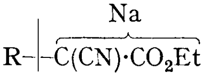
91. *Studies on the Michael Reaction. Part I. The Condensation of Ethyl Benzylmalonate with Ethyl Fumarate.*

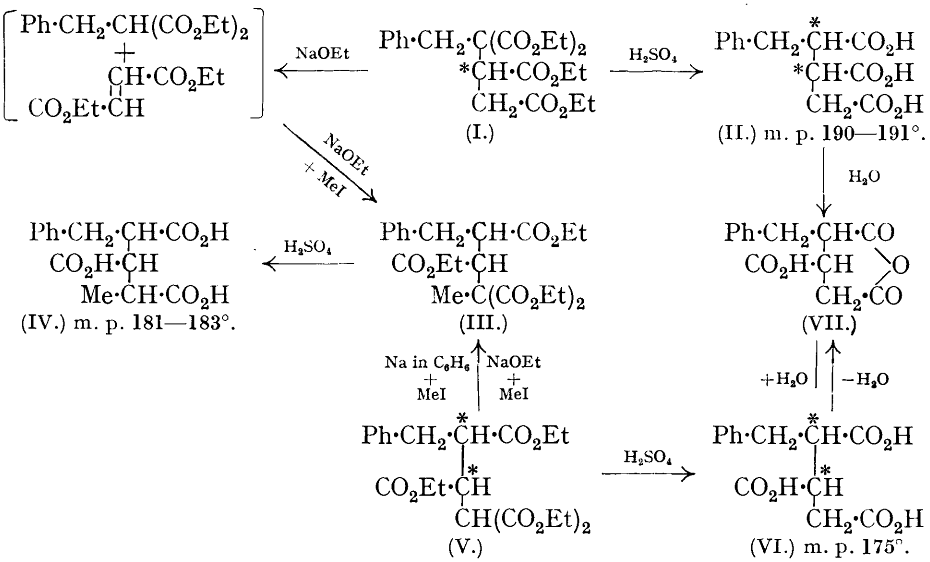
By H. N. Rydon.



The view that the sodio-derivatives of alkylcyanoacetic esters underwent partition in the sense $\text{R}-\overset{\text{Na}}{|}-\overbrace{\text{C(CN)}\cdot\text{CO}_2\text{Et}}$ during the Michael reaction was first advanced by Thorpe (J., 1900, **77**, 923). Michael and Ross (*J. Amer. Chem. Soc.*, 1930, **52**, 4600) obtained evidence for a similar partition of alkylmalonic esters in the presence of one molecular proportion of sodium ethoxide. Holden and Lapworth (J., 1931, 2370) challenged these conclusions, pointing out that this apparent partition could equally well be explained by a migration of the carbethoxy- or cyano-group and postulating an intermediate cyclisation of the Dieckmann type to account for this. Although Michael and Ross replied to this criticism (*J. Amer. Chem. Soc.*, 1932, **54**, 407; 1933, **55**, 1632), the point was left open to doubt, since no evidence was put forward that could not be explained by the mechanism of Holden and Lapworth.

Connor (*ibid.*, 1933, **55**, 4597) attempted to throw light on the problem by studying the Michael reaction with phenylmalonic ester, supposing the phenyl group to be particularly favourable to partition in the manner proposed by Thorpe; his work was fruitless, since no condensation could be brought about. Recently, however, Duff and Ingold (J., 1934, 87), by the condensation of ethyl fumarate and of ethyl α-bromosuccinate with ethyl benzylmalonate, obtained two isomeric tetracarboxylic esters, which, on hydrolysis and decarboxylation, gave rise to a pair of, presumably, stereoisomeric phenylbutanetricarboxylic acids. Inasmuch as the intermediate tetracarboxylic ester (I) contains only one asymmetric carbon atom, only one inactive isomeride is capable of existence (Duff and Ingold, *loc. cit.*, p. 88, incorrectly postulate the existence of two forms). It appeared, therefore, to be of interest to repeat this work, in order to elucidate the nature of these isomeric esters and so throw further light on this important problem.

