401. *The Michael Reaction with Acetylenic Esters.*

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Some uncertainty still exists regarding the mechanism by which compounds of the type of ethyl sodiomalonate are added to αβ-unstaurated esters. Two principal questions have given rise to discussion : (i) what are the actual components which participate in the addition, and (ii) which of these initiates the attack leading to their ultimate addition.

With regard to the former question, Michael originally suggested that sodio-esters gave rise to two fragments, sodium and an organic residue (*J. pr. Chem.*, 1887, **35**, 349). Later, he found that in such compounds the metal was attached to oxygen, and a similar discovery was made by Thorpe regarding the sodio-derivatives of ethyl cyanoacetate and ethyl α-cyanopropionate (J., 1900, **77**, 923), on the strength of which he suggested that these esters add in the form of the fragments R (hydrogen or methyl) and

$$C(CN)\colon C(OEt){\cdot}ONa.$$

More recently Michael and Ross (*J. Amer. Chem. Soc.*, 1930, **52**, 4598) have provided further evidence in support of this view and, indeed, claimed to have proved its correctness. They showed that, if ethyl methylmalonate is added to ethyl crotonate in the presence of a small amount of sodium ethoxide, the fragments added are H and $CMe(CO_2Et)_2$; with an equivalent of sodium ethoxide, they appear to be Me and $C(CO_2Et)_2\}Na$.

This view was criticised by Holden and Lapworth (J., 1931, 2368), who suggested that the isolation of the compound $CO_2Et{\cdot}CHMe{\cdot}CHMe{\cdot}CH(CO_2Et)_2$ was due, not to the addition of the fragments Me and $C(CO_2Et)_2\}Na$, but to a rearrangement of the addition product resulting (in effect) in a migration of a CO_2Et group from the α- to the γ-carbon atom.

It appeared desirable to obtain further evidence on this problem without, if possible, relying on the result of hydrolysis experiments. The present work is an extension of the observations made by Gidvani, Kon, and Wright (J., 1932, 1027) and by Gidvani and Kon (*ibid.*, p. 2443) on the addition of ethyl malonate and methylmalonate to ethyl phenylpropiolate. In the addition of these esters to acetylenic esters, the products are unsaturated and it is an easy matter to determine by oxidation the fate of the fragments which participate in the addition.

The addition of ethyl sodiomalonate and ethyl sodiomethylmalonate was tried with ethyl phenylpropiolate, ethyl acetylenedicarboxylate, ethyl tetrolate, and ethyl propiolate, a non-polar solvent being used in every case.

The reaction proceeded in the same way with all these esters; the products were yellow or brown sodio-derivatives to which the structure (I) is assigned :

$$CO_2Et{\cdot}C{\vdots}CR + \overbrace{CR'(CO_2Et)_2}^{Na} = \overbrace{CO_2Et{\cdot}C}^{Na}{:}CR{\cdot}CR'(CO_2Et)_2 \quad \text{(I.)}$$
$$(R' = H \text{ or } Me)$$

These compounds are characterised by the fact that they cannot be alkylated without much difficulty even when $R' = H$, and require treatment with a mineral acid to liberate the free ester; benzoic acid in ether only liberates the ester in the course of several days. It had already been observed by Gidvani and Kon (*loc. cit.*) that the free ester

$$CO_2Et{\cdot}CH{:}CPh{\cdot}CH(CO_2Et)_2$$

forms a sodio-derivative with great readiness when treated with sodium in a non-polar solvent, and that the colourless sodio-derivative so formed can be easily alkylated, whereas the yellow sodio-derivative produced as the result of the Michael reaction requires the addition of alcohol to bring about reaction. This observation has now been extended to other similar esters, except that it has been found possible to alkylate the original yellow sodio-derivatives in a non-polar solvent, provided sufficiently drastic conditions are adopted.

