13. *Studies on the Michael Reaction. Part IV. The Addition of Alkylmalonic Esters to Some α-Substituted Δ^{α}-Unsaturated Esters: General Conclusions.*

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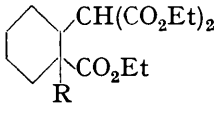
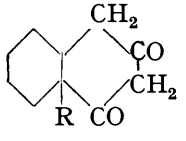
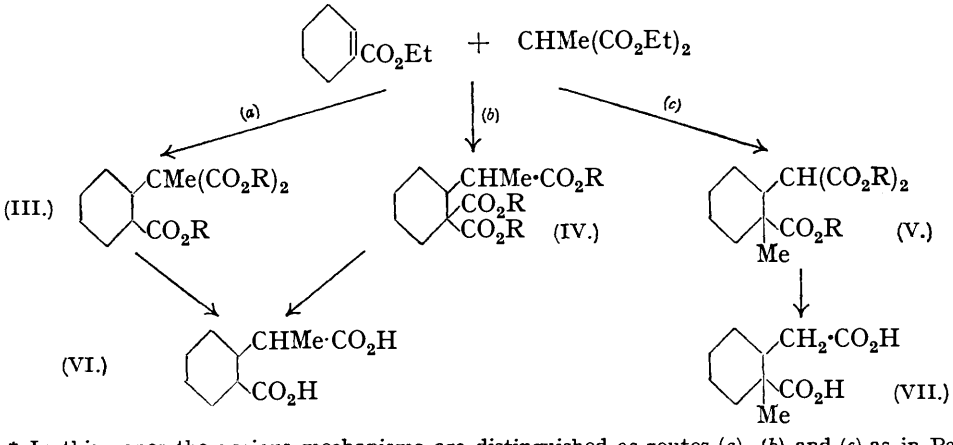
The condensations of ethyl methylmalonate with ethyl Δ^1-tetrahydrobenzoate and with ethyl α-ethylcrotonate and of ethyl ethylmalonate with ethyl tiglate have been studied. Comparison of the products with synthetic materials shows that in every case the reaction proceeds normally, *i.e.*, without apparent wandering of alkyl or carbethoxyl. The results of Parts I—IV and of other workers are correlated and are all shown to be in accordance with predictions based on Holden and Lapworth's theory of abnormal reactions. It is concluded that, although no direct proof has been obtained, this agreement of theory and practice points strongly to the validity of Holden and Lapworth's views.

THE addition of alkylmalonic esters to ethyl Δ^1-tetrahydrobenzoate is of great interest at the present time, since, if it could be established that such additions are abnormal and proceed by route (*c*),* yielding (I), an obvious extension, using acetoacetic esters and Δ^1-

(I.)   (II.)

tetrahydroacetophenone, should give rise to substances of type (II), by ring closure after the manner of Vorländer's well-known synthesis of dimethyldihydroresorcinol (*Annalen*, 1897, **294**, 314).

The products to be expected, according to the prevailing mechanism, in the condensation of ethyl methylmalonate with ethyl Δ^1-tetrahydrobenzoate are shown in the following scheme :



* In this paper the various mechanisms are distinguished as routes (*a*), (*b*) and (*c*) as in Part III (p. 45).

in which, when R = Et, (III), (IV) and (V) represent the reaction products and, when R = H, the tribasic acids obtainable therefrom by alkaline hydrolysis, and (VI) and (VII) represent the dibasic acids to be expected on acid hydrolysis. Of the esters (III), (IV) and (V), only the last should be capable of ready alkylation.

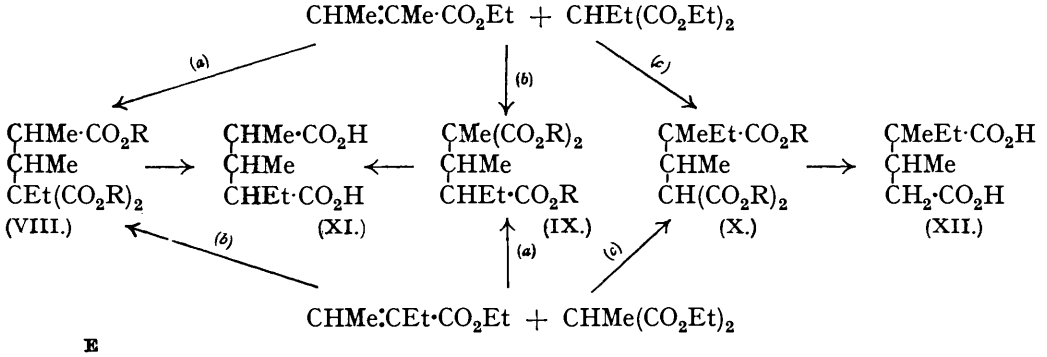
Of these products, the two forms of 1-methyl*cyclo*hexane-1-carboxylic-2-acetic acid (VII) are known. The *cis*(?)-acid, m. p. 163—164°, was prepared by the method of Linstead and Millidge (J., 1936, 840; cf. Chuang, Tien, and Huang, *Ber.*, 1935, **68**, 864), and the *trans*(?)-acid, m. p. 174° (Linstead and Millidge, *loc. cit.*; Newitt, Linstead, Sapiro, and Boorman, J., 1937, 879), was kindly supplied by Dr. Linstead.

