R = R′ = Et) was accomplished by formation of the copper enolate, $(C_{13}H_{17}O_7)_2Cu$, a beautifully crystalline green substance with m. p. 159°.

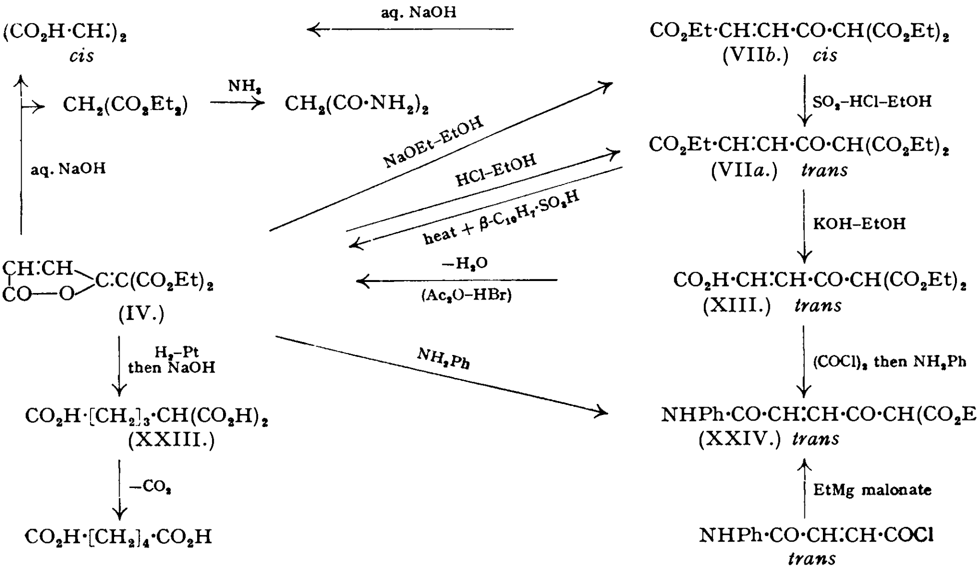
(c) *Lactones.*—First attempts to lactonise dihydro-β-ketomuconic acid (XV) with acetyl chloride, in the cold or by heating, and with ultra-violet irradiation, afforded only syrups, possibly of acid chlorides and mixed anhydrides, which on exposure to the air gradually reverted to the solid starting material. By the use of hot acetic anhydride–acetic acid in the presence of anhydrous hydrogen bromide [to permit inversion of the double bond of (XV)], a mixture of substances resulted from which a small quantity of an acid, m. p. 156°, was isolated. This gave no ferric chloride colour, gave analytical results expected for the lactonic acid (III; R = H) (γ-carboxymethylenebutenolide), $C_6H_4O_4$, and showed light-absorption properties consistent with that structure (see Table). In view of the very poor yield of lactonic product, cyclodehydration of the dibromo-keto-acid (XVIII) was examined, and found to proceed readily with acetyl chloride, as expected for a saturated γ-keto-acid. The product, however, was not the expected dibromo-lactonic acid from which (III; R = H) might have been derived by treatment with magnesium or zinc. It had the composition $C_6H_3O_4Br$ and was therefore a bromo-substituted derivative of (III; R = H), evidently formed by loss of hydrogen bromide from the initial product of cyclodehydration. Structure (XX) for the product seems probable and is consistent with the observed ultra-violet absorption spectrum (Table).

$$CO_2R{\cdot}CH{:}CH{\cdot}CO{\cdot}CH_2{\cdot}CO_2R' \qquad \text{(XXI.)}$$

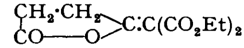
It appeared at this stage, particularly in view of the inaccessibility of dihydro-β-ketomuconic acid, that the required type of doubly-unsaturated γ-lactone might best be obtained in sufficient quantities for chemical study by cyclodehydration of the acid esters (XXI; R = H, R′ = Et) and (XIII), of which the latter was readily available. An attempt to obtain the former led to an unexpected result. It was proposed to pyrolyse the triethyl ester (VII; R = R′ = Et) to the diester (XXI; R = R′ = Et) and then to half-hydrolyse this to (XXI; R = H, R′ = Et). Application of Riegel and Lilienfeld's pyrolytic decarbethoxylation conditions (*loc cit.*) to the triester (VII; R = R′ = Et) produced a complex mixture, difficult to separate by fractionation, but from which small yields of two neutral products, m. p. 62° and 78°, were isolated, neither of which gave a ferric chloride colour. The latter compound, $C_8H_8O_4$, was γ-carbethoxymethylenebutenolide (III; R = Et). This was shown by the ultra-violet absorption spectrum (Table) and by its preparation from the lactonic acid (III; R = H) and diazoethane.

Acetic anhydride–hydrogen bromide converted the readily accessible acid ester (XIII) in good yield into the expected lactonic diester (IV) (γ-dicarbethoxymethylenebutenolide). The compound melted at 62° and was identical with the substance already obtained from the pyrolysis of the ester (VII; R = R′ = Et). It was neutral, and had the molecular formula $C_{11}H_{12}O_6$, and the ultra-violet absorption characteristics recorded in the Table.

Attempts to convert the lactonic diester (IV) into the mono-ester (III; R = Et) showed that the ester groups were extremely stable. This is generally to be expected for esters of the type $C{:}C(CO_2R)_2$. Pyrolysis with naphthalene-β-sulphonic acid, following the method of Riegel and Lilienfeld (*loc. cit.*) for malonic esters, and attempted trans-esterification with propionic acid failed. Other methods for the removal of an ester group were not applicable, as will be apparent from the reactions of the lactone (IV) described below.