These observations are consistent with the view that the yellow sodio-derivatives originally formed in the Michael reaction are represented by (I), in which the metal is firmly held, and this accounts for the difficulty experienced in alkylating them and also in liberating the free esters. The latter on treatment with sodium form isomeric sodio-derivatives of the structure $CO_2Et{\cdot}CH{:}CR{\cdot}\overbrace{C(CO_2Et)_2}^{Na}$ (II). The metal is here attached to the malonic residue and is readily removed or replaced by an alkyl group; a sodio-derivative of the type (II) is also formed when the original yellow sodio-derivative is boiled with alcohol, the action of that solvent in promoting alkylation thus becoming readily explicable. Nevertheless, such a conversion can occur, though very slowly, in a non-polar solvent, because the alkyl derivative formed under these conditions is the same as that produced in alcoholic solution.

When ethyl methylmalonate is the addendum employed, the product is a sodio-derivative of the type (I) and it has already been shown that with ethyl phenylpropiolate the ester obtained after acidification is $CO_2Et{\cdot}CH{:}CPh{\cdot}CMe(CO_2Et)_2$. The components of the addendum must therefore be Na and $CMe(CO_2Et)_2$, and this observation has now been confirmed in the other cases investigated. Moreover, it has been found possible to alkylate the sodio-derivatives under somewhat drastic conditions; the products are the only possible ones of the type $CO_2Et{\cdot}CR''{:}CR{\cdot}CR'(CO_2Et)_2$, and their formation is in excellent agreement with the interpretation developed above.

The formation of α-alkyl derivatives from the metallic compounds of the type (I), when the α-carbon (*i.e.*, the malonic residue) is not substituted, in no way invalidates this conclusion; it merely means that the velocity of interconversion of (I) and (II) is greater than the rate of alkylation of (I).

From these experiments it can be concluded (i) that in none of the cases now examined does ethyl methylmalonate add in the form of Me and $C(CO_2Et)_2$, and (ii) that ethyl sodiomalonate also dissociates in the same way, namely, into Na and $CH(CO_2Et)_2$.

The reactions between acetylenic esters and ethyl malonate and methylmalonate have also been brought about by the addition of small amounts of sodium ethoxide; the products were the free esters of the type $CO_2Et{\cdot}CH{:}CR{\cdot}CR'(CO_2Et)_2$, as expected.

It is, we think, only reasonable to assume that this mode of reaction is a general one. When addition is carried out in the presence of a small amount of sodium ethoxide, the free ester is produced owing to the extensive alcoholysis of the small amount of sodio-derivative originally formed. The action of piperidine in bringing about condensation is similar, being probably due to the formation of a minute amount of an organic anion, which then initiates the attack on the unsaturated molecule (compare Bloom and Ingold, J., 1931, 2765).

There still remains the difficulty presented by Michael and Ross's observations (*loc. cit.*). It should be noted that ethyl methylmalonate adds to ethyl crotonate to give $CO_2Et{\cdot}CH_2{\cdot}CHMe{\cdot}CMe(CO_2Et)_2$, that is, adds normally, *unless* an equivalent of sodium ethoxide is present; the product is then the αβ-dimethyl ester

$$CO_2Et{\cdot}CHMe{\cdot}CHMe{\cdot}CH(CO_2Et)_2.$$

The latter is also formed when the isomeric βγ-dimethyl ester is treated with sodium ethoxide. It is not unreasonable to assume, with Holden and Lapworth, that the αβ-dimethyl ester is in all cases produced by the rearrangement of the βγ-ester primarily formed; it would then remain to decide by what mechanism this change takes place. For a solution of this problem further evidence is required.

EXPERIMENTAL.

Condensation of Ethyl Phenylpropiolate with Ethyl Sodiomalonate.—16 G. of ethyl malonate were added to 2·3 g. of molecular sodium suspended in 150 c.c. of ether and the mixture was kept overnight to complete the formation of the sodio-derivative, then cooled in ice, and treated dropwise with 17 g. of ethyl phenylpropiolate in 170 c.c. of ether. The whole was kept at room temperature for 4 days and the yellow sodio-derivative formed was then collected, washed with petroleum, and dried in a vacuum desiccator. The conversion of this yellow sodium compound into a colourless one on boiling with alcohol (Gidvani and Kon, *loc. cit.*) has been confirmed.