The " normal " addition product (III; R = Et) was synthesised by condensing ethyl Δ^1-tetrahydrobenzoate with ethyl sodiomalonate (cf. Helfer, *Helv. Chim. Acta*, 1926, **9**, 816; Boorman and Linstead, J., 1935, 258) and methylating the product in the usual way. Alkaline hydrolysis of ethyl *cyclo*hexane-1-carboxylate-2-methylmalonate (III; R = Et) so obtained could not be made to yield any of the desired tribasic acid (III; R = H) owing to extensive decarboxylation, but acid hydrolysis readily yielded cyclo*hexane*-1-*carboxylic*-2-α-*propionic acid* (VI), m. p. 184°. Since Boorman and Linstead (*loc. cit.*) showed that the parent unmethylated ester gave only *trans*-hexahydrohomophthalic acid on acid hydrolysis, the disposition of the groups about the ring is probably *trans*; the stereochemical arrangement with respect to the methyl group is uncertain, but evidence was obtained of change on heating with hydrochloric acid at 190°, indicating that the acid may have the *trans-cis*-configuration.

The addition of ethyl methylmalonate to ethyl Δ^1-tetrahydrobenzoate under the influence of one equivalent of sodium ethoxide was very incomplete; after many trials the best yield (6%) was obtained by heating the reactants together on the steam-bath for 56 hours. This disappointing yield is in marked contrast to the 46% yield obtained by using ethyl malonate and the reaction affords an extreme example of the reduced tendency to addition caused by alkylation of the malonic ester (cf. Cooper, Ingold, and Ingold, J., 1926, 1868). The product had physical properties ($d_{4^\circ}^{20^\circ}$ 1·080, $n_D^{20^\circ}$ 1·463) which were very close to those ($d_{4^\circ}^{20^\circ}$ 1·079, $n_D^{20^\circ}$ 1·463) of the synthetic ester (III; R = Et) (values corrected to 20°). Alkaline hydrolysis gave no tribasic acid but only a dibasic acid, m. p. 184°, which was identified as *cyclo*hexane-1-carboxylic-2-α-propionic acid (VI) by a mixed m. p. determination with the synthetic specimen. Attempted methylation of the condensation product, using " molecular " sodium in benzene, gave considerable amounts of retrogression products, one of which was identified as ethyl·dimethylmalonate, but no methylated material.

The identification of the dibasic acid and the failure of the attempted methylation clearly exclude route (*c*); the very close approximation of the physical constants for the synthetic ester (III; R = Et) and the condensation product is strong evidence in favour of route (*a*), as is the identification of ethyl dimethylmalonate among the retrogression products from the attempted methylation. We are thus led to conclude that in this reaction the normal mode of addition [route (*a*)] prevails.

The additions of ethyl ethylmalonate to ethyl tiglate and of ethyl methylmalonate to ethyl α-ethylcrotonate were studied together, since the expected products are closely related:



Of the acids required for reference, (XI) and (IX; R = H) were synthesised. Condensation of ethyl tiglate and ethyl malonate, under the influence of cold alcoholic sodium ethoxide for 14 days, gave a 60% yield of ethyl γ-carbethoxy-αβ-dimethylglutarate; Michael and Ross (*J. Amer. Chem. Soc.*, 1930, **52**, 4602), using ethereal sodium ethoxide, record a yield of only 15%. Ethylation of this product in benzene yielded *ethyl γ-carbethoxy-αβ-dimethyl-γ-ethylglutarate* (VIII; R = Et); neither alkaline nor acid hydrolysis gave crystalline products.

Ethyl α-ethylcrotonate readily condensed with ethyl malonate, under the influence of alcoholic sodium ethoxide, to yield *ethyl α-carbethoxy-β-methyl-γ-ethylglutarate*, which was methylated in benzene solution to *ethyl α-carbethoxy-αβ-dimethyl-γ-ethylglutarate* (IX; R = Et). Alkaline hydrolysis of the latter yielded *α-carboxy-αβ-dimethyl-γ-ethylglutaric acid* (IX; R = H) as a solid, m. p. 161°; acid hydrolysis gave a semi-solid product, from which one of the stereoisomeric *αβ-dimethyl-γ-ethylglutaric acids* (XI), m. p. 123°, was readily isolated.

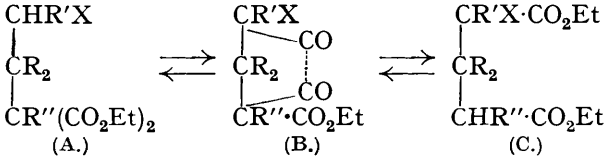
The formation of different stereoisomerides, or mixtures of stereoisomerides, from the esters (VIII; R = Et) and (IX; R = Et) is not without precedent; thus, in the analogous and stereochemically less complicated case of the methylethylcarboxysuccinic esters, Bischoff and Mintz (*Ber.*, 1890, **23**, 647) showed that, whereas the ester $CO_2Et{\cdot}CHEt{\cdot}CMe(CO_2Et)_2$ gave a mixture of *cis*- and *trans*-methylethylsuccinic acids on acid hydrolysis, the ester $CO_2Et{\cdot}CHMe{\cdot}CEt(CO_2Et)_2$ gave only the *trans*-acid.

