CCCXXIV.—*The Additive Components of Ethyl Sodiomalonate and Related Compounds.*

By NORMAN ELLERSHAW HOLDEN and ARTHUR LAPWORTH.

THORPE and YOUNG (J., 1900, **77**, 939) investigated the products formed by heating ethyl ββ-dimethylacrylate with ethyl sodiomethylcyanoacetate. They were unable to detect the formation of any of the compound

$$(A)\ CO_2Et\cdot CH\mathit{Na}\cdot C(CH_3)_2\cdot C(\mathit{CH}_3)(CN)\cdot CO_2Et^*$$

which would result from the simple union of the unsaturated ester with the sodio-compound in its ionic components, $Na^{\cdot}$ and $C(CH_3)(CN)\cdot CO_2Et'$, in accordance with Michael's original formulation of such addition processes (*J. pr. Chem.*, 1887, **35**, 349). The only condensation product detected was an isomeride of A; this isomeride had the structure:

$$(A')\ CO_2Et\cdot CH(\mathit{CH}_3)\cdot C(CH_3)_2\cdot C\mathit{Na}(CN)\cdot CO_2Et$$

Howles, Thorpe, and Udall (J., 1900, **77**, 943) studied the action of ethyl sodiocyanoacetate on α-methylacrylate in alcoholic solution. The properties of the product did not correspond with the structure:

$$(B)\ CO_2Et\cdot C\mathit{Na}(CH_3)\cdot CH_2\cdot CH(CN)\cdot CO_2Et$$

but with the isomeric structure:

$$(B')\ CO_2Et\cdot \mathit{CH}(CH_3)\cdot CH_2\cdot C\mathit{Na}(CN)\cdot CO_2Et$$

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* For simplicity the sodio-derivatives are represented throughout the present communication as containing sodium directly attached to carbon.

It will be observed that in each of these condensations the constitution of the product obtained differs from that of the compound to be expected on the basis of Michael's original formulation (*loc. cit.*) by the apparent interchange of the positions of the two atoms or radicals exhibited in italics.

Thorpe, in the course of a theoretical paper on the constitution of sodio-derivatives of cyanoacetic esters (J., 1900, **77**, 923 *et seq.*), advanced the ingenious hypothesis that the reactive parts of ethyl sodiocyanoacetate are H and $CNa(CN){\cdot}CO_2Et$, those of ethyl sodiomethylcyanoacetate being, similarly, CH_3 and $CNa(CN){\cdot}CO_2Et$. Later he quite logically extended the hypothesis to the mechanism of the action of ethyl sodiocyanoacetate on ethyl acetoacetate and related compounds (J., 1905, **87**, 1685); these he supposed to react in their enolic forms as follows:

$$\vdots CR{-}OH + H{\cdot}CNa(CN){\cdot}CO_2Et \longrightarrow \vdots CR{-}CNa(CN){\cdot}CO_2Et + H_2O$$

The interaction between cyanohydrins and ethyl sodiocyanoacetate was interpreted in a similar way (J., 1906, **89**, 1456). Others, attracted perhaps by the apparent simplicity of such schemes, were led to imagine that the Knoevenagel reaction involved the participation of the enolic form of the aldehyde or ketone used (J., 1908, **93**, 1944). Quite recently it has been pronounced that "there is as yet no conclusive evidence to show that the Knoevenagel reaction is uniquely a reaction involving the non-enolised form of a ketone or aldehyde," (*Ann. Reports*, 1930, 85), a statement which illustrates how lasting the repercussions of the hypothesis have been in spite of the lack of direct experimental support.

The genesis of all these ideas is to be found in Thorpe's original assumption that the appearance of B′ instead of B (present paper, p. 2368) in the one experiment is due to causes similar to those which lead to the appearance of A′ instead of A in the other experiment.

Dealing first with the appearance of B′, where B might have been anticipated, the present authors believe that there will be fairly general agreement that simple carboxylic esters, contrasted with esters of the malonic and acetoacetic types, are extremely feeble pseudo-acids and that their sodio-derivatives would undergo extensive decomposition by alcohol. Such esters, dissolved in alcohol containing sodium ethoxide, do not display to any marked extent properties associated with the presence of sodio-derivatives, and there can be little or no doubt that, normally, equilibrium in the system

$$CNaR_1R_2{\cdot}CO_2Et + HOEt \longleftrightarrow CHR_1R_2{\cdot}CO_2Et + NaOEt$$

strongly favours the components on the right-hand side of the equation.