Ethylation. The yellow sodio-derivative prepared as above was heated in a sealed tube with a slight excess of ethyl iodide, diluted with benzene, for 7 days in a bath of boiling water. The product was evaporated to dryness under reduced pressure, the residue taken up in ether, and the solution washed with aqueous sodium carbonate, then water, dried, and evaporated; the residue gave on distillation a 25% yield of a fraction, b. p. 212—213°/10 mm., $d_{4°}^{22°}$ 1·1063, n_D 1·5050, evidently *ethyl α-carbethoxy-β-phenyl-α-ethylglutaconate* (Found: C, 66·2; H, 7·1. $C_{20}H_{26}O_6$ requires C, 66·3; H, 7·2%).

Ozonisation. The ester (10 g.), dissolved in ice-cold chloroform, was treated with ozonised oxygen until no absorption took place (48 hours). The solvent was removed under reduced pressure, the ozonide decomposed by shaking with cold water overnight, and the products taken up in ether; the ethereal extract was washed with aqueous sodium bicarbonate. These washings and the water used for decomposing the ozonide were found to contain oxalic acid. The dried ethereal solution was evaporated, and the residue distilled at 25 mm.; a few drops collected at 90—115° could not be identified, but nearly the whole boiled at 180—200°. This was hydrolysed with alcoholic potash, the alcohol removed under reduced pressure, and the residue taken up in a little water and acidified with dilute hydrochloric acid at 0°. Benzoic acid was precipitated and filtered off and further traces of it were removed by distilling the mother-liquors in steam. The cooled solution was then extracted with ether in a continuous extractor; on evaporation of the dried extract ethylmalonic acid was obtained and identified.

Condensation of Ethyl Phenylpropiolate with Ethyl Sodiomethylmalonate.—This was carried out as described above, except that benzene was used as a solvent and the reaction mixture was heated under reflux for 8 hours. After removal of the solvent under reduced pressure the residue of sodio-derivative was rubbed with petroleum and collected.

Ethylation. This was carried out as described above. After two fractionations 5 g. of oil, b. p. 211—213°/15 mm., were collected, $d_{4°}^{21°}$ 1·0958, n_D 1·5015, consisting of *ethyl α-carbethoxy-β-phenyl-α-methyl-γ-ethylglutaconate* (Found: C, 67·1; H, 7·2. $C_{21}H_{28}O_6$ requires C, 67·0; H, 7·4%); it was not hydrogenated with Adams's catalyst in alcoholic solution. The ester was hydrolysed by boiling for 3 days with a slight excess of 5% alcoholic potash, the alcohol distilled off, and the residue taken up in water and acidified. The acid was extracted with ether, and the extract dried and evaporated. The viscous residue solidified in a vacuum desiccator after 3 weeks and had m. p. 75—76° after crystallisation from benzene–petroleum (Found: C, 73·1; H, 6·1. $C_{14}H_{14}O_3$ requires C, 73·0; H, 6·1%); it was evidently *β-phenyl-α-methyl-γ-ethylglutaconic acid*, the position of the double bond being uncertain.

Ozonisation. The ethylated tribasic ester was ozonised as described above; the acidic products isolated were a little oxalic acid (due to incomplete ethylation of the parent ester) and propionic acid, which was identified by the *p*-bromophenacyl ester, m. p. 62°. The neutral product, b. p. 190—200°/20 mm., was ethyl benzylmethylmalonate, as it gave benzoic and methylmalonic acids on hydrolysis with potash.

Condensation with ethyl bromoacetate. Ethyl phenylpropiolate was condensed with ethyl methylmalonate as above; after refluxing for 8 hours, the mixture was treated with a slight excess of ethyl bromoacetate without isolation of the sodio-derivative formed. After a further 3 days' boiling, a test portion poured into water was neutral; the solvent was then distilled off under reduced pressure, the residue taken up in ether, and the solution washed with sodium carbonate, then water, dried, and evaporated. The residual oil, which could not be distilled without decomposition, was ozonised, and the products worked up as described on p. 1806. Oxalic acid was identified. The neutral products were distilled, two main fractions being obtained. The first, b. p. 120—135°/15 mm., gave a red colour with ferric chloride and was shown to consist mainly of ethyl oxaloacetate by the preparation of the semicarbazone, m. p. 159—160° (Michael, *J. Amer. Chem. Soc.*, 1919, **41**, 424). The higher fraction, b. p. 180—200°/15 mm., was ethyl benzoylmethylmalonate and gave benzoic and methylmalonic acids on hydrolysis. The ester ozonised was therefore essentially $CO_2Et{\cdot}CH_2{\cdot}C(CO_2Et){:}CPh{\cdot}CMe(CO_2Et)_2$.