As expected, none of the substituted protoanemonins described in this paper exhibited the tendency towards ready polymerisation of the parent compound (V). In many of its reactions the doubly-unsaturated ($\Delta^{\alpha\gamma}$-) lactone (IV) behaved like the γ-unsaturated γ-lactone (I), previously studied by Eisner, Elvidge, and Linstead (*loc. cit.*), but in being more stable to water it resembled (II) (Elvidge, Linstead, Orkin, Sims, Baer, and Pattison, *loc. cit.*). Unlike the simpler lactones (I) and (II), the new material (IV) showed no reducing properties. The Légal test was negative, and ammoniacal silver nitrate and dichlorophenol-indophenol were unaffected. Towards aqueous alkali, however, it was unexpectedly labile, and with very dilute sodium hydroxide in aqueous dioxan was readily cleaved in high yield to maleic acid and ethyl malonate: the former product was isolated, and further characterised by conversion into the anhydride, and the latter was converted to the solid diamide. The expected ethyl β-carboxyacrylylmalonate was not obtained. In view of the comparative stability of this keto-acid towards dilute aqueous alkali, at least when in the *trans*-form (XIII), it appears that the elimination of the side chain proceeds direct and not *via* an acyclic hydrolysis product. This interesting reaction is paralleled by the behaviour towards alkali of γ-dicarbethoxymethylenebutanolide (XXII) (Ruggli and Maeder, *Helv. Chim. Acta*, 1943, **26**, 1476), and of phthalylidenemalonic ester (Wislicenus, *Annalen*, 1887, **242**, 23). It is particularly significant that the latter reaction yields phthalic *anhydride*. This indicates the primary reaction in these fissions.



$$\begin{matrix}CH_2\cdot CH_2 \\ CO\text{——}O\end{matrix}\!\!>\!C{:}C(CO_2Et)_2$$

(XXII.)

Hydrogenation of the lactonic ester (IV) in the presence of platinum resulted in an uptake of 3 mols. of hydrogen and an oily acid was formed, which did not give a ferric chloride colour. Hydrolysis of the oil afforded crystalline α-carboxyadipic acid (XXIII), decarboxylated to adipic acid when heated. 50% Hydrogenation of (IV) and separation of the resulting mixture into acidic and neutral fractions showed that no mono-unsaturated lactone [*e.g.*, (XXII)] was formed. Hydrolysis and decarboxylation of the acid fraction gave only adipic acid, and the neutral fraction was identified as the starting material (IV). Neither fraction gave a ferric chloride colour, which again shows the absence of any ketonic product. The behaviour on reduction of the unsaturated system present in (IV) thus falls into line with that of the γ-unsaturated lactone (I) (Eisner, Elvidge, and Linstead, *loc. cit.*), and with that of (XXII) (Ruggli and Maeder, *loc. cit.*). All of these compounds resemble the simple $\beta\gamma$-unsaturated γ-lactones studied by Jacobs and Scott (*J. Biol. Chem.*, 1930, **87**, 601; 1931, **93**, 139) in their complete conversion into deoxy-acid. There does not seem to be any preferential hydrogenation of the exocyclic double bond of (IV). The first stage of the process may be either $\alpha\beta$- or $\alpha\delta$-addition of hydrogen to the $\Delta^{\alpha\gamma}$-butenolide system. Further reduction of the respective possible intermediate Δ^{γ}- or Δ^{β}-lactones would in each case be expected to give the deoxy-acid as end product: the rates of these second stages must be at least as rapid as the first.

We completed our investigation of the $\Delta^{\alpha\gamma}$-lactone (IV) by examining its behaviour towards aniline, and to ethanol under anhydrous acid and alkaline conditions. Ring-opening occurred (with appearance of strong ferric chloride reactions) to yield a keto-anilide (XXIV) and keto-esters (VII), respectively, as was similarly observed with (I), but in the present reactions stereochemical complications arose. The double bond in the ring of (IV) necessarily had a *cis*-configuration, and it was of interest to determine in which, if any, of the acyclic products this configuration was preserved [cf. the opening of the mono-olefinic lactone (II), Elvidge, Linstead, Sims, and Orkin, *J.*, 1950, 2235].

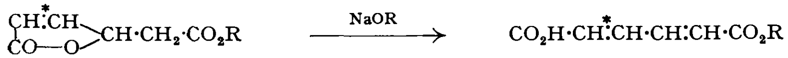
Somewhat unexpectedly, the anilide (XXIV) formed from the lactone (IV) was found to be the *trans*-compound. This was proved unambiguously by a synthesis from fumaric half-anilide half-chloride (Anschütz, *Annalen*, 1890, **259**, 137) and ethyl magnesiomalonate. Moreover, the product from the lactone underwent no change in ethanol solution containing hydrogen chloride and sulphur dioxide—agents which normally readily transform maleic into fumaric derivatives. A second preparation of (XXIV) was also achieved, of interest from a synthetical viewpoint, but which by itself would not rigidly have proved the *trans*-configuration. The *trans*-acid (XIII) was treated with oxalyl chloride under mild conditions to afford an acid chloride, which with aniline formed (XXIV) at once.

The product from reaction of the lactone (IV) with ethanol and hydrogen chloride under reflux was also found to have the *trans*-configuration (VII*a*), but this was to be expected. The derived copper enolate from the ester product gave no melting-point depression with that previously prepared from ethyl *trans*-β-carbethoxyacrylylmalonate.

The product from treatment of the lactone (IV) with cold ethanolic sodium ethoxide was likewise (from its superficial properties) an oily keto-ester. It gave a copper enolate which existed in two forms, green needles, melting at 55° and 101° severally. These are probably polymorphs or else represent different states of solvation. Their interconversion is described in the experimental section. Neither is identical with the copper enolate of the *trans*-isomeride, m. p. 159°.

Proof that the product from the lactone (IV) and sodium ethoxide was indeed the *cis*-keto-ester (VII*b*) was finally obtained in two ways. First, with cold aqueous alkali the ester was cleaved to maleic acid, and no fumaric acid (which would have been readily apparent) could be detected. Secondly, after treatment of the ester in ethanol with hydrogen chloride and sulphur dioxide, a copper enolate was given, identical with that prepared from authentic ethyl *trans*-β-carbethoxyacrylylmalonate. The inversion of the *cis*-ester product (VII*b*) to the established *trans*-form (VII*a*) thus left the chemical constitution of the former in no doubt whatever, whilst the steric configuration was proved by the cleavage reaction.

Now in their work on the muconic acids, Elvidge, Linstead, Sims, and Orkin (*J.*, 1950, 2235) assumed that, in ring-opening of the lactone (II) with sodium alkoxide to give a doubly-



(II.) (XXV.)

unsaturated acyclic product (XXV), the *cis*-configuration about the double bond * in the lactone was preserved in the acyclic product. This assumption was confirmed by a self-consistent series of chemical transformations, but no direct correlation with compounds of established steric configuration was possible.

In the present work we have been able to relate the acyclic products obtained by ring-opening of the lactone (IV) directly to maleic and fumaric acids. The finding that only the reaction with sodium alkoxide leads to a *cis*-product, uncontaminated with any detectable amount of *trans*-material, is of particular interest and confirms the validity of the argument in our earlier paper.