When, however, R_2 (say) is CO·Alk, CO·Ar, CO·OEt or CN, the sodio-derivative is much more stable and more readily formed; for instance Thorpe and Young (*loc. cit.*, p. 938) were able to obtain ethyl sodiomethylcyanoacetate by mere addition of ether to an alcoholic solution originally containing sodium ethoxide and the free ester. Hence, the equilibrium in the system

$$CNaR_1(CN)\cdot CO_2Et + HOEt \longleftrightarrow CHR_1(CN)\cdot CO_2Et + NaOEt$$

is favourable to high concentrations of both the components on the left-hand side of the equation.

Clearly B, in spite of the presence of the groups CN and CO_2Et at some distance from the Na atom, corresponds with the former case, and it is therefore to be expected from purely *a priori* reasons that B would largely undergo conversion into B′ in the conditions of the experiment. Even a direct exchange of H for Na between two different molecules * in absence of free alcohol cannot be regarded as unlikely. A reminder may be added that the formation of dialkylated esters when ethyl sodiomalonate and similar compounds are operated on with alkyl halides (1 mol.) has long been recognised as an indication of the partition of " available sodium " between unalkylated and monoalkylated esters.

The question as to the cause of the appearance of A′ instead of A comes in quite a different category and cannot be answered by reference to similar *a priori* considerations. Thorpe, however, held it to be *proved* (*loc. cit.*, p. 934) " that in these condensations the sodium remains attached to the carbon atom with which it was originally combined." It is clear from his expressed approval of scheme ii (*loc. cit.*, p. 932) for the mode of addition of ethyl sodiomethylcyanoacetate to ethyl dimethylacrylate that he regarded this process as involving the addition of the former compound in the two parts, CH_3 and $CNa(CN)\cdot CO_2Et$.

Recently, Michael and Ross (*J. Amer. Chem. Soc.*, 1930, **52**, 4598 *et seq.*) carried out a series of experiments with several αβ-unsaturated esters and examined the products obtained on condensing them with ethyl methylmalonate in presence of various proportions of sodium ethoxide. They found that, when quantities considerably less than 1 mol. of the ethoxide were used, the addition product had the constitution corresponding with the apparent addition of the ethyl methylmalonate in the parts H and $C(CH_3)(CO_2Et)_2$. When a whole mol. of sodium ethoxide was used, the product contained a con-

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* Strictly speaking, no doubt, the case is rather one of competition between the anions of the sodio-derivatives for available protons. The authors' reasons for adopting a terminology more consistent with the simple formulæ chosen for convenience to represent the sodio-derivatives need not be elaborated.

siderable quantity of an isomeric ester in which the ethyl sodiomethylmalonate had apparently entered into combination in the parts CH_3 and $CNa(CO_2Et)_2$. An ester of the former type could be converted into one of the latter by heating with a large proportion of sodium ethoxide, and this was attributed to a reversal of the Michael addition process (Michael, *Ber.*, 1900, **33**, 3750; Ingold and Powell, J., 1921, **119**, 1976), followed by union, in accordance with Thorpe's hypothetical scheme, of the resulting αβ-unsaturated ester with the ethyl sodiomethylmalonate also formed. Sodium ethoxide, in small proportion, was assumed to act " catalytically," that is to say, by promoting in some undefined way the direct union of the free malonic ester with the unsaturated compound.

Michael and Ross claim that their results " have rigorously proved the correctness of Thorpe's conclusions." This pronouncement by such high authority might well give rise to further confusion of ideas on reaction mechanism in this and related chapters of organic chemistry, which reflection has led to the present communication.