The experimental results are outlined in the following scheme :

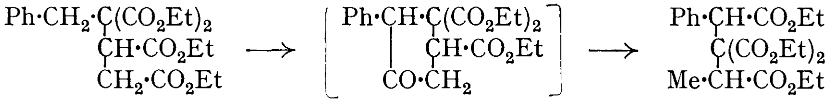


The constitution of the product obtained from ethyl α-bromosuccinate and ethyl benzylmalonate is not open to serious doubt. Condensation by means of sodium ethoxide yielded the tetracarboxylic ester (I); this, on acid hydrolysis, afforded a δ-phenyl-*n*-butane-αβγ-tricarboxylic acid (II), m. p. 190—191°, undoubtedly identical with the acid, m. p. 187—190°, obtained in a similar manner by Duff and Ingold (*loc. cit.*). The ester (I) could not be hydrolysed to the parent tetracarboxylic acid owing to the ease with which decarboxylation occurred. It was readily methylated by means of sodium ethoxide and methyl iodide, yielding a mixture of products. The lower-boiling products were identified as ethyl fumarate and ethyl benzylmethylmalonate, evidently produced by a retrograde Michael reaction, followed by methylation of the ethyl benzylmalonate so produced. The principal product of the reaction was *ethyl δ-phenyl-α-methyl*-n-*butane-αα*-trans-*βγ-tetracarboxylate* (III). On boiling with acid this was smoothly hydrolysed and decarboxylated to *δ-phenyl-α-methyl*-n-*butane-α*-trans-*βγ-tricarboxylic acid* (IV), m. p. 178—182°. In this case, also, the tetracarboxylic acid could not be obtained in a pure condition. Attempted methylation of the ester (I) with "molecular" sodium in benzene in place of sodium ethoxide was unsuccessful. No product of the molecular complexity of the methylated ester (III) could be isolated, the only substance obtained being a comparatively small amount of a mixture of isomeric malonic acids, $C_{11}H_{12}O_4$, one component of which was identified as benzylmethylmalonic acid. Extensive and deep-seated decomposition occurred during the reaction and the conclusion may safely be drawn that the ester (I) contains no hydrogen atom normally replaceable by sodium—an additional confirmation of the structure assigned.

Condensation of ethyl fumarate with ethyl benzylmalonate in the presence of one molecular proportion of sodium ethoxide yielded a tetracarboxylic ester (V); this, on acid hydrolysis, readily afforded δ-phenyl-*n*-butane-α-*trans*-βγ-tricarboxylic acid (VI), m. p. 175°, evidently the same as that obtained by Duff and Ingold (*loc. cit.*; m. p. 168°). Since no other isomeride could be isolated, the configuration ascribed to this compound, and to its derivatives described below, follows from its production from ethyl fumarate. Once again the tetracarboxylic acid was too unstable to permit of satisfactory purification. The ester (V), on treatment with methyl iodide in the presence of sodium ethoxide, yielded certain amounts of retrogression products corresponding to the possible presence of not more than 16% of (I) in (V), together with ethyl δ-phenyl-α-methyl-*n*-butane-αα-*trans*-βγ-tetracarboxylate (III). The same ester was produced in good yield when "molecular" sodium in benzene was substituted for sodium ethoxide in alcohol; this difference in behaviour with sodium affords strong evidence for the view that the ester (V) differs from (I) in possessing a hydrogen atom normally, and readily, replaceable by sodium. That the methylated ester (III) produced by these methods was identical with that obtained from the ester (I) was easily demonstrated, acid hydrolysis yielding the same δ-phenyl-α-methyl-*n*-butane-α-*trans*-βγ-tricarboxylic acid (IV), m. p. 181—183° and 180—181°, respectively; the identity was confirmed by mixed melting points.

The marked difference in behaviour of the esters (I) and (V) towards sodium points clearly to a structural difference, the benzyl group having, in some manner yet to be determined, migrated from the α- to the γ-carbon atom during the Michael addition. If this migration occurs by the "Dieckmann mechanism" of Holden and Lapworth (*loc. cit.*), there are only two possibilities which need be considered.