EXPERIMENTAL.

Ethyl trans-*β-Carbomethoxyacrylylmalonate* (XI).—According to the directions of Erlenmeyer (*Helv. Chim. Acta*, 1937, **20**, 1008) methyl fumarate (2 × 72 g.) was hydrolysed to methyl hydrogen fumarate (75 g., 58%; m. p. 141°, from water). This with an excess of thionyl chloride at 100° afforded *trans*-β-carbomethoxyacrylyl chloride (65 g.; b. p. 55—60°/6 mm.), which was treated in ether with ethyl magnesiomalonate (from 72 g. of ethyl malonate) following the method of Riegel and Lilienfeld (*J. Amer. Chem. Soc.*, 1945, **67**, 1273). The mixture was stirred and heated under reflux for 2 hours, then cooled and cautiously treated with 2N-sulphuric acid. The aqueous layer was extracted with ether, and the combined organic solutions were washed successively with dilute sulphuric acid, water, a small volume of aqueous sodium hydrogen carbonate, and water. After being dried ($MgSO_4$) and concentrated, finally under reduced pressure, a brown oily residue was obtained which deposited solid (S) (27 g.; m. p. 45—80°). The oil was decanted and distilled under reduced pressure to give: (i) forerun, b. p. 50—120°/0·15 mm. (12·5 g.) (largely ethyl malonate); (ii) b. p. 150—160°/1 mm., m. p. 43—110° (26·9 g.); (iii) b. p. 160—167°/1·5 mm., m. p. 47—48° (32·5 g.). The last fraction contained mainly *ethyl* trans-*β-carbomethoxyacrylylmalonate*, which crystallised from light petroleum (b. p. 40—60°) as prisms, m. p. 54—54·5° (Found: C, 52·8; H, 6·0. $C_{12}H_{16}O_7$ requires C, 52·9; H, 5·9%). Its solution in aqueous sodium hydrogen carbonate is yellow, and it gives a blood-red colour with ferric chloride in aqueous alcohol. Fraction (ii) contained methyl hydrogen fumarate (1·46 g.; m. p. 130—140°), separated by filtration at 50°.

trans-1 : 1 : 6 : *6-Tetracarbethoxyhex-3-ene-2 : 5-dione* (VIII).—The solid S (above) crystallised from methanol to give the *tetraethyl* ester (VIII) as cream-coloured needles, m. p. 117° (Found: C, 54·0; H, 6·0. $C_{18}H_{24}O_{10}$ requires C, 54·0; H, 6·0%), which gave a red ferric chloride colour. From the mother-liquors, methyl fumarate was isolated, m. p. 97—100° undepressed in admixture with an authentic specimen.

Fumaryl chloride (34·8 g.; b. p. 56—59°/18—19 mm.; prepared in 81% yield by heating fumaric acid with 2 mols. of phosphorus pentachloride on the steam-bath for 1 hour) in dry ether (200 c.c.) was added during 2 hours to a stirred solution of ethyl magnesiomalonate (from 80 g. of ethyl malonate) in dry ether (300 c.c.), and the mixture heated under reflux for 3 hours longer. Next day, the mixture was decomposed with cold 2N-sulphuric acid (300 c.c.), whereupon the ester (VIII) crystallised (58 g., 64%; m. p. 106—110°). When the ester (1 g.) was heated in chloroform with phenylhydrazine (0·5 c.c., 2 mols.) under reflux for 1 hour, trans-1 : *2-di-(5-keto-1-phenyl-4-phenylhydrazido-3-pyrazolinyl)ethylene* separated and was obtained from pyridine–light petroleum (b. p. 100—120°) as a yellow micro-crystalline powder, m. p. 291—292° (decomp.) (Found: N, 18·5. $C_{34}H_{28}O_4N_8$ requires N, 18·3%).

The ester (VIII) (8 g.) in propionic acid (24 c.c., 16 mols.) containing toluene-*p*-sulphonic acid (0·32 g.) was boiled under reflux for 13 hours. The solution was cooled, made alkaline with aqueous sodium carbonate, and extracted with ether, and the organic layer was dried ($MgSO_4$) and evaporated. Treatment of the residue with methanolic 2 : 4-dinitrophenylhydrazine yielded the derivative of ethyl β-acetylacrylate, which crystallised from methanol as plates, m. p. 147° (lit., m. p. 150°) (Found : C, 48·5; H, 4·65; N, 16·9. Calc. for $C_{13}H_{14}O_6N_4$: C, 48·3; H, 4·7; N, 17·3%).

Reactions of Ethyl trans-*β-Carbomethoxyacrylylmalonate.*—(a) *Condensation with phenylhydrazine.* On keeping the tri-ester (1·37 g.) in alcohol with phenylhydrazine (0·5 c.c.) in 50% aqueous acetic acid (4 c.c.) for 2 days, colourless needles of *methyl* 4-*carbethoxy*-5-*keto*-1-*phenylpyrazoline*-3-*β*-trans-*acrylate* separated, which after three crystallisations from carbon tetrachloride–light petroleum (b. p. 60—80°) had m. p. 147° (Found : N, 8·9. $C_{16}H_{16}O_5N_2$ requires N, 8·9%).

(b) *Fission with aqueous potassium hydroxide.* A solution of the tri-ester (1 g.) in N-potassium hydroxide (15 c.c.) was kept at room temperature overnight, and then acidified. Solid separated (0·18 g.; m. p. 94°), and was identified as ethyl *trans*-*β*-carboxyacrylylmalonate (XIII) (see below). The filtrate was extracted continuously with ether overnight, and the extract dried ($MgSO_4$) and evaporated to give a residue (0·6 g.), which was extracted with acetone. Fumaric acid (0·1 g.; m. p. 290° with sublimation) remained undissolved. The filtrate was evaporated to dryness, the residue extracted with benzene, and the extract filtered and treated with light petroleum (b. p. 60—80°). Malonic acid separated (0·14 g.; m. p. 105—120°), which after crystallisation from ethyl acetate had m. p. 127—129° (decomp.), and m. p. 130° when mixed with an authentic specimen.