Condensation of Ethyl Phenylpropiolate with Ethyl Methylmalonate in the Presence of Sodium Ethoxide.—Attempts to effect condensation in the presence of 1 mol. of sodium ethoxide were unsuccessful, the reactants being recovered unchanged. Reaction occurred when the two esters (17·4 g. of each) were diluted with a few c.c. of ether and treated with 0·23 g. of sodium in 2·5 c.c. of alcohol, the mixture being warmed under reflux for 24 hours. The product was taken up in ether, washed, dried, and recovered; on distillation some 5 g., b. p. 208—210°/10 mm., were collected. The unchanged materials contained in the fraction b. p. 80—160°/10 mm. were again condensed, with half the amount of sodium previously employed, and yielded a further quantity of condensation product. The combined high-boiling material was refractionated, 5 g., b. p. 210—212°/13 mm., being obtained, evidently consisting of ethyl α-carbethoxy-β-phenyl-α-methylglutaconate (Found: C, 65·4; H, 6·7. Calc.: C, 65·5; H, 6·7%).

Ethyl Acetylenedicarboxylate.—The acid was prepared by Perkin and Simonsen's method (J., 1907, **91**, 834); after the addition of alcoholic potash to the dibromosuccinic acid it is essential to maintain the temperature at 60—65° for an hour. If the temperature is allowed to rise above this, the yield is practically nil. The acid was esterified by the method of Ruhemann and Beddows (J., 1900, **77**, 1121).

Condensation of Ethyl Acetylenedicarboxylate with Ethyl Sodiomethylmalonate.—This was carried out in ethereal solution as described on p. 1806. The yellow sodio-derivative could not be satisfactorily separated by filtration owing to its fine state of division; it was therefore washed with light petroleum by decantation and used *in situ*.

The sodio-derivative from 1/10 g.-mol. of reactants was shaken with a slight excess of benzoic acid in ether for 7 days, but the ester was not liberated. Acidification with dilute hydrochloric acid, followed by extraction with ether, gave a product, b. p. 206—210/20 mm., from which on refractionation 10 g. of *ethyl α-carbethoxy-α-methylaconitate* were obtained; this had b. p. 206—207°/20 mm., $d_{4°}^{21·5°}$ 1·1237, n_D 1·4560, $[R_L]_D$ 83·2 (Found: C, 55·7; H, 6·9. $C_{16}H_{24}O_8$ requires C, 55·8; H, 6·9%).

Ozonisation. This was carried out as described on p. 1806. The acidic product consisted of oxalic acid; the neutral product boiled at 160—175°/12 mm. and consisted of ethyl oxalylmethylmalonate, because it gave on treatment with phenylhydrazine in ether two derivatives, m. p. 120° and 275°, identical with the synthetic specimens described on p. 1809.

Ethylation. The yellow sodio-derivative prepared as above from 1/10 g.-mol. of reactants was ethylated as described on p. 1806. After two distillations the main fraction (10 g.) had b. p. 210—211°/20 mm., $d_{4°}^{20°}$ 1·1377, n_D 1·4564, $[R_L]_D$ 88·9 and consisted of *ethyl α-carbethoxy-α-methyl-γ-ethylaconitate* (Found: C, 57·8; H, 7·3. $C_{18}H_{28}O_8$ requires C, 58·1; H, 7·5%).