The first, which is unlikely, but rendered possible by the activating influence of the phenyl group (cf. the formation of a sodio-derivative by phenylacetonitrile), is outlined in the scheme:

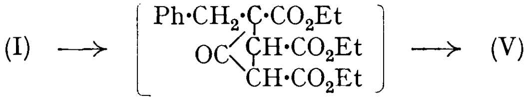


$$\begin{array}{r}Ph\cdot CH_2\cdot C(CO_2Et)_2\\ CH\cdot CO_2Et\\ CH_2\cdot CO_2Et\end{array} \longrightarrow \left[\begin{array}{l}Ph\cdot CH\cdot C(CO_2Et)_2\\ \quad | \quad CH\cdot CO_2Et\\ CO\cdot CH_2\end{array}\right] \longrightarrow \begin{array}{r}Ph\cdot CH\cdot CO_2Et\\ C(CO_2Et)_2\\ Me\cdot CH\cdot CO_2Et\end{array}$$

(I.) (V.) (?)

On this hypothesis the acids (II) and (VI) should be structurally different, (II) being a benzyltricarballylic acid and (VI) a phenylmethyltricarballylic acid.

The second, and more likely, mechanism is the following:

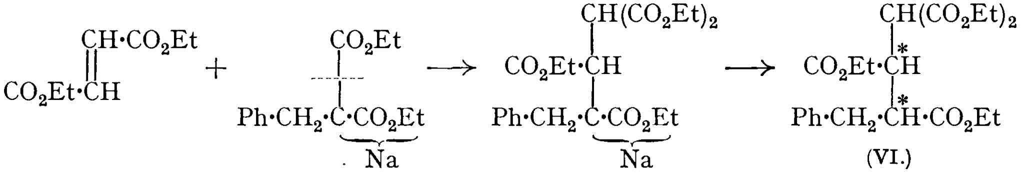


$$(I) \longrightarrow \left[\begin{array}{l}Ph\cdot CH_2\cdot C\cdot CO_2Et\\ OC \langle \begin{array}{l}CH\cdot CO_2Et\\ CH\cdot CO_2Et\end{array}\end{array}\right] \longrightarrow (V)$$

In this case the acids (II) and (VI) should be identical, since stereoisomerism, as already pointed out (p. 421), is not possible owing to the presence of only one asymmetric carbon atom in (I). This hypothesis is thus not consistent with the experimental facts and must be rejected.

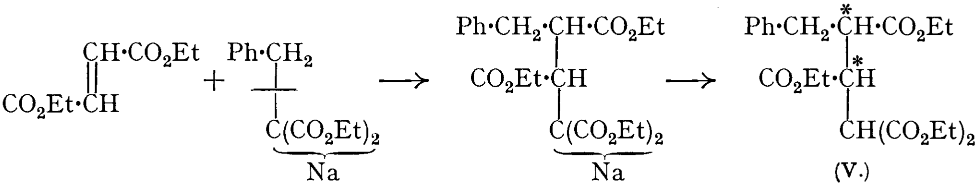
The acids (II) and (VI) both yielded the same anhydro-acid (VII), m. p. 110—112° (Thiele and Meisenheimer, *Annalen*, 1899, **306**, 247; Duff and Ingold, *loc. cit.*). This anhydro-acid was readily hydrolysed back to the acid (VI), m. p. 176°, identified by mixed m. p. The acids are therefore stereoisomeric, and the first hypothesis advanced above must also be rejected. The configuration of the acid (II) is uncertain; it may be either the *cis*-compound or a mixture of the *cis*- and the *trans*-; such mixtures are often exceedingly difficult to separate by crystallisation and at times behave like pure substances. A parallel for the production of only one compound is afforded by the work of Henstock and Sprankling (J., 1907, **91**, 355), who obtained only one, apparently homogeneous, αα′α′-trimethyltricarballylic acid by a similar reaction.

The only way in which ethyl benzylmalonate can react with ethyl fumarate so as to preserve the two asymmetric centres necessary for the production of this stereoisomeride is by fission at the moment of addition. This may occur in two ways—first, as follows :


(VI.)

In this case, although two asymmetric carbon atoms are produced, they are not the carbon atoms originally present in the ethyl fumarate; there is no reason for anticipating the formation of the *trans*-ester in preference to the *cis*-; this hypothesis thus demands that (II) and (VI) be identical; for this reason it must be rejected.