The yield in the condensation of ethyl ethylmalonate with ethyl tiglate was 15%. Acid hydrolysis of the condensation product gave an oil, but alkaline hydrolysis yielded a solid tribasic acid, $C_{10}H_{16}O_6$, m. p. 159°; on admixture with the acid (IX) a considerable depression of m. p. was observed and, for reasons enumerated below, the substance is considered to be *γ-carboxy-αβ-dimethyl-γ-ethylglutaric acid* (VIII; R = H). Attempted methylation of the condensation product was unsuccessful [(X; R = Et) should be methylated readily], the only substances isolated being 35% of recovered condensation product (identified by hydrolysis to the tribasic acid, m. p. 159°) and 65% of a mixture of retrogression products, which were identified as ethyl tiglate and ethyl methylethylmalonate by conversion into the anilides (IX; R = Et should, and does, give ethyl α-ethylcrotonate as the unsaturated retrogression product on attempted methylation). There is thus no doubt that the condensation product is ethyl γ-carbethoxy-αβ-dimethyl-γ-ethylglutarate (VIII; R = Et), the reaction having proceeded by route (*a*), *i.e.*, normally.

The course of the reaction between ethyl α-ethylcrotonate and ethyl methylmalonate is even clearer. A 40% yield of condensation product was obtained which, on alkaline hydrolysis gave α-carboxy-αβ-dimethyl-γ-ethylglutaric acid (IX; R = H), m. p. 161° alone or mixed with an authentic specimen. Acid hydrolysis yielded αβ-dimethyl-γ-ethylglutaric acid (XI), m. p. 123°, not depressed on admixture with the synthetic material. Attempted methylation of the condensation product brought about complete retrogression to a mixture of ethyl α-ethylcrotonate and ethyl dimethylmalonate, both of which were identified as the corresponding anilides. It is evident, therefore, that the condensation product is ethyl α-carbethoxy-αβ-dimethyl-γ-ethylglutarate (IX; R = Et), having been formed, normally, by route (*a*).

Thus, all the reactions examined in this paper have been shown to proceed by route (*a*), *i.e.*, by the normal mechanism, and no evidence for any reaction by Thorpe's mechanism [route (*c*)] has been obtained.

Holden and Lapworth's mechanism (J., 1931, 2370) may be generalised in the following scheme (or the analogous scheme in which CN replaces CO_2Et and C:NH replaces CO) :



in which (A) is the normal addition product, which, it is assumed, is always the initial product of the reaction; (B) is a hypothetical intermediate keto-ester derived from one or

more molecules of (A) by a ring closure of the Dieckmann type [the two keto-groups in the formula may be one and the same, in which case (B) is a *cyclo*butanone derivative]; and (C) is an isomer of (A) in which apparent migration of a carbethoxyl group has taken place, and which is formed by alcoholysis of (B) by the alternative to the route (B) $\longrightarrow$ (A).

Holden and Lapworth regarded the successive reactions (A) $\rightleftarrows$ (B) $\rightleftarrows$ (C) as equilibria and pointed out that the series of reactions is likely to proceed from left to right if (a) the labile H in (A) is one of a pair attached to the same carbon atom and (b) the labile H in (C) is solitary. Further consideration of these conditions enables certain predictions to be made as to what types of reaction will show abnormality and what types will be normal. It should be pointed out, with Holden and Lapworth, that abnormality of the type encountered by Howles, Thorpe, and Udall (J., 1900, **77**, 943) in the condensation of ethyl α-methylacrylate with ethyl sodiocyanoacetate is of a different type and explicable in quite another way not involving this series of changes.

Condition (a) ($R' = H$) is the necessary condition for any keto-ester formation, *i.e.*, only if $R' = H$ will the reaction (A) $\longrightarrow$ (B) take place. Thus, if $R' = H$, the reaction *may* be abnormal; if $R' \neq H$, the reaction *must* be normal.

Condition (b) ($R'' \neq H$) is the condition for preferential fission of (B) to give (C) rather than (A). Now we have just shown that (B) is only formed if $R' = H$. With this proviso, if $R'' = H$, the reaction *may* be abnormal, whereas if $R'' \neq H$, the reaction *must* be abnormal.

Holden and Lapworth's theory thus requires normal reaction when $R' \neq H$ (whether or not $R'' = H$), abnormal reaction when $R' = H$ and $R'' \neq H$, and makes no prediction when $R' = R'' = H$.

We are thus led to formulate the following two general rules:

(i) All condensations of unsaturated compounds of the type $CR_2{:}CR'X$ with malonic esters (and similar substances) and their alkyl derivatives will be normal [route (*a*)].

(ii) All condensations of unsaturated compounds of the type $CR_2{:}CHX$ with alkylmalonic esters (and similar compounds) will be abnormal [route (*b*)].

Rule (i) is fulfilled by the three condensations described in this paper, in all of which the unsaturated reactant is an α-substituted unsaturated ester and all of which have been shown to be normal. Neither, so far as we are aware, has any exception to this rule been found in any well-authenticated case.