Consideration of A (this paper, p. 2368) will show that its structure may be changed to that of A′, not only by interchanging the positions of the Na and CH_3, but equally well by interchanging the positions of the H (of the ·CH*Na*·) for the CN. Such an occurrence, either inter- or intra-molecularly, is not inconsistent with the known relations between nitriles and imino-compounds. Thus, when R·H and R′·H are weak acids or pseudo-acids, the following changes are possible in presence of sodium ethoxide :

$$R{\cdot}H + CN{\cdot}R' \longleftrightarrow R{\cdot}C(\colon NH){\cdot}R' \longleftrightarrow R{\cdot}CN + H{\cdot}R'$$

and, similarly, in the cases examined by Michael and Ross :

$$R{\cdot}H + CO_2Et{\cdot}R' \longleftrightarrow R{\cdot}CO{\cdot}R' + HOEt \longleftrightarrow R{\cdot}CO_2Et + H{\cdot}R'$$

these schemes being used without prejudice to any theory of the rôles played by the sodio-derivatives.

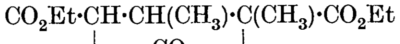
Conditions under which the latter series of reactions is likely to proceed from left to right are (*a*) that the labile H in R·H is one of a pair attached to the same carbon atom and (*b*) that the labile H in H·R′ is solitary, the CO_2Et group in the $CO_2Et{\cdot}R'$ residue therefore being attached to a hydrogen-free carbon atom. Condition (*a*) follows directly from the well-known empirical rule that two saturated ethyl esters do not undergo to any appreciable extent the acetoacetic ester type of condensation unless one of them (R·H) contains the group $\cdot CH_2{\cdot}CO_2Et$. Condition (*b*) follows indirectly from the same rule, because the latter precludes effective resynthesis of R·CO·R′ from $R{\cdot}CO_2Et$ and H·R′. The rule, be it noted, may not be quoted as a proof that the " precluded " reactions do not take place at all; it is merely a statement of the fact that such reactions have never been found to yield isolable quantities of the expected products, and in the light of Dieckmann's experiments on the decomposition of ethyl dimethylacetoacetate by alcohol and sodium ethoxide (*Ber.*, 1900, **33**, 2670; compare J., 1908, **93**, 31) is more consistent with the idea of a reversible reaction for which the equilibrium constant is extremely small.

The experimental data relating to the case of formation and decomposition of the corresponding imino-compounds are too meagre in themselves to admit of application with the same degree of certainty. The reversibility of a reaction of this kind has, however, been established by E. H. Ingold (J., 1924, **125**, 1319) and it would be surprising if the rules which determine the relative ease of formation and decomposition of β-ketonic esters had no counterpart in the closely related series of β-imino-esters.

In each of the cases to which Michael and Ross extended Thorpe's hypothesis the above conditions are present, and therefore an interchange of positions between CO_2Et and H is possible either in the same molecule or in two different molecules. Thus with the less stable ester (I) from ethyl crotonate and ethyl methylmalonate con-

$$\text{(I.)}\quad CO_2Et\cdot CH_2\cdot CH(CH_3)\cdot C(CH_3)(CO_2Et)_2$$

densations of the acetoacetic ester type are possible. If a condensation takes place in the intramolecular mode with which Dieckmann's name is associated (*Ber.*, 1894, **27**, 102), the products would be alcohol and the cyclic ketonic ester



$$CO_2Et\cdot\underbrace{CH\cdot CH(CH_3)\cdot C}_{CO}(CH_3)\cdot CO_2Et$$

and this, being an α-disubstituted β-ketonic ester, would be very prone, in presence of alcohol and sodium ethoxide, to reabsorb the elements of alcohol, not with formation of the original tricarboxylic ester (I) but of its isomeride (II)

$$\text{(II.)}\quad (CO_2Et)_2CH\cdot CH(CH_3)\cdot CH(CH_3)\cdot CO_2Et$$

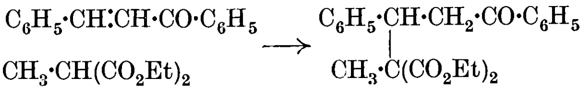
This is the constitution assigned by Michael and Ross to the more stable ester which they obtained in their experiments and which they assumed to be formed independently of the less stable ester (I). Their experiments are therefore not calculated to lead to a decision for or against Thorpe's hypothesis.

In all the cases actually examined by Thorpe, Michael, and their co-workers, the constitution of the final (or more stable) product must be the same whether the process occurs as envisaged by these workers or in the mode suggested by the present authors. It may be added that a double process of exchange of CO_2Et (or CN) for

H between two different molecules would also lead to the same structure for the final product.