There remains only partition in the manner advanced by Thorpe, *viz.* :


(V.)

In this case the two asymmetric carbon atoms formed are those derived from the ethyl fumarate; we should thus expect to obtain the *trans*-acid on hydrolysis, *i.e.*, the acids (II) and (VI) should be stereoisomeric. Since this has been shown to be the case, this hypothesis is the only one that can be accepted.

The anhydro-acid, reverting as it does to the *trans*-acid (VI), must be formed by the elimination of water from the α- and the γ-carboxyl group (which are necessarily in the *cis*-position), *i.e.*, it is α-benzyl-β-carboxyglutaric anhydride (VII, p. 421).

On the basis of the above reasoning it may be concluded that, in the condensation of ethyl benzylmalonate with ethyl fumarate, partition of the sodio-derivative of the malonic ester occurs in such a way that the sodium remains attached to the malonic residue. In this particular instance the reaction appears to proceed in this manner to the extent of at least 85%; whether this is general or whether, with other alkylmalonic esters, the alkyl group may remain attached wholly or partly (in the statistical sense) to the malonic residue is a matter for further experiment. It is perhaps significant that, whereas Auwers, Köbner, and von Meyenburg (*Ber.*, 1891, **24**, 2897) obtained an α-ethyltricarballylic acid, m. p. 147—148°, from ethyl fumarate and ethyl ethylmalonate, Jowett (J., **1901**, **79**, 1349) obtained another form (?) of the same acid, m. p. 157°, from ethyl bromoacetate and ethyl α-cyano-α′-ethylsuccinate, a pair of reactions analogous to those described in this paper; this work is being re-investigated with a view to determining the range of applicability of the above mechanism.

EXPERIMENTAL.

Condensation of Ethyl Benzylmalonate with Ethyl α-Bromosuccinate.—The condensation, essentially by Duff and Ingold's method (*loc. cit.*), afforded a 45% yield of ethyl δ-phenyl-*n*-butane-αβγγ-tetracarboxylate (I), b. p. 203—209°/2·5 mm. (Duff and Ingold, *loc. cit.*, give b. p. 184—186°/0·6 mm.).

Hydrolysis. The ester (I) was hydrolysed by Duff and Ingold's method (*loc. cit.*); the product, which separated in almost theoretical yield on cooling, was recrystallised from acetic acid. The δ-phenyl-*n*-butane-αβγ-tricarboxylic acid (II) [Found : C, 58·6; H, 5·6; equiv., 88·3. Calc. for $C_{13}H_{14}O_6$ (tribasic) : C, 58·6; H, 5·2%; equiv., 88·7] obtained had m. p. 190—191° (decomp.) [Duff and Ingold, *loc. cit.*, record m. p. 187—190° (decomp.)], and was apparently homogeneous, all crops having similar m. p.'s.

The acid (II) on boiling with nitrobenzene for a few minutes, followed by precipitation with petroleum, yielded β-carboxy-α-benzylglutaric anhydride (VII) in long needles, m. p. 111—113°. This was also prepared, in good yield, by heating the acid at 200° for 30 minutes; recrystallised from benzene–petroleum, it formed rosettes of needles, m. p. 112°.

Methylation in alcoholic solution. 10·5 G. of the ester (I) were added to sodium ethoxide (from sodium, 0·575 g., and absolute alcohol, 20 c.c.), 3 c.c. (2 mols.) of methyl iodide added, and the mixture refluxed over-night. The neutral product was poured into water, acidified, and extracted with ether. Removal of the ether from the dried extract, followed by distillation, yielded (i) 2 g., b. p. 80—110°/1·5 mm., (ii) 2 g., b. p. 110—135°/1·5 mm., (iii) 3 g., b. p. 136—150°/1·5 mm., and (iv) 7 g. of *ethyl δ-phenyl-α-methyl-*n*-butane-αα-*trans*-βγ-tetracarboxylate* (III), b. p. 175—195°/1·5 mm. Fractions (i) and (iii) were identified as ethyl fumarate and ethyl benzylmethylmalonate respectively, and fraction (ii) as a mixture of the two, by hydrolysis to the parent acids, identified by mixed m. p. with authentic specimens.