(c) *Bromination.* A solution of the tri-ester (15·8 g.) in chloroform was kept with bromine (9·3 g., 1 mol.) at 0° overnight, then evaporated, finally under reduced pressure. *Ethyl β-carbomethoxy*(erythro)-*αβ-dibromopropionylmalonate* (XII) (11·7 g.) crystallised from light petroleum (b. p. 40—60°) in rhombs, m. p. 67—68° (Found : C, 33·3; H, 3·75. $C_{12}H_{16}O_7Br_2$ requires C, 33·35; H, 3·7%). It was unchanged by stirring with concentrated hydrobromic acid (150 c.c.; *d* 1·5) for 6 days : no *αβ*-dibromo-*β′*-ketoadipic acid was found in the filtrate.

(d) *Methanolysis.* The tri-ester (5 g.) was treated overnight with saturated methanolic hydrogen chloride (50 c.c.) containing concentrated aqueous hydrochloric acid (5 c.c.). On evaporation under reduced pressure, a mixture (3·65 g.) of a solid, m. p. 90—100°, with an oil was obtained. The solid, washed with a small quantity of methanol, and crystallised from light petroleum (b. p. 60—80°), was identified (mixed m. p.) as methyl dihydro-*β*-ketomuconate (below).

(e) *Hydrolysis with methanolic lithium hydroxide.* The tri-ester (2·7 g.) was allowed to react overnight with methanolic 0·34N-lithium hydroxide (90 c.c., 3 equivs.). The solvent was removed under reduced pressure, the residue dissolved in water, and the solution acidified. Ethyl *β*-carboxyacrylylmalonate (0·3 g.) separated, m. p. 97—98°, and m. p. 100—101° when mixed with an authentic specimen (see below). On concentration of the filtrate under reduced pressure fumaric acid (0·3 g.), m. p. 280° (with sublimation), was obtained.

Attempted Preparation of cis-*β-Carbethoxyacrylyl Chloride.*—A solution of maleic anhydride (100 g.) in ethanol (60 c.c.) was heated on the steam-bath for 1 hour, cooled, treated with thionyl chloride (110 c.c.) and then heated under reflux for 1 hour longer. Distillation under reduced pressure (20 mm.) through a Dufton column (8″) afforded a liquid of steadily increasing b. p. and falling refractive index (n_D^{21}), collected in the following arbitrary fractions : (i) 86—88°, 1·4643 (56 g.); (ii) 88—94°, 1·4620; (iii) 94—100°, 1·4575; (iv) 100—105°, 1·4535 (Found : C, 38·85; H, 4·35. Calc. for $C_6H_7O_3Cl$: C, 44·3; H, 4·3. Calc. for $C_6H_8O_3Cl_2$: C, 36·2; H, 4·0%) [(ii) + (iii) + (iv) = 27·5 g.]. 1-G. portions of fractions (i) and (iv) were added dropwise, with stirring, to separate solutions of *p*-aminobenzenesulphonamide (2·2 g.) in dry dioxan (15 c.c.). After 5 minutes, each mixture was diluted with water to 250 c.c. and cooled in ice. Recrystallisation of the precipitates from *n*-butanol yielded, respectively, needles (0·95 g.) (negative Beilstein test), m. p. 219°, of fumaric half-ethyl ester half-sulphanilamide (Bergmann and Schapiro, *loc. cit.*, give m. p. 219°), and plates (0·55 g.) (positive Beilstein test), m. p. 190—195° (depressed to 175—178° by the preceding amide), presumably of mixed stereoisomeric chlorosuccinyl half-ethyl ester half-sulphanilamides (Found : C, 43·6; H, 4·7; N, 8·8. Calc. for $C_{12}H_{15}O_5N_2ClS$: C, 43·1; H, 4·5; N, 8·4%).

Ethyl Hydrogen Fumarate.—A *well-mixed* solution of maleic anhydride (100 g.) in hot ethanol (60 c.c.) was treated with thionyl chloride (1 c.c.) and heated on the steam-bath for 5—10 minutes. Carbon tetrachloride (100 c.c.) was added cautiously, and the hot mixture filtered (with gentle suction through 2 papers on a warm funnel, $\not<$10 cm. diam., to obviate clogging). The fumaric acid (7—12 g. in different runs), m. p. 286° (with sublimation), was washed with boiling carbon tetrachloride (15 c.c.), and the combined filtrate cooled thoroughly in ice. The paste was transferred to a filter, drained, washed with cold carbon tetrachloride (2 × 20 c.c.), and dried : yield, 100—95 g., plates, m. p. 67—68° undepressed by authentic material from half-hydrolysis of ethyl fumarate. When the heating (following the thionyl chloride addition) was prolonged to 15 minutes, the yield fell to 88 g. and more fumaric acid (16 g.) was formed.

trans-*β-Carbethoxyacrylyl Chloride.*—Ethyl hydrogen fumarate (100 g.) and thionyl chloride (100 c.c.) were heated on the steam-bath under reflux for 1·5 hours, and the product fractionated under reduced pressure to give fumaric half-ester chloride (92 g., 82%), b. p. 74—75°/10 mm., 86°/20 mm., n_D^{22} 1·4610.

Methyl Hydrogen Fumarate.—A warm *well-mixed* solution of maleic anhydride (100 g.) in methanol (50 c.c.) was treated with thionyl chloride (1 c.c.) and heated on the steam-bath for 10 minutes. On cooling, the mixture set to a solid. This was stirred vigorously with excess of aqueous sodium hydrogen carbonate, and the insoluble material collected, washed with water, and recrystallised from methanol–benzene to give methyl fumarate (51 g.), m. p. 98—100°. The aqueous filtrate was concentrated under reduced pressure to ~150 c.c. (to remove any methanol), and then cooled in ice and acidified to thymol-blue with concentrated hydrochloric acid. The precipitate (m. p. >200° with softening at ~135°) was extracted with boiling chloroform : insoluble fumaric acid (12·5 g.) remained. On concentration and cooling, the extract afforded pure methyl hydrogen fumarate (21·5 g., 16%), m. p. 141°.

trans-*β-Carbomethoxyacrylyl Chloride*.—Methyl hydrogen fumarate (21·5 g.) and excess of thionyl chloride (70 c.c.) were heated on the steam-bath under reflux for 1 hour, and the product fractionated to yield the half-chloride (20 g., 81%), b. p. 76°/20 mm., n_D^{20} 1·4710.