Ozonisation. This was carried out as described on p. 1806. Some oxalic acid was isolated from the alkaline washings, showing that ethylation was not complete. The neutral product consisted of two fractions; the first, b. p. 65—75°/17 mm., consisted of ethyl α-ketobutyrate and formed the semicarbazone, m. p. 144°, identical with a synthetic specimen; the higher fraction, b. p. 170—180°/17 mm., was ethyl oxalylmethylmalonate, recognised by the formation of the phenylhydrazine derivatives of m. p.'s 120° and 275°.

Condensation of Ethyl Acetylenedicarboxylate with Ethyl Methylmalonate.—This was carried out as described above and about 4 g. of a fraction, b. p. 210°/22 mm., were obtained; the unchanged reactants were again condensed, and the combined high fractions redistilled, yielding 5 g. of condensation product, b. p. 206—207°/20 mm., $d_{4°}^{21°}$ 1·1232, n_D 1·4560 (Found: C, 55·5;

H, 6·8. Calc.: C, 55·8; H, 6·9%). On ozonisation the same products, namely, oxalic acid and ethyl oxalylmethylmalonate, were obtained.

Condensation of Ethyl Acetylenedicarboxylate with Ethyl Sodiomalonate.—This was carried out in ethereal solution as described on p. 1806. The yellow sodio-derivative, formed in a fine state of division, was washed with petroleum by decantation and used *in situ*.

The ester was not liberated from the sodio-derivative by shaking with benzoic acid for several days, but treatment with dilute hydrochloric acid gave an ester, b. p. 204—205°/15 mm.

Methylation. The crude sodio-derivative was heated with methyl iodide and a little benzene for 5 days as described on p. 1806; from 1/10 g.-mol., about 20 g. of crude product were obtained and this gave on refractionation 12 g. of ethyl α-carbethoxy-α-methylaconitate, b. p. 206—207°/20 mm. (Found: C, 55·5; H, 6·7. Calc.: C, 55·8; H, 6·9%). This was ozonised, yielding the products described on p. 1807. The same ester was also produced by treating the free ester obtained above with molecular sodium suspended in benzene and heating the mixture under reflux for 6 hours to complete the reaction; methyl iodide was then added, and the mixture heated overnight. The methylated ester had b. p. 201—203°/16 mm., $d_{4^\circ}^{21^\circ}$ 1·1241, n_D 1·4559; its structure was confirmed by ozonisation.

Condensation of Ethyl Tetrolate with Ethyl Methylmalonate.—When ethyl tetrolate was condensed with ethyl sodiomethylmalonate in ether, benzene or dioxan solution, a light brown, very hygroscopic sodio-derivative was produced. Acidification of this with ice-cold dilute hydrochloric acid gave a product which was almost wholly acidic and only a very small amount of neutral material, b. p. 80—125°/15 mm., was obtained; the sodium carbonate washings gave on acidification a viscous brown oil which could not be purified. The condensation was, however, successfully achieved by using a 1/10-molecular proportion of sodium ethoxide; a 66% yield of *ethyl α-carbethoxy-αβ-dimethylglutaconate* was then obtained, b. p. 170°/15 mm., $d_{4^\circ}^{20^\circ}$ 1·0766, n_D 1·4557, $[R_L]_D$ 71·9 (Found: C, 58·4; H, 7·6. $C_{14}H_{22}O_6$ requires C, 58·7; H, 7·7%).

Ozonisation. This was carried out as described on p. 1806. The acidic product isolated was oxalic acid. The neutral product gave on distillation a negligible fraction, b. p. 80—110°/17 mm., which gave no colour with ferric chloride and could not be identified, together with a main fraction, b. p. 110—130°/17 mm., consisting of ethyl acetylmethylmalonate, which was characterised by its phenylhydrazone, m. p. and mixed m. p. 128° (Michael, *J. Amer. Chem. Soc.*, 1892, **14**, 510); it also gave a *semicarbazone*, m. p. 137° after crystallisation from alcohol; the fact that this requires a day for its formation may account for Michael's failure to prepare it (*ibid.*, 1919, **41**, 423) (Found: C, 48·5; H, 7·0. $C_{11}H_{19}O_5N_3$ requires C, 48·3; H, 6·9%).