Hydrolysis. 6·3 G. of the ester (III), prepared as above, were refluxed over-night with concentrated sulphuric acid (6 c.c.), water (2 c.c.), and formic acid (19 c.c.). An almost theoretical yield of the crude product was obtained on cooling. Two recrystallisations from acetic acid yielded *δ-phenyl-α-methyl-*n*-butane-α-*trans*-βγ-tricarboxylic acid* (IV) in sheaves of thin prismatic needles, m. p. 178—182° (decomp.) [Found : C, 59·7; H, 5·8; equiv., 94·3. $C_{14}H_{16}O_6$ (tribasic) requires C, 60·0; H, 5·7%; equiv., 93·3]. The m. p. of this product was depressed to 165—174° (decomp.) on admixture with the unmethylated acid (II).

Attempted methylation in benzene solution. 0·77 G. of pulverised sodium was treated with a solution of 14 g. of the ester (I) in 50 c.c. of benzene. A slight reaction occurred at first, but this rapidly abated; the sodium was brought into solution only by long boiling under reflux, yielding a deep brown solution with a greenish fluorescence. 10 G. (2 mols.) of methyl iodide were added to this and the mixture was refluxed; after 48 hours the still strongly alkaline mixture was poured into water and extracted with benzene. Distillation of the dried extract yielded 6 g. of a product, b. p. 140—170°/1—1·5 mm.; the large amount of residue decomposed vigorously, leaving a hard black mass, and was not further investigated.

The product was boiled under reflux over-night with a solution of 6·5 g. of potassium hydroxide in 13 c.c. of water. On dilution and acidification a good yield of crystalline material slowly separated. Recrystallisation from benzene–petroleum yielded splendid shining plates, m. p. 140° (decomp.), with considerable shrinking and softening at 129°. This mixture had the composition $C_{11}H_{12}O_4$ [Found : C, 63·8; H, 6·0; equiv., 100·3; *M* (Rast), 195. Calc. (dibasic) : C, 63·5; H, 5·8%; equiv., 104; *M*, 208]. It was undoubtedly a mixture of malonic acids, since, when heated at 160° for 15 minutes, it evolved much carbon dioxide, yielding an oily product distinguished from the original mixture by being very soluble in cold benzene. Refluxing with acetyl chloride for 30 minutes, removal of the acetyl chloride, etc., left an oily anhydride. This, heated at 150—180° with urea, yielded *β-phenyl-α-methylpropionamide* (Found : N, 8·9. $C_{10}H_{13}ON$ requires N, 8·6%), m. p. 106° after two recrystallisations from petroleum, identified by mixed m. p. with a sample prepared similarly from authentic benzylmethylmalonic acid. The mixture of acids crystallised from benzene in stellate clusters of needles, and from water in beautiful compact prisms. All attempts to identify the other constituent were fruitless.

Condensation of Ethyl Benzylmalonate with Ethyl Fumarate.—The condensation, by Duff and Ingold's method (*loc. cit.*), with 1 mol. of sodium ethoxide, gave a 53% yield of ethyl δ-phenyl-*n*-butane-αα-*trans*-βγ-tetracarboxylate (V), as a thick yellow oil, b. p. 215—220°/1·5 mm. (the b. p., 204—208°/0·09 mm., recorded by Duff and Ingold, *loc. cit.*, is undoubtedly too high).

Hydrolysis. The ester (V) was hydrolysed as described by Duff and Ingold (*loc. cit.*); a good yield of the crude acid separated on cooling. Crystallisation from acetic acid afforded pure δ-phenyl-*n*-butane-α-*trans*-βγ-tricarboxylic acid (VI) as small prismatic needles, m. p. 175° (decomp.) [Duff and Ingold, *loc. cit.*, record m. p. 168° (decomp.)] [Found : C, 58·7; H, 5·5; equiv., 87·4. Calc. for $C_{13}H_{14}O_6$ (tribasic) : C, 58·6; H, 5·2%; equiv., 88·7]. No trace of any other isomeride could be isolated, successive crops having very similar m. p.'s. The m. p. of this product was depressed to 160—165° on admixture with the stereoisomeric acid (II).