Methyl trans-*β-Carbomethoxyacrylylmalonate* (VII; R = R′ = Me).—Methyl malonate (20 g.) in methanol (9 c.c.) was added to a mixture of magnesium powder (3·3 g.), dry methanol (3·3 c.c.), and carbon tetrachloride (0·2 c.c.). When the initially vigorous reaction had subsided, methanol (20 c.c.) and dry ether (100 c.c.) were added, and the mixture was heated under reflux overnight. By evaporation, and repeated distillation to dryness with dry benzene (3 × 100 c.c.), finally under reduced pressure, the excess of methanol was removed. The magnesium complex, dissolved in benzene (100 c.c.), was then treated dropwise with *trans-β*-carbomethoxyacrylyl chloride (20 g.) in benzene (30 c.c.), and the stirred mixture heated under reflux for 3 hours. Next day, the mixture was shaken mechanically with 2N-sulphuric acid, the aqueous layer extracted with ether, and the combined organic solution washed with a small volume of aqueous sodium hydrogen carbonate and water, and dried ($MgSO_4$). The solvent was distilled, and the solid residue (28·3 g., 87%) purified by dissolution in dilute sodium hydroxide and precipitation with hydrochloric acid. From light petroleum (b. p. 40—60°) *methyl* trans-*β-carbomethoxyacrylylmalonate* formed colourless needles, m. p. 89° (Found: C, 49·1; H, 5·1. $C_{10}H_{12}O_7$ requires C, 49·2; H, 4·9%). The ester gives a red colour with ferric chloride in aqueous alcohol.

Ethyl trans-*β-Carbethoxyacrylylmalonate* (VII*a*).—*trans-β*-Carbethoxyacrylyl chloride (112·4 g.) and ethyl magnesiomalonate [from ethyl malonate (120 g.) and magnesium turnings (16·6 g.)] were allowed to react in ether, and the complex decomposed in the usual manner [as for (XI)] to yield *ethyl* trans-*β-carbethoxyacrylylmalonate* (149 g., 75%), b. p. 144°/0·5 mm., 110—111°/2 × 10^{-2} mm., n_D^{22} 1·4960 (Found: C, 54·2; H, 6·2. $C_{13}H_{18}O_7$ requires C, 54·5; H, 6·3%). It gives a red colour with ferric chloride.

Treatment of the ester (1·43 g.) in ethanol with cupric acetate (0·5 g.) in a minimum of water gave an oil which solidified on scratching (1·27 g.; m. p. 153—154°); a second crop (0·12 g.; m. p. 156—158°) separated from the filtrate on addition of water. From aqueous ethanol the *copper* enolate of the *trans*-keto-ester (VII*a*) formed shining green plates, m. p. 159—159·5° [Found: C, 49·2; H, 5·6. $(C_{13}H_{17}O_7)_2Cu$ requires C, 49·2; H, 5·4%].

Ethyl trans-*β-Carboxyacrylylmalonate* (XIII).—(a) Ethyl *trans-β*-carbomethoxyacrylylmalonate (XI) (1 g.) was dissolved in potassium hydroxide (1·5 g.) in methanol (5 c.c.). After 2 days, dilute hydrochloric acid was added, and the precipitated *ethyl* trans-*β-carboxyacrylylmalonate* (0·46 g., 54%) crystallised from benzene–light petroleum (b. p. 60—80°) in white needles, m. p. 107° (Found: C, 51·2; H, 5·6. $C_{11}H_{14}O_7$ requires C, 51·2; H, 5·5%). It gives a red colour with ferric chloride.

(b) Ethyl *trans-β*-carbethoxyacrylylmalonate (VII*a*) (40 g.) in ethanol (1 vol.) was added to a solution of potassium hydroxide (32 g.) in ethanol (200 c.c.) and kept overnight. The potassium salt was collected, washed with alcohol and ether, and dissolved in a minimum of water, and the ice-cooled solution acidified with concentrated hydrochloric acid. The precipitated ethyl *trans-β*-carboxyacrylylmalonate (34·1 g., 95%; m. p. 102°) was sufficiently pure for lactonisation.

trans-*Dihydro-β-ketomuconic* (trans-3-*Ketobut*-1-*ene*-1 : 4-*dicarboxylic*) *Acid* (XV).—(a) A solution of ethyl *trans-β*-carbomethoxyacrylylmalonate (XI) (5 g.) in acetic acid (20 c.c.) and concentrated hydrochloric acid (10 c.c.) was saturated with gaseous hydrogen chloride, and kept at room temperature for 2 days. A white solid (1 g.) separated, which from acetone–light petroleum (b. p. 40—60°) gave trans-*dihydro-β-ketomuconic acid* as a microcrystalline powder, m. p. 164° (decomp.) (Found: C, 45·7; H, 3·8. $C_6H_6O_5$ requires C, 45·6; H, 3·8%). The acid gives a deep purple colour with ferric chloride in aqueous alcohol.

In another experiment, the ester (XI) (32 g.) was dissolved in formic acid, concentrated hydrochloric acid (50 c.c.) was added, and the suspension redissolved by addition of more formic acid. After treatment with gaseous hydrogen chloride, the solution was kept at 30° for 4 days. The acid which separated (8·7 g.) had an indefinite m. p.: it was twice extracted with boiling acetone, and the combined filtrate treated progressively with light petroleum (b. p. 40—60°) to yield fumaric acid, m. p. 285° (with sublimation), and two crops of nearly pure dihydro-*β*-ketomuconic acid, m. p. 152—155° (decomp.) and 165—167° (decomp.).

(b) A solution of methyl *trans-β*-carbomethoxyacrylylmalonate (VII; R = R′ = Me) (5 g.) in acetic acid (100 c.c.) and concentrated hydrochloric acid (100 c.c.) was kept at room temperature for 6 days, then evaporated to dryness under reduced pressure, and the residue extracted with acetone. Dihydro-*β*-ketomuconic acid (0·62 g.), m. p. 167° (decomp.) (contaminated with traces of fumaric acid), remained undissolved.

Reactions of Dihydro-β-ketomuconic Acid.—(a) *Decarboxylation*. The acid (0·5 g.) was boiled in water for 15 minutes, and the solution evaporated to dryness under reduced pressure. Extraction of the residue (0·34 g.), m. p. 112—117°, with benzene left fumaric acid (0·03 g.), m. p. and mixed m. p. 290° (with sublimation), and from the filtrate, *β*-acetylacrylic acid (0·14 g.) crystallised with m. p. and mixed m. p. 118—120° [authentic material, prepared from lævulic acid (Wolff, *Annalen*, 1891, **264**, 229), had m. p. 122—123°].