Condensation of Ethyl Tetrolate with Ethyl Sodiomalonate.—This was carried out in ethereal solution, the mixture being kept at 0° overnight, then at room temperature for 2 days. No solid sodio-derivative separated and on treatment with petroleum only a semi-solid brown mass was obtained.

Methylation. The crude sodio-derivative obtained as above was methylated as described on p. 1806, the process being complete after 4 days; the yield of ethyl α-carbethoxy-αβ-dimethylglutaconate was 37%. This had b. p. 176—178°/19 mm., $d_{4^\circ}^{20\cdot8^\circ}$ 1·0865, n_D 1·4588, $[R_L]_D$ 71·5 (Found: C, 58·4; H, 7·5. Calc.: C, 58·7; H, 7·7%). The structure of the ester was confirmed by ozonisation, the products described above being obtained and identified as before.

In another experiment, the free ester was liberated from the crude sodio-derivative obtained as above, 12 g. of b. p. 175—177°/17 mm. being collected; this was then methylated as described above. The product had p. b. 172—174°/16 mm., $d_{4^\circ}^{21^\circ}$ 1·0853, n_D 1·4560 and gave on ozonisation the products described above.

Condensation of Ethyl Tetrolate with Ethyl α-Cyanopropionate.—This was carried out in the usual way, but scarcely any neutral product was obtained on acidification of the reaction mixture, the bulk being a viscous acidic oil which could not be purified.

Condensation of Ethyl Propiolate with Ethyl Methylmalonate.—Although the reaction between ethyl sodiomethylmalonate and ethyl propiolate in ether was very vigorous, a definite reaction product could not be isolated (compare above). A better result was obtained by using a 1/10 molecular proportion of sodium ethoxide; from 8·7 g. of ethyl methylmalonate, 4 g. of unchanged reactants were obtained, 2 g. of condensation product, b. p. 175°/20 mm., and a trace of a product, b. p. 220°/20 mm., partly solidifying to a substance of m. p. 134—135°, which was not further characterised (Found: C, 61·0; H, 6·2%). The main fraction on redistillation had $d_{4^\circ}^{20\cdot5^\circ}$ 1·0768, n_D 1·4495, and was presumably ethyl α-carbethoxy-α-methylglutaconate (Gidvani, Kon, and Wright, *loc. cit.*).

Ozonisation. The main fraction described above gave on ozonisation oxalic acid and a neutral oil, b. p. 100—110°/20 mm., which was probably ethyl formylmethylmalonate; owing to an oversight, it was characterised, not by the known phenylhydrazone, but by the *semicarbazone*, m. p. 178° (Found : C, 46·1; H, 6·3. $C_{10}H_{17}O_5N_3$ requires C, 46·3; H, 6·5%).

Ethyl Oxalylmethylmalonate.—Ethyl methylmalonate was added to an ice-cold suspension of 1·15 g. of molecular sodium in ether; after being kept overnight, the mixture was treated dropwise with 7 g. of ethyl oxalochloride in 10 vols. of ether with frequent shaking. Next day water was added, the product extracted with ether, and the extract washed with sodium carbonate solution, then water, dried, and evaporated; the bulk of the product boiled at 173—175°/22 mm. A weighed quantity of this was kept overnight with phenylhydrazine (1 mol.) in a little ether; the *phenylhydrazide* which had separated was recrystallised from alcohol and had m. p. 120° (Found : C, 56·7; H, 5·9. $C_{16}H_{20}O_6N_2$ requires C, 57·1; H, 6·0%). With phenylhydrazine (2 mols.) a very sparingly soluble *compound* was formed, which could not be recrystallised and was purified by washing with ether; it had m. p. 275° (Found : C, 61·6; H, 5·7. $C_{22}H_{26}O_5N_4$ requires C, 61·9; H, 6·1%). It is probable that these two compounds are represented by the formulæ $NHPh{\cdot}NH{\cdot}CO{\cdot}CO{\cdot}CMe(CO_2Et)_2$ and

$$NHPh{\cdot}NH{\cdot}CO{\cdot}C(:N{\cdot}NHPh){\cdot}CMe(CO_2Et)_2.$$

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