To rule (ii) conform the additions of alkylmalonic esters to ethyl fumarate, which are known to be abnormal (Michael and Ross, *J. Amer. Chem. Soc.*, 1931, **53**, 1150; Duff and Ingold, J., 1934, 87; Rydon, J., 1935, 420; Ingold and Rydon, *ibid.*, p. 857; Part II, this vol., p. 42); the abnormal additions of ethyl α-cyanopropionate to ethyl ββ-dimethylacrylate (Thorpe, J., 1900, **77**, 923) and to ethyl crotonate (Michael and Ross, *J. Amer. Chem. Soc.*, 1931, **53**, 1150) and the abnormal additions of ethyl methylmalonate to crotonic and cinnamic esters (Michael and Ross, *J. Amer. Chem. Soc.*, 1930, **52**, 4598) and to benzylideneacetophenone (Holden and Lapworth, *loc. cit.*). There are, however, two apparent exceptions among well-authenticated reactions of this type. The first of these is the normality of a number of additions of alkylmalonic esters to acetylenic esters of the type $CR{:}C{\cdot}CO_2Et$, which has been clearly shown by Farmer, Ghosal, and Kon (J., 1936, 1804). These acetylenic esters, however, contain no α-hydrogen, and the mobile hydrogen in (A) is, therefore, not one of a pair; in fact, they may be regarded as α-substituted ethylenic esters, the α-substituent being the β-carbon atom and the group R which it carries. Once this is clear it is evident that rule (i) and not rule (ii) is applicable and the observed normality falls into line with the theory. The other exception to rule (ii) is the normality of the addition of ethyl benzylmalonate to αβ-dibenzoylethylene; this is, no doubt, to be ascribed to the insolubility of the initial product (A) in the reaction medium, which results in its removal from active participation in the reaction before any conversion into the intermediate (B) can take place.

To sum up, in spite of the absence of very clear and definite evidence as to the mechanism of abnormal cases of the Michael reaction, the success of Holden and Lapworth's theory in predicting the occurrence of such abnormal reactions seems to us sufficient evidence, on pragmatic grounds, of its validity. It is, perhaps, hardly necessary to add that the theory is only applicable to additions carried out in the presence of a whole equivalent

of sodium ethoxide or, more strictly, an amount sufficient to bring about the series of reactions (A) $\rightleftarrows$ (B) $\rightleftarrows$ (C); additions in the presence of small, "catalytic" amounts of ethoxide doubtless proceed by quite a different mechanism to which the theory is not, and was not intended to be, applicable.

Experimental.

Synthesis of cyclo*Hexane*-1-*carboxylic*-2-α-*propionic Acid*.—17 G. of ethyl *cyclo*hexane-1-carboxylate-2-malonate (Helfer, *Helv. Chim. Acta*, 1926, **9**, 816; Boorman and Linstead, J., 1935, 261) were added to 1·25 g. of "molecular" sodium under light petroleum (b. p. 60—80°); formation of the sodio-derivative was complete after 2 hours' refluxing. 35 G. of methyl iodide were added, and the mixture refluxed for a further 3 hours. The sodium iodide was filtered off, and the filtrate washed with water, dried, and distilled, yielding 12·8 g. (72%) of ethyl *cyclo*hexane-1-carboxylate-2-methylmalonate (III; R = Et), b. p. 164—166°/3 mm., $n_D^{16°}$ 1·4647, $d_4^{15°}$ 1·0828, $[R_L]_D$ 83·70 (calc., 83·47).

Acid hydrolysis. 8 G. of the above ester (III; R = Et) were refluxed for several days with 40 c.c. of concentrated hydrochloric acid. The solution was boiled with charcoal and filtered; on cooling, 2·9 g. (60%) of solid acid, m. p. 165—169°, were deposited. Three crystallisations from dilute acetic acid yielded cyclo*hexane*-1-*carboxylic*-2-α-*propionic acid* (VI) in clusters of small prisms, m. p. 184° [Found: C, 60·1; H, 8·2; equiv. (by titration), 100·1. $C_{10}H_{16}O_4$ (dibasic) requires C, 60·0; H, 8·0%; equiv., 100·0]. 0·8 G., heated in a sealed tube with 10 c.c. of concentrated hydrochloric acid for 40 hours, gave, on crystallisation, 0·45 g. of an acid, m. p. 172—175° [mixed m. p. with (VI), 175—178°], and 0·15 g. of an acid, m. p. 130—135° [mixed m. p. with (VI), 135—139°], indicating a partial conversion into a stereoisomeride, presumably *trans-trans* (cf. p. 49).

Alkaline hydrolysis. 5 G. of the ester (III; R = Et) were refluxed overnight with 25 c.c. of 30% alcoholic potassium hydroxide. The alcohol was removed, and the residue taken up in water, acidified and extracted with ether. 3·3 G. of an acid which quickly solidified were obtained. This was fractionally crystallised from water, yielding 0·8 g. of the dicarboxylic acid (VI), m. p. 184°, and 1·2 g. of a mixture of acids, m. p. 170—173°, which could not be further separated and was shown by analysis to be a mixture of the dibasic acid (VI) and the desired tribasic acid (III; R = H) (Found: C, 56·9; H, 7·3. Calc. for $C_{10}H_{16}O_4$: C, 60·0; H, 8·0%. Calc. for $C_{11}H_{16}O_6$: C, 54·1; H, 6·5%).