The acid (VI), heated at 200° for 30 minutes, yielded a product, from which α-benzyl-β-carboxyglutaric anhydride (VII) was isolated in good yield by recrystallisation from benzene–petroleum, forming clusters of needles, m. p. 110—112°, not depressed on admixture with the anhydride produced from the acid (II).

This anhydride, on boiling with water, regenerated the acid (VI), m. p. 176° (decomp.) after one crystallisation from acetic acid. The m. p. was not depressed on admixture with other specimens of this acid, but was depressed to 165—172° (decomp.) on admixture with the acid (II).

Methylation in alcoholic solution. 10·5 G. of the ester (V) were added to sodium ethoxide from sodium, 0·575 g., and absolute alcohol, 20 c.c.), 2 c.c. (excess) of methyl iodide added, and the mixture boiled under reflux over-night. The quite neutral product was poured into water and extracted with ether. Removal of the ether from the dried extract left an oil which, on distillation, yielded two fractions. The low fraction (1·5 g.), b. p. 110—160°/2 mm., yielded on hydrolysis a mixture of fumaric and benzylmethylmalonic acids (both identified by mixed m. p. with authentic samples) and was thus a mixture of their esters. The high-boiling fraction (8 g.), b. p. 170—190°/1 mm., consisted of ethyl δ-phenyl-α-methyl-*n*-butane-αα-*trans*-βγ-tetracarboxylate (III), a thick yellow oil.

Hydrolysis. 3 G. of the ester (III), prepared as above, were refluxed with concentrated sulphuric acid (3 c.c.), water (3 c.c.), and formic acid (9 c.c.) for 20 hours. The rather tarry product was filtered from the cooled solution. Crystallisation from acetic acid yielded δ-phenyl-α-methyl-*n*-butane-α-*trans*-βγ-tricarboxylic acid (IV) in sheaves of prismatic needles, m. p. 181—183° (decomp.) [Found: C, 59·8; H, 5·7; equiv., 94·6. Calc. for $C_{14}H_{16}O_6$ (tribasic): C, 60·0; H, 5·7%; equiv., 93·3]. The m. p. was not depressed on admixture with the similar product obtained by methylation of the ester (I), but was depressed to 161—169° (decomp.) on admixture with the unmethylated acid (VI).

Alkaline hydrolysis of the ester (III) proceeded readily, but the product underwent decarboxylation with extraordinary ease, a single crystallisation from formic acid yielding the acid (IV), m. p. 180—182° (decomp.), identified by mixed m. p.

Methylation in benzene solution. 0·77 G. of pulverised sodium was treated with a solution of 14 g. of the ester (V) in 50 c.c. of benzene. Reaction was fairly vigorous in the cold and was completed by boiling under reflux for 4 hours. The resulting opalescent orange-red solution was treated with 10 g. (2 mols.) of methyl iodide. Reaction proceeded in the cold with deposition of sodium iodide and was completed by boiling under reflux over-night. The neutral product was poured into water, acidified, and extracted with benzene. Distillation of the dried extract afforded ethyl δ-phenyl-α-methyl-*n*-butane-αα-*trans*-βγ-tetracarboxylate (9·6 g.), b. p. 188—198°/2 mm.

Hydrolysis. 3·2 G. of the above ester were refluxed over-night with concentrated sulphuric acid (3 c.c.), water (3 c.c.), and formic acid (9 c.c.). The hot liquid was filtered from a little tar and cooled; 1·8 g. (90%) of crude product crystallised. Recrystallisation from acetic acid yielded δ-phenyl-α-methyl-*n*-butane-α-*trans*-βγ-tricarboxylic acid (IV), m. p. 180—181° (decomp.), not depressed on admixture with samples prepared in other ways (above and p. 424).

The author is indebted to the Chemical Society for a grant, to Professor J. F. Thorpe, F.R.S., for his encouragement, and to Dr. F. Barrow (of Birkbeck College) for providing facilities for the micro-analyses.

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[*Received, January* 21*st*, 1935.]