The authors have therefore tried the experiment of condensing benzylideneacetophenone (III) with the sodio-derivative of ethyl methylmalonate (IV), anticipating that the sodio-derivative of the normal addition product (V) would be formed in the first instance and

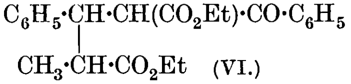
(III.) (IV.)



$$\begin{array}{l} C_6H_5{\cdot}CH{:}CH{\cdot}CO{\cdot}C_6H_5 \\ CH_3{\cdot}CH(CO_2Et)_2 \end{array} \longrightarrow \begin{array}{l} C_6H_5{\cdot}CH{\cdot}CH_2{\cdot}CO{\cdot}C_6H_5 \\ \qquad | \\ CH_3{\cdot}C(CO_2Et)_2 \end{array}$$

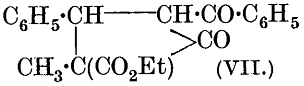
(V.)

that in (V) there would subsequently occur an exchange (in effect) of CO_2Et for H, yielding the ester (VI), with, possibly, the unstable ketonic ester (VII) as intermediate step.



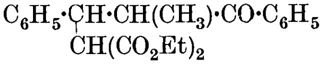
$$\begin{array}{l} C_6H_5{\cdot}CH{\cdot}CH(CO_2Et){\cdot}CO{\cdot}C_6H_5 \\ \qquad | \\ \; CH_3{\cdot}CH{\cdot}CO_2Et \end{array}$$

(VI.)



(VII.)

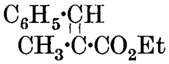
According to the ideas of Michael and Ross, the compound (V) is to be expected from the reversible union of (III) and (IV) under the catalytic influence of sodium ethoxide, but (III) combining with the *sodio-derivative* of (IV) should yield the *sodio-derivative* of (VIII).



$$\begin{array}{l} C_6H_5{\cdot}CH{\cdot}CH(CH_3){\cdot}CO{\cdot}C_6H_5 \\ \qquad CH(CO_2Et)_2 \end{array}$$

(VIII.)

Actually there was isolated from the acidified product a mixture of ethyl benzoylacetate (X) and ethyl α-methylcinnamate (IX).



$$\begin{array}{l} C_6H_5{\cdot}CH \\ \; CH_3{\cdot}C{\cdot}CO_2Et \end{array}$$

(IX.)

$CH_2(CO_2Et){\cdot}CO{\cdot}C_6H_5$
(X.)

These two compounds bear no simple relation to either (V) or (VIII), but on the other hand they are precisely the components into which (VI) would be resolved by a reversed " Michael addition " reaction.

It may also be noted that the residue $CH_3{\cdot}\dot{C}(CO_2Et)_2$ of the original ethyl methylmalonate has *lost*, while the residue $\dot{C}H{\cdot}CO{\cdot}C_6H_5$ of the acetophenone has *gained*, the group CO_2Et. The " proof " offered by Michael and Ross of the correctness of Thorpe's hypothesis is based on the implicit assumption that such a loss and gain of CO_2Et is impossible and is therefore shown to be fallacious.

Thorpe, in his original " proof," overlooked the by no means remote possibility of a similar loss and gain of the CN group.

EXPERIMENTAL.

Interaction between Benzylideneacetophenone and Ethyl Sodiomethylmalonate.—A preliminary experiment on the point gave a product in which, after acidification, the presence of a β-ketonic ester containing the group $\cdot CO\cdot CH_2\cdot CO_2Et$ was detected by its reactions with ferric chloride and copper acetate respectively. Hydrolysis of the product with alkali yielded a mixture of acids from which benzene extracted one which appeared to be α-methylcinnamic acid. These observations led the authors to modify their original plan of procedure and to concentrate attention on the lower-boiling products of the reaction.

Powdered sodium (1·72 g.) was covered with benzene (60 c.c.) and a solution of ethyl methylmalonate (13·05 g.) in benzene (60 c.c.) was slowly added. When action had ceased, a solution of benzylideneacetophenone (15·6 g.) in benzene (35 c.c.) was dropped in. Each small addition caused a bright but fugitive orange coloration, and the sodium derivative slowly passed into solution. The whole was heated on the steam-bath under reflux for one hour, and next day was shaken with acetic acid (5 g.) and water. The upper layer was separated, dried, freed from benzene on the steam-bath, and fractionated under pressure of 20 mm. In addition to unchanged ethyl methylmalonate (about 4 g.) and residues boiling above 155° (10 g.), there were obtained 12 g. of a fraction, b. p. 125—155°. This gave with ferric and copper salts the characteristic colour reactions of an ester of the ethyl benzoylacetate type. To a portion (9·6 g.), dissolved in dilute alcohol, was therefore added excess of aqueous copper acetate, the resulting yellow-green microcrystalline copper derivative (about 3·8 g.) being removed by filtration.