(b) *Hydrogenation*. The acid (XV) (1 g.) in alcohol (50 c.c.) was shaken in hydrogen in the presence of Adams's catalyst (100 mg.). Uptake (235 c.c. at 25°/765 mm. Calc. for 2 mols: 308 c.c.) ceased after 2 hours. The filtered solution was evaporated under reduced pressure to leave an oily residue (0·7 g.), from which crude *β*-ketoadipic acid crystallised (0·21 g., 20%), m. p. 94° (decomp.): it was separated by washing with ether–hexane, and characterised as lævulic acid semicarbazone, m. p. and mixed m. p. 184° (decomp.).

After a solution of *β*-ketoadipic acid (1·6 g.) in ethanol (20 c.c.), containing Adams's catalyst (100 mg.), had been shaken with hydrogen under similar conditions for 19 hours (no uptake), an oily residue was eventually obtained. This afforded lævulic acid 2 : 4-dinitrophenylhydrazone in 73% yield, m. p. 201—202°, and 203° when mixed with an authentic specimen.

(c) *Esterification.* The acid (XV) (0·5 g.) in methanol (100 c.c.) was treated with ethereal diazomethane, the solution evaporated under reduced pressure, and the residual solid extracted with ether. The ether was filtered and evaporated, and the residue sublimed at 100°/20 mm. and recrystallised from *cyclo*hexane to give *methyl* trans-*dihydro-β-ketomuconate* (XIV) as shining needles, m. p. 95·5—98° (Found: C, 51·4; H, 5·4. $C_8H_{10}O_5$ requires C, 51·6; H, 5·4%). The ester gives a red colour with ferric chloride in aqueous alcohol.

(d) *Bromination.* To the acid (XV) (1·6 g.) suspended in acetic acid (50 c.c.), bromine (1·6 g., 1 mol.) in acetic acid was added slowly with stirring. Unchanged material (0·2 g.) was filtered off, the solution evaporated to dryness under reduced pressure, and the residue (1·25 g., 45%) washed with chloroform and light petroleum. From ethyl acetate–carbon tetrachloride (erythro)-*αβ-dibromo-β′-ketoadipic acid* (XVIII) crystallised as needles, m. p. 148—149° (decomp.) (Found: Br, 50·3. $C_6H_6O_5Br_2$ requires Br, 50·3%). The acid gives a deep purple with ferric chloride.

α-Bromo-γ-carboxymethylenebutenolide (XX).—The preceding acid (1·5 g.) was kept with acetyl chloride (20 c.c.) for 3 days at room temperature and the solution then evaporated under reduced pressure, finally in a desiccator. The *lactone* crystallised from chloroform and ethyl acetate–light petroleum (b. p. 60—80°) as minute prisms, m. p. 182—183° (decomp.) (Found: C, 32·9; H, 1·8. $C_6H_3O_4Br$ requires C, 32·9; H, 1·4%). It does not give a ferric chloride colour.

Lactonisation Experiments with Dihydro-β-ketomuconic Acid.—(a) A suspension of the acid (1 g.) in acetyl chloride (25 c.c.) was heated under reflux for 24 hours and filtered, and the filtrate evaporated under reduced pressure to afford a brown syrup. This gave a red ferric chloride colour and on exposure to the air slowly solidified. Crystallisation from acetone–light petroleum (b. p. 40—60°) gave starting material (0·29 g.), m. p. and mixed m. p. 154° (decomp.).

(b) *γ-Carboxymethylenebutenolide* (III; R = H). The acid (XV) (2 g.), acetic anhydride (20 c.c.), and acetic acid (20 c.c.) were heated together on the steam-bath for 2 hours, whilst hydrogen bromide was passed through. The solution was evaporated under reduced pressure, and the residue (1·1 g.) taken up in acetone, and treated with charcoal. The filtrate was concentrated, filtered from sparingly-soluble matter, and evaporated under reduced pressure, the residue taken up in ethylene dichloride, and the solution again clarified and then cooled in ice. *γ-Carboxymethylenebutenolide* crystallised from ethylene dichloride as needles (75 mg.), m. p. 156° (Found: C, 51·7; H, 3·1. $C_6H_4O_4$ requires C, 51·4; H, 2·9%). It does not give a colour with ferric chloride. Treatment in ether with ethereal diazoethane (Adamson and Kenner, *J.*, 1937, 1551) afforded an ester identified by mixed m. p. with that next described.

Pyrolysis of Ethyl trans-*β-Carbethoxyacrylylmalonate.*—(a) The ester (VII*a*) (20·8 g.) and naphthalene-β-sulphonic acid (1 g.) were heated to 190° during 30 minutes. Vigorous evolution of gas took place at 140—160°. The cooled reaction product was taken up in ether, washed with 5% sodium hydrogen carbonate (35 c.c.) and water, dried ($MgSO_4$), and evaporated: distillation under reduced pressure failed to afford any material of constant b. p., but from a fraction of b. p. 100—118°/0·5—1 mm., a neutral solid crystallised on standing. From light petroleum (b. p. 60—80°), *γ-carbethoxymethylenebutenolide* (III; R = Et) (150 mg.) formed prisms, m. p. 77·5—78·5° (Found: C, 57·0; H, 5·0. $C_8H_8O_4$ requires C, 57·1; H, 4·8%). It does not give a colour with ferric chloride.

(b) The triester (30 g.) and naphthalene-β-sulphonic acid (3 g.) were heated rapidly (5—10 minutes) to 250° and kept at that temperature for 20 minutes. The product was worked up as previously, and the following fractions were collected at 0·05 mm.: (i) b. p. 50—100°; (ii) 100—125°; (iii) 125—170°. At 0°, fraction (i) deposited a crystalline solid (82 mg.), m. p. 77—78·5° alone and in admixture with γ-carbethoxymethylenebutenolide, whilst (ii) and (iii) solidified partially: the solids had m. p.s 41—55° (0·6 g.) and 58—60° (1·76 g.), respectively. After single crystallisations from ether–light petroleum (b. p. 40—60°), these two solids had m. p.s 47—58° and 59—61°: the latter was not depressed by γ-dicarbethoxymethylenebutenolide (below).