Attempted methylation. 5 G. of the ester (III; R = Et) were added to 0·35 g. of "molecular" sodium in benzene. The initial slight reaction quickly abated and 4 hours' refluxing was necessary to complete the solution of the sodium. 10 G. of methyl iodide were added, sodium iodide being precipitated at once. Refluxing was continued overnight, and the product worked up in the usual manner. The following fractions were collected: (1) b. p. 96—104°/20 mm., 1·8 g.; (2) 100—156°/2 mm., 0·5 g.; (3) 156—158°/2 mm., 0·9 g. Fraction (1) was identified as ethyl dimethylmalonate by conversion into the anilide with anilinomagnesium bromide (Hardy, J., 1936, 398; cf. Bodroux, *Compt. rend.*, 1904, **138**, 1427). One crystallisation of the product from alcohol gave pure dimethylmalonanilide, m. p. 202°, identified by mixed m. p. with a specimen prepared similarly from authentic ethyl dimethylmalonate. Fraction (3) was refluxed with 10 c.c. of concentrated hydrochloric acid for 40 hours. 0·4 G. of acid crystallised from the cooled solution; two crystallisations from dilute acetic acid raised the m. p. to 178—180°, mixed m. p. with the acid (VI), 179—181°; fraction (3) thus consisted of unchanged ester (III; R = Et).

Ethyl Δ^1-*Tetrahydrobenzoate*.—In the preparation of Δ^1-tetrahydrobenzoic acid from Δ^1-tetrahydrobenzonitrile by the method of Boorman and Linstead (J., 1935, 261) steam-distillation was found to be unnecessary. The solid acid was refluxed with a 10% excess of thionyl chloride for an hour, and the crude chloride poured into absolute alcohol (3 vols.). After refluxing for an hour, the mixture was poured into water and extracted with ether. Distillation of the dried extract gave a 90% yield of pure ethyl Δ^1-tetrahydrobenzoate, b. p. 95—97°/15 mm., $n_D^{16°}$ 1·4716, $d_4^{16°}$ 1·0018, $[R_L]_D$ 43·01 (calc., 42·75) (Boorman and Linstead, *loc. cit.*, give $n_D^{20°}$ 1·4700, $d_4^{20°}$ 0·9999 for a specimen prepared through the silver salt).

Ethyl methylmalonate was prepared from ethyl α-bromopropionate through the cyano-ester by Steele's method (*J. Amer. Chem. Soc.*, 1931, **53**, 286); b. p. 94°/16 mm.; $n_D^{16·8°}$ 1·4148, $d_4^{16·8°}$ 1·0256, $[R_L]_D$ 42·46 (calc., 42·45) (Auwers, *Ber.*, 1913, **46**, 509, gives $n_D^{18·7°}$ 1·4137, $d_4^{18·7°}$ 1·0192).

Condensation of Ethyl Δ^1-*Tetrahydrobenzoate with Ethyl Methylmalonate*.—Sodium (1 equiv.) was dissolved in ten times its weight of absolute alcohol, and equivalent weights of ethyl methyl-

malonate and ethyl Δ^1-tetrahydrobenzoate added to the solution. The mixtures were left in the cold and/or heated on the steam-bath for various times. They were then poured into much water, acidified, and extracted with ether. The extract was washed with 10% sodium carbonate solution and water, dried, and distilled. After a large low fraction, consisting of unchanged reactants, the product was collected at 160—166°/2 mm. The yields under various conditions were : ½ hour on steam-bath, trace; 2 days in the cold, trace; 20 hours on steam-bath, 2 days in the cold, 2%; 6 days in the cold, 17 hours on steam-bath, 3%; 5 days in the cold, 7½ hours on steam-bath, 4%; 8 days in the cold, 5%; 3 days in the cold, 24 hours on steam-bath, 5%; 56 hours on steam-bath, 6%. The various high fractions were combined and redistilled. The condensation *product* had b. p. 158—160°/1·5 mm., $n_D^{20\cdot6°}$ 1·4627, $d_{4°}^{20\cdot6°}$ 1·0789, $[R_L]_D$ 83·69 (calc., 83·47) (Found : C, 62·1; H, 8·7. $C_{17}H_{28}O_6$ requires C, 62·2; H, 8·5%).

Hydrolysis. 5 G. of the condensation product were refluxed overnight with 30 c.c. of 30% alcoholic potassium hydroxide. The alcohol was removed and the residue treated with water, acidified, and extracted with ether. Evaporation of the dried extract yielded 2·6 g. of an oil which rapidly solidified. Five crystallisations from water yielded 1·1 g. of pure dibasic acid, m. p. 184° (Found : C, 60·2; H, 8·05. Calc. for $C_{10}H_{16}O_4$: C, 60·0; H, 8·0%). Admixture with either form of 1-methyl*cyclo*hexane-1-carboxylic-2-acetic acid (VII) depressed the m. p. to 140—150°, whereas a mixture with the synthetic *cyclo*hexane-1-carboxylic-2-α-propionic acid (VI) was unchanged in m. p.