The copper derivative was identified as that of benzoylacetic ester by its melting point (180°, whether alone or when mixed with an authentic specimen). The free ester was liberated by means of dilute sulphuric acid, and part of it was converted by hydroxylamine hydrochloride into 3-phenyl*iso*oxazol-5-one (needles; m. p. 151—152°, alone or mixed with authentic substance) and another part by hydrazine hydrate into 3-phenylpyrazol-5-one (m. p. 237—238°, alone or mixed with authentic substance. Found: N, 17·4. Calc. for $C_9H_8ON_2$ N, 17·5%).

The filtrate from the solid copper derivative was diluted with water and extracted with ether. The ethereal solution, which was bluish-green owing to the presence of dissolved ethyl cupribenzoylacetate which had escaped precipitation, was shaken with dilute sulphuric acid until colourless (the quantity of copper in the acid extract, determined by precipitation with hydrogen sulphide, corresponded with 0·35 g. of benzoylacetic ester), and evaporated, and the residue heated for 2 hours with a solution of potassium hydroxide (6 g.) in methyl alcohol; the odour of acetophenone then became plainly perceptible. The liquid was diluted with water, exhaustively extracted with ether, then heated on the steam-bath for some time, cooled, and acidified with hydrochloric acid. The resulting precipitate was collected after ½ hour, washed with cold water, and dried. It weighed 4·1 g., had m. p. 80—81°, and displayed all the properties of slightly impure α-methylcinnamic acid.

The identity of the acid obtained in this as well as in the preliminary experiment is established by the following data :

The melting point of the acid recrystallised from water or distilled under ordinary pressure was 82—83°. Its equivalent (determined by titration with *N*/10-NaOH) was 165, and, after recrystallisation from light petroleum, 163. Analysis gave C, 74·2; H, 6·2 (a monobasic acid, $C_{10}H_{10}O_2$, requires C, 74·0; H, 6·2%; equivalent, 162). A cold solution of its sodium salt at once decolourised (*a*) bromine, giving a precipitate accompanied by a characteristic pungent odour, and (*b*) permanganate, the odour of benzaldehyde becoming perceptible.

A specimen of α-methylcinnamic acid ("phenylcrotonic acid") was made in accordance with Perkin's directions (J., 1877, **31**, 391) from sodium propionate, propionic anhydride, and benzaldehyde and its properties were compared in detail with those of the above acid. The results, including mixed melting points, confirmed the identification.

The sodium salt of the acid in aqueous solution was readily and quantitatively reduced by shaking it for some time with clean, liquid sodium amalgam. The reduced acid, solidified on distillation (b. p. about 160°/16—17 mm.), and a portion, after draining on porous earthenware, had m. p. 36·5° and equivalent 163·5 (a monobasic acid, $C_{10}H_{12}O_2$, requires 164); on nitration the acid gave a nitro-derivative, m. p. 123°. These characters correspond closely with those ascribed by previous workers to benzylmethylacetic acid and its *p*-nitro-derivative (Conrad and Hodgkinson, *Annalen*, 1878, **193**, 302; Conrad and Bischoff, *ibid.*, 1880, **204**, 181; Edeleanu, J., 1888, **53**, 558).

From data given in the preceding pages it may be calculated that, of the fraction (b. p. 125—155°) taken from the mixed product arising from the reaction between ethyl sodiomethylmalonate and benzylideneacetophenone, about 50% was ethyl α-methylcinnamate and at least 38% was ethyl benzoylacetate.

It is proposed to extend the experiments and to investigate other instances of reaction of monoalkylated malonic and cyanoacetic esters with αβ-unsaturated ketones, which reactions, unlike those with αβ-unsaturated esters, may be used to ascertain whether change takes place to any extent in the sense of Thorpe's hypothetical scheme.

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