γ-Dicarbethoxymethylenebutenolide (IV).—Ethyl β-carboxyacrylylmalonate (XIII) (7·5 g.) was heated in acetic anhydride (80 c.c.) on the steam-bath for 6 hours whilst dry hydrogen bromide was passed through. The solution was evaporated to dryness under reduced pressure, and the residue distilled at 100°/10^{-4} mm. *γ-Dicarbethoxymethylenebutenolide* (6·0 g., 73%) was obtained as a pale yellow solid which crystallised from ether–light petroleum (b. p. 40—60°) as colourless prisms, m. p. 62° [Found: C, 54·8; H, 5·1%; *M* (Rast), 215. $C_{11}H_{12}O_6$ requires C, 55·0; H, 5·0%; *M*, 240]. The lactone crystallises with great ease and is readily soluble in most organic solvents.

Attempted Decarbethoxylation of (IV).—(a) The lactone (10 g.) and naphthalene-β-sulphonic acid (1 g.) were heated to 250° (*ca.* 30 minutes): slight evolution of gas occurred at 150—160°. The dark oil was cooled, taken up in ether, and filtered, and the solution washed with aqueous sodium hydrogen carbonate and water. After being dried ($MgSO_4$), the ether was evaporated, and the residue distilled at 100°/10^{-4} mm. The distillate (4·8 g.) slowly crystallised and then had m. p. 51—56° alone and in admixture with the starting material.

(b) The lactone (7·2 g.), propionic acid (40 c.c.; redistilled), propionic anhydride (2 c.c.), and toluene-*p*-sulphonic acid (0·4 g.) were heated together in a flask surmounted by a fractionating column and a total-reflux, variable-take-off head. During 11 hours, 2 c.c. of distillate were collected, which had an odour of ethyl propionate but were completely soluble in alkali. The distilland was concentrated under reduced pressure and taken up in ether. The solution was washed with sodium hydrogen carbonate and water, dried ($MgSO_4$), and evaporated, and the residue distilled at 100°/10^{-4} mm., to yield a solid (5·16 g.), m. p. 45—50°, which after recrystallisation from ether–light petroleum had m. p. 59—61° alone and in admixture with the starting material.

Properties of the Lactone (IV).—(a) *Colour reactions.* The lactone did not give a colour immediately with ferric chloride in aqueous alcohol: on standing overnight, or on boiling, a red colour developed.

The Légal test was negative. Ammoniacal silver nitrate and dichlorophenol-indophenol were not reduced (cf. Kuehl, Linstead, and Orkin, *J.*, 1950, 2213).

(b) *Stability to water.* A solution of the lactone (0·5 g.) in dioxan (4·5 c.c.) and water (3·5 c.c.) was kept at room temperature for 22 hours, then evaporated to dryness under reduced pressure. The oily residue gave a very faint red colour with ferric chloride, and on seeding with the starting material it solidified (0·42 g., 84%), m. p. and mixed m. p. 48—51°.

(c) *Fission with aqueous alkali.* The lactone (2·4 g., 0·01 mol.) in dioxan (50 c.c.) was treated with 0·1N-potassium hydroxide (100 c.c., 1 equiv.), and after 3 days the solution was concentrated under reduced pressure at $<37°$, acidified with 2N-sulphuric acid (5 c.c.), and extracted with ether for 6 hours. By evaporation of the extract, maleic acid (1·44 g.) was obtained, which after being washed with cold chloroform and crystallised from ethyl acetate, had m. p. and mixed m. p. 135—136°. Vacuum sublimation at 160—170° gave maleic anhydride, m. p. 51—53° not depressed by an authentic specimen. The chloroform washings from the maleic acid were evaporated to dryness, and the residue kept with ammonia solution (*d* 0·88) for several days. Aqueous barium hydroxide was added, barium maleate removed, the filtrate evaporated to dryness under reduced pressure, and the residue twice extracted with boiling dioxan. Evaporation of the filtered extract under reduced pressure afforded malonamide, m. p. 163—164° (decomp.) undepressed by authentic material.

(d) *Hydrogenation.* (i) Reduction of the lactone (0·6 g.) in ethanol (5 c.c.) with hydrogen (at room temperature and pressure) and Adams's catalyst (50 mg.) was essentially complete in 2 hours (Hydrogen uptake, after 5 hours : 149 c.c. Calc. for 3 mols. : 165 c.c.). The filtered solution was concentrated under reduced pressure, and the oily residue heated under reflux with potassium hydroxide (0·75 g.) in water (3·5 c.c.) for 1·5 hours. Acidification with hydrochloric acid, evaporation to dryness under reduced pressure, and extraction with ether gave crude α-carboxyadipic acid (0·33 g.; m. p. 95—105°), separated by crystallisation from ethyl acetate–benzene into fractions of m. p. 132—133° and 110—115° (Ruggli and Maeder, *Helv. Chim. Acta*, 1943, **26**, 1476, give m. p. 139° for α-carboxyadipic acid). Each fraction on pyrolysis yielded adipic acid, m. p. 146° (from water), and m. p. 148° when mixed with authentic material.

(ii) The lactone (0·84 g.) in purified ethyl acetate was 50% hydrogenated in the presence of Adams's catalyst (50 mg.). The allowed uptake of hydrogen (122 c.c. at 24°/762 mm.) (Calc. for 3 mols. : 255 c.c.) took 1 hour. The dark solution was filtered and evaporated under reduced pressure, and the oily residue (0·76 g.) in ether was separated by extraction with aqueous sodium hydrogen carbonate into an acid fraction (0·31 g.) and a neutral oil (0·24 g.). The latter crystallised on cooling and after distillation at 170—190°/0·05 mm. had m. p. 47°, and m. p. 52—53° when mixed with the starting material. The acid fraction was boiled under reflux with concentrated hydrochloric acid (10 c.c.) for 3 hours, and the solution treated with charcoal and evaporated to dryness under reduced pressure. The residue crystallised from ethyl acetate–light petroleum (b. p. 60—80°) with m. p. 143—145° : a mixture with adipic acid had m. p. 147—149°.

(e) *Reaction with ethanol.* (i) A solution of the lactone in ethanol gave, on spontaneous evaporation, only unchanged material, m. p. and mixed m. p. 60°. (ii) The lactone (0·5 g.) in dry ethanol (10 c.c.) was heated under reflux for 2·5 hours, and next day the solution was evaporated to dryness under reduced pressure. The residue, which gave a faint red with ferric chloride, soon set to a solid (0·27 g., 54%), m. p. 53—55° (softened at 42°) alone and in admixture with the starting material. (iii) A solution of the lactone (0·5 g.) in dry ethanol (10 c.c.) containing a trace of hydrogen chloride was boiled under reflux for 2·5 hours and evaporated under reduced pressure. Treatment of the mobile oily residue in alcohol with aqueous cupric acetate afforded the copper enolate of ethyl *trans*-β-carbethoxyacrylylmalonate, m. p. 141—143°, and m. p. 151° when mixed with an authentic specimen.