Attempted methylation. 5 G. of the addition product were added to 0·35 g. of pulverised sodium suspended in dry benzene. The initial slight reaction soon abated and 4 hours' refluxing was required to bring the sodium into solution. 10 G. of methyl iodide were added, and the mixture refluxed overnight. It was then poured into water and extracted with ether. Distillation of the dried extract at 4 mm. gave three fractions : (1) b. p. 80—120°, 1·9 g.; (2) b. p. 120—168°, 0·2 g.; (3) b. p. 168—173°, 1·2 g. Fraction (1) was identified as ethyl dimethylmalonate by conversion into the dianilide, m. p. and mixed m. p. 202°, by Hardy's method. Fraction (3) was identified as unchanged starting material by refluxing with 10 c.c. of concentrated hydrochloric acid : extraction with ether gave 0·48 g. (60%) of crude acid, m. p. 165—170°; two crystallisations raised the m. p. to 179—181°, mixed m. p. with the acid (VI) 180—182°.

Ethyl Tiglate (cf. Ray, *J. Amer. Chem. Soc.*, 1928, **50**, 560).—135 G. of methylethylacetic acid (Gilman and Parker, *Org. Synth.*, 1925, **5**, 75) were treated with 120 c.c. of thionyl chloride, and the mixture refluxed for an hour on the steam-bath. 225 G. of bromine were then added dropwise, and heating continued till all the bromine had reacted. The cooled product was poured into 150 c.c. of absolute alcohol and refluxed for an hour. It was then poured into water and extracted with ether. The extract was washed with 10% sodium carbonate solution and water, dried, and distilled; yield of ethyl methylethylbromoacetate, b. p. 73—76°/14 mm., 230 g. (86%). This was refluxed for 2 hours with 127 g. of dimethylaniline and kept overnight. The ester was decanted, taken up in ether, and washed successively with dilute hydrochloric acid, 10% sodium carbonate solution, and water. Careful distillation of the dried extract yielded 110 g. (78%) of pure ethyl tiglate, b. p. 55—57°/15 mm., $n_D^{16\cdot8°}$ 1·4347, $d_{4°}^{16\cdot8°}$ 0·9239, $[R_L]_D$ 36·13 (calc., 35·71) (Auwers and Wissebach, *Annalen*, 1923, **432**, 71, give b. p. 55·5°/11 mm., $n_D^{19\cdot5°}$ 1·4355, $d_{4°}^{19\cdot5°}$ 0·9247).

Synthesis of αβ-Dimethyl-γ-ethylglutaric Acid.—24 G. of ethyl tiglate and 30 g. of ethyl malonate were added to sodium ethoxide [from sodium (4·6 g.) and ethyl alcohol (70 c.c.)], and the solution kept for 14 days. It was then poured into water and extracted with ether, and the extract washed with 10% sodium carbonate solution and water. Distillation of the dried extract yielded 34 g. (63%) of ethyl γ-carbethoxy-αβ-dimethylglutarate, b. p. 147—150°/3 mm. (Found : C, 58·7; H, 8·4. Calc. for $C_{14}H_{24}O_6$: C, 58·3; H, 8·3%).

An attempt to ethylate this product with the aid of " molecular " sodium in light petroleum (b. p. 60—80°) was unsuccessful. Accordingly, 1·6 g. of sodium, suspended in ether, were treated with 4·0 c.c. of absolute alcohol, and the mixture kept overnight. When 19·2 g. of the above ester were added, the sodium ethoxide dissolved almost immediately. 13 G. of ethyl iodide were added and, after standing at room temperature overnight, the mixture was refluxed on the steam-bath until neutral (6 hours). Working-up in the usual manner gave 13·5 g. (64%) of *ethyl γ-carbethoxy-αβ-dimethyl-γ-ethylglutarate* (VIII; R = Et), b. p. 145—146°/2 mm., $n_D^{18\cdot8°}$ 1·4430, $d_{4°}^{18\cdot8°}$ 1·0480, $[R_L]_D$ 80·02 (calc., 81·05) (Found : C, 60·6; H, 8·9. $C_{16}H_{28}O_6$ requires C, 60·8; H, 8·8%).

Ethyl α-Ethylcrotonate (cf. Auwers and Meissner, *Annalen*, 1923, **432**, 76).—75 G. of diethylacetic acid (Conrad, *Annalen*, 1880, **204**, 141) were treated with 84 g. of thionyl chloride and refluxed for an hour; while steam-heating continued, 35 c.c. of bromine were added dropwise

very slowly. When the colour of the bromine had vanished, the liquid was cautiously poured into 120 c.c. of absolute alcohol and refluxed for an hour. The product was poured into water, extracted with ether, washed with 10% sodium carbonate solution and water, dried, and distilled; yield of ethyl α-bromodiethylacetate, b. p. 78—81°/9 mm., 105 g. (85%). This was refluxed for 2 hours with 150 g. of dimethylaniline, and the product poured into dilute hydrochloric acid and extracted with ether. The extract was washed with 10% sodium carbonate solution and water, dried, and distilled, affording 54 g. (80%) of ethyl α-ethylcrotonate, b. p. 62—64°/12 mm., $n_D^{17°}$ 1·4339, $d_4^{17°}$ 0·9071, $[R_L]_D$ 40·76 (calc., 40·33).

Synthesis of αβ-Dimethyl-γ-ethylglutaric Acid.—21 G. of ethyl α-ethylcrotonate and 23 g. of ethyl malonate were added to sodium ethoxide (from 3·3 g. of sodium and 40 c.c. of absolute alcohol). After 14 days the product was poured into water, extracted with ether, and washed with 10% sodium carbonate solution and water. Distillation of the dried extract yielded 21 g. (48%) of *ethyl α-carbethoxy-β-methyl-γ-ethylglutarate*, b. p. 148—150°/3 mm. (Found : C, 59·5; H, 8·7. $C_{15}H_{26}O_6$ requires C, 59·6; H, 8·6%).

20 G. of this ester were added to ethereal sodium ethoxide (from 1·6 g. of sodium and 4·0 c.c. of absolute alcohol). The sodium ethoxide dissolved at once and 12 g. of methyl iodide were added. After 12 hours the product was refluxed until neutral (4 hours), poured into water, and worked up. Distillation gave 14 g. (67%) of *ethyl α-carbethoxy-αβ-dimethyl-γ-ethylglutarate* (IX; R = Et), b. p. 154—156°/4 mm., $n_D^{18·8°}$ 1·4430, $d_4^{18·8°}$ 1·0432, $[R_L]_D$ 80·34 (calc., 81·05) (Found : C, 60·5; H, 8·8. $C_{16}H_{28}O_6$ requires C, 60·8; H, 8·8%).

Alkaline hydrolysis. 4 G. of the above ester were refluxed for 4 days with 6 g. of potassium hydroxide in 20 c.c. of alcohol. On removal of the alcohol, solution of the residue in water, acidification and extraction, 2·0 g. of an oil were obtained which slowly solidified. After being washed with chloroform, the solid had m. p. 140—145°; two crystallisations from chloroform–acetone yielded *α-carboxy-αβ-dimethyl-γ-ethylglutaric acid* (IX; R = H) in short prisms, m. p. 161° [Found : C, 51·3; H, 7·0; equiv. (by titration), 77·2. $C_{10}H_{16}O_6$ (tribasic) requires C, 51·7; H, 6·9%; equiv., 77·3].

Acid hydrolysis. 5 G. of the ester (IX; R = Et) were refluxed for a week with 50 c.c. of concentrated hydrochloric acid. The residual oil was removed with charcoal, and the filtrate evaporated. 1·3 G. of an oil were obtained which rapidly solidified; two crystallisations from benzene–light petroleum, followed by one from water, yielded *αβ-dimethyl-γ-ethylglutaric acid* (XI) in clusters of prisms, m. p. 123° (Found : C, 57·2; H, 8·9. $C_9H_{16}O_4$ requires C, 57·4; H, 8·5%).

Ethyl Ethylmalonate.—The following is based on the method of Michael (*J. pr. Chem.*, 1905, **72**, 548) : Crude ethyl ethylmalonate (235 g.), b. p. 102°/18 mm.—98°/11 mm., prepared by ethylation of ethyl malonate in ethereal solution, was shaken for 30 minutes with 130 c.c. of 25% potassium hydroxide solution. The aqueous layer was run off, and the residue boiled with a solution of 75 g. of potassium hydroxide in 300 c.c. of water for an hour. After cooling and separation, the ester was run carefully, with mechanical stirring, into 90 c.c. of water containing 75 g. of potassium hydroxide, and the mixture kept overnight. Unchanged diethylmalonic ester was removed by three extractions with ether. The water layer was then added to 140 g. of potassium hydroxide in 500 c.c. of water, and the whole was boiled for 2 hours, diluted to 3 l., neutralised with hydrochloric acid, and made just alkaline with ammonia, and 500 c.c. of saturated calcium chloride solution added to the hot solution. After several hours' heating on the steam-bath the calcium salt was filtered off, dried, suspended in 500 c.c. of absolute alcohol, and dry hydrogen chloride passed in to saturation. The solution was refluxed for 6 hours, poured into water, and extracted with ether. The extract was washed with 10% sodium carbonate solution and water and dried. Distillation gave 100 g. of pure ethyl ethylmalonate, b. p. 98—99°/12 mm., $n_D^{14°}$ 1·4181, $d_4^{14°}$ 1·0101, $[R_L]_D$ 46·91 (calc., 47·07).

Condensation of Ethyl Tiglate with Ethyl Ethylmalonate.—43 G. of ethyl tiglate and 63 g. of ethyl ethylmalonate were added to sodium ethoxide [from sodium (7·7 g.) and absolute alcohol (100 c.c.)]. The mixture was left at room temperature for 14 days and then poured into a large volume of water and extracted with ether. Distillation of the dried extract, after washing with 10% sodium carbonate and water, yielded 15 g. (14%) of condensation product, which is considered to be ethyl γ-carbethoxy-αβ-dimethyl-γ-ethylglutarate (VIII; R = Et), b. p. 151—152°/2·5 mm., $n_D^{18·8°}$ 1·4435, $d_4^{18·8°}$ 1·0396, $[R_L]_D$ 80·66 (calc., 81·05) (Found : C, 60·2; H, 8·7. Calc. : C, 60·8; H, 8·8%).

Acidification of the alkaline washings gave an oil from which ethylmalonic and tiglic acids were isolated and identified by mixed m. p.