(f) *Reaction with sodium ethoxide. Formation of ethyl* cis-*β-carbethoxyacrylylmalonate* (VII*b*). The lactone (1·2 g., 0·005 mol.) in dry ethanol (20 c.c.) was kept for 30 minutes with ethanolic sodium ethoxide (5 c.c.; N.). The solvent was evaporated, the residue taken up in water, and the solution acidified to thymol-blue with dilute sulphuric acid and extracted with ether. Evaporation of the extract afforded a mobile oil (1·2 g.) which gave a bright red colour with ferric chloride : portions were treated separately as follows :

(i) On addition of cupric acetate (0·15 g.) in water (6 c.c.) to the oil (0·16 g.) in ethanol (2 c.c.) and cooling in ice and stirring with a glass rod, a green solid separated (0·12 g.), m. p. 49—55°. From aqueous ethanol, the *copper* enolate (*form A*) of ethyl *cis*-β-carbethoxyacrylylmalonate crystallised as green solvated needles, m. p. 54—55° (Loss in weight on drying at 20 mm. over silica gel : 5·6%) [Found, on dried material : C, 48·0; H, 5·5. $(C_{13}H_{17}O_7)_2Cu,H_2O$ requires C, 47·9; H, 5·6%]. During the recrystallisation of form A, green needles, m. p. 101—102°, of *form B* were obtained (Loss in weight on drying as above : 4·35%) (Found, on dried material : C, 48·0; H, 5·45%).

A mixture of A and B softened at ~64° and had m. p. 101—101·5°. Mixtures of the copper enolate of ethyl *trans*-β-carbethoxyacrylylmalonate (plates, m. p. 159°) with A and B melted progressively from 51° and 94°, respectively. Form A was unchanged by crystallisation from ethanol–water and seeding with B. Form B was converted into A by similar crystallisation and seeding with A. In a vacuum desiccator over calcium chloride, form A fell to a dark glass which on exposure to the air resolidified (becoming pale green) and then had m. p. 100—101° alone and in admixture with B : on further drying, the enolate became dark and glassy once more. The water of constitution was not removed at 10^{-4} mm. over phosphoric oxide (Found : C, 47·7; H, 5·6%).

(ii) A solution of the oil in ethanol containing traces of hydrogen chloride and sulphur dioxide was kept at room temperature for 3 days, then evaporated under reduced pressure and again after addition of fresh ethanol. The residue in ethanol was treated with aqueous cupric acetate to yield a copper enolate, m. p. 149·5—151·5°, which, after one crystallisation from ethanol–water, had m. p. 154—155°, and m. p. 158° when mixed with the copper enolate of ethyl *trans*-β-carbethoxyacrylylmalonate.

(iii) The oil (0·54 g.) was dissolved in aqueous sodium hydroxide (10 c.c.; 1·04N.). Next day, the solution was acidified to thymol-blue with dilute sulphuric acid and extracted with ether for 7 hours. The ether was evaporated, and the residue taken up in ether (1 c.c.), cooled, and scratched. The solid which separated was washed with ether–hexane (3 : 2) and then had m. p. 136—137°, and m. p. 137° in admixture with maleic acid (m. p. 137°); the yield was 17 mg. A mixture with malonic acid had m. p. 108—111° (after softening at 75°). It was found that a solution of maleic acid in ethyl acetate when treated with traces of hydrogen chloride and sulphur dioxide deposited a nearly equal weight of fumaric acid during 24 hours. The preceding filtrate and washings were accordingly evaporated, and the residue in ethyl acetate treated similarly: sparingly soluble fumaric acid separated (60 mg.), recognised by m. p. and mixed m. p.

(g) *Reaction with aniline.* The lactone (0·9 g.) in dioxan was kept with aniline (0·35 g., 1 mol.) overnight. Removal of the solvent under reduced pressure afforded an oil which solidified to a yellow mass (0·77 g.; m. p. 111—112°). This was washed with ether and crystallised from benzene and aqueous ethanol to yield *ethyl* trans-*β-anilidoacrylylmalonate* (XXIV) as beautiful pale yellow needles, m. p. 114—114·5°, identical with the material synthesised below (Found: C, 61·3; H, 5·9; N, 4·4. $C_{17}H_{19}O_6N$ requires C, 61·25; H, 5·7; N, 4·2%). After treatment at room temperature for several days in ethanol containing traces of hydrogen chloride and sulphur dioxide, the anilide was recovered, m. p. 106—109° not depressed by the starting material.

Synthesis of Ethyl trans-*β-Anilidoacrylylmalonate.*—(a) Fumaric half-anilide half-chloride (2 g.; m. p. 119—120°) (Anschütz, *Annalen*, 1890, **259**, 137) in benzene (100 c.c.) was heated with a benzene solution (50 c.c.) of ethyl magnesiomalonate (from 3·2 c.c. of malonic ester and 0·5 g. of magnesium) for 6 hours on the steam-bath. The cooled mixture was shaken with 2N-sulphuric acid (30 c.c.), and the benzene layer separated, washed with water, filtered, and evaporated. The residue crystallised on treatment with ether and had m. p. 110—111°, and m. p. 113—114° in admixture with the anilide obtained from the lactone.

(b) Ethyl *trans-β*-carboxyacrylylmalonate (1·3 g.) in dry benzene containing pyridine (1 drop) was treated with oxalyl chloride (0·5 c.c.) at 0°. The solution was warmed to room temperature and after 1·5 hours was heated at 40° for a further 1·5 hours, and then evaporated under reduced pressure. Dry benzene was added and evaporated again, and to the residual oil in dry ether aniline (0·9 c.c., 2 mols.) in ether was added slowly at 0° with shaking. The mixture was washed successively with water, dilute acid, sodium hydrogen carbonate, and water, and the ethereal solution dried ($MgSO_4$) and evaporated. The anilide (1·14 g.; m. p. 110°) crystallised from benzene–light petroleum (b. p. 60—80°) with m. p. 111—112° undepressed by the product from the lactone (IV) and aniline.

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