Alkaline hydrolysis. 3 G. of the condensation product were refluxed for 4 days with 5 g. of

potassium hydroxide in 20 c.c. of alcohol. The alcohol was removed, and the residue taken up in water, acidified, and extracted with ether. Evaporation of the dried extract gave 1·5 g. (70%) of an oil which slowly solidified in a vacuum desiccator. The solid was washed with chloroform, and two crystallisations from benzene–acetone–light petroleum then yielded small cubes (0·6 g.), m. p. 158—159°, of a tribasic acid (Found : C, 52·0; H, 7·0. $C_{10}H_{16}O_6$ requires C, 51·7; H, 6·9%) which is considered to be *γ-carboxy-αβ-dimethyl-γ-ethylglutaric acid* (VIII; R = H).

Attempted methylation. 0·6 G. of " molecular " sodium was suspended in dry ether, and 1·5 c.c. of absolute alcohol added, followed after 12 hours by 8 g. of the above condensation product with ice-cooling; the sodium ethoxide took nearly 2 hours to dissolve and heating on the steam-bath was necessary to complete solution. 10 G. of methyl iodide were added, sodium iodide being precipitated immediately; the mixture was kept overnight and poured into water, and the ethereal solution separated, washed with 10% sodium carbonate solution and water, dried, and distilled. Four fractions were collected : (1) b. p. 63—75°/18 mm., 1·3 g.; (2) b. p. 100—115°/18 mm., 2·4 g.; (3) b. p. 115°/18 mm.—135°/1 mm., 0·2 g.; (4) b. p. 135—140°/1 mm., 2·5 g. Fraction (1) was identified as ethyl tiglate by conversion by Hardy's method into the anilide, m. p. and mixed m. p. 75°. Fraction (2) was similarly identified as ethyl methylethylmalonate by conversion into *methylethylmalondianilide*, m. p. 174° (Found : C, 73·3; H, 6·9. $C_{18}H_{20}O_2N_2$ requires C, 73·0; H, 6·7%), not depressed by a sample similarly prepared from authentic ethyl methylethylmalonate. Fraction (4) was refluxed for 5 days with 4 g. of potassium hydroxide in 15 c.c. of alcohol. After the usual treatment 1·3 g. of a solid acid were obtained, m. p. 140—144°; one recrystallisation from benzene–acetone–light petroleum yielded the same tribasic acid (VIII; R = H) as was obtained by hydrolysis of the original condensation product, m. p. and mixed m. p. 159°.

Condensation of Ethyl Methylmalonate with Ethyl α-Ethylcrotonate.—40 G. of ethyl α-ethylcrotonate and 49 g. of ethyl methylmalonate were added to a cold solution of sodium ethoxide [from sodium (6·6 g.) and absolute alcohol (70 c.c.)]. The mixture was kept at room temperature for 14 days and then poured into a large volume of water and extracted with ether. Distillation of the dried extract, after washing with 10% sodium carbonate solution and water, yielded 35 g. (39%) of condensation product, considered to be ethyl α-carbethoxy-αβ-dimethyl-γ-ethylglutarate (IX; R = Et), b. p. 152—158°/4 mm. On redistillation it had b. p. 153—155°/3·5 mm., $n_D^{18\cdot8°}$ 1·4437, $d_4^{18\cdot8°}$ 1·0399, $[R_L]_D$ 80·67 (calc., 81·05) (Found : C, 60·3; H, 8·9. Calc. : C, 60·8; H, 8·8%).

Acid hydrolysis. 5 G. of the above addition product were refluxed for a week with 50 c.c. of concentrated hydrochloric acid. The solution was then boiled with charcoal, filtered, and evaporated, yielding 1·8 g. of an oil which partly solidified. The solid was crystallised twice from benzene–light petroleum and once from water, 0·7 g. of αβ-dimethyl-γ-ethylglutaric acid (XI) being obtained in long prisms, m. p. and mixed m. p. with an authentic specimen, 123°.

Alkaline hydrolysis. 3·6 G. of the above addition product were refluxed for 5 days with 6 g. of potassium hydroxide in 20 c.c. of alcohol. The alcohol was removed, and the residue taken up in water, acidified, and extracted with ether; evaporation of the dried extract yielded 2·3 g. (80%) of an oil which solidified almost immediately in a vacuum desiccator. After being washed with cold chloroform, the product had m. p. 145—148°; two crystallisations from chloroform–acetone yielded 1·4 g. of α-carboxy-αβ-dimethyl-γ-ethylglutaric acid (IX; R = H), m. p. and mixed m. p. with an authentic specimen, 161°.

Attempted methylation. 8 G. of the addition product were added to sodium ethoxide (from 0·6 g. of sodium and 1·5 c.c. of absolute alcohol) in ether. The mixture was refluxed until the sodium ethoxide dissolved; the solution was then cooled, and 10 g. of methyl iodide added. There was a vigorous reaction accompanied by the precipitation of sodium iodide; the solution was refluxed overnight and worked up in the usual manner. Distillation at 24 mm. gave two fractions : (1) b. p. 70—85°, 2·3 g., and (2) b. p. 85—110°, 3·0 g. There was no appreciable residue. Fraction (1) was identified as a mixture of ethyl α-ethylcrotonate and ethyl dimethylmalonate by conversion into the corresponding anilides, m. p. and mixed m. p. 95° and 202°, respectively. Fraction (2) was similarly shown to be ethyl dimethylmalonate by conversion into the anilide, m. p. and mixed m. p. 202°.

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