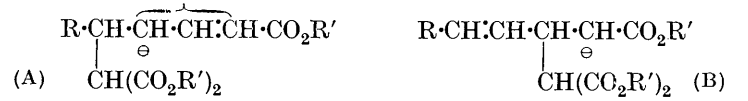
CCCLVII.—*Properties of Conjugated Compounds. Part XIII. The Michael Reaction and the Manner of Formation of Certain Saturated Double-addition Products.*

By ERNEST HAROLD FARMER and THAKORBHAI NARANJI MEHTA.

As a consequence of the authors' demonstration that a plural mode of attachment of ester-addenda to butadienoid compounds could obtain (J., 1930, 1610), it seemed probable that a detailed study of the course followed by the Michael and other allied reactions which proceed in alkaline solution could ultimately give unequivocal information as to the order of events in these reactions and consequently as to the mechanism of an important type of unsymmetrical addition and the manner of polarisation of conjugated esters. If, during addition, the anionic component of the addendum were the first to become attached, the resulting system could be prototropic (A) or non-tautomeric (B) :



(A) (B)

in the former case the completion of addition could yield a Δ^{α}- or Δ^{β}-form of an $\alpha\delta$-addition product (in most cases, probably, the latter almost exclusively in view of the relative activating tendencies of the groups attached to the prototropic system) and in the latter case an ordinary $\alpha\beta$-addition product. This means that the complex anions necessarily formed intermediately could not be in equilibrium with one another, so that there is no possibility of $\alpha\beta$, $\alpha\delta$-isomerisation except *via* the retrograde Michael reaction, thus : $\alpha\beta$-Product $\rightleftharpoons$ Reactants $\rightleftharpoons$ $\alpha\delta$-Product. If, on the other hand, the

kationic component first became attached, the resulting system would be anionotropic,

$$R\cdot\overbrace{CH{:}CH\cdot CH}^{\oplus}\cdot CH_2\cdot CO_2R \qquad R\cdot\overbrace{CH\cdot CH{:}CH}^{\oplus}\cdot CH_2\cdot CO_2R$$

so that a direct mechanism for the production of isomeric forms akin to the mechanism of bromination would be provided. Both views have been put forward in connexion with the addition of unsymmetrical addenda to mono-olefinic esters, nitriles and ketones. It is important to note, however, that if the initiation of $\alpha\delta$-ester addition to butadienoid compounds is dependent on the appearance of positive polarity on the δ-carbon atom of the butadiene chain, then polarisation of the Thiele type is effectively produced before reaction commences.

In the preceding paper consideration has been given to the ratio in which $\alpha\beta$- and $\alpha\delta$-addition products are formed from various butadienoid esters and ketones: the results which have been obtained do not give clear and definite support to the view that an anionotropic mechanism determines the additive mode. There is, however, a series of observations on record which seems to indicate that a consideration other than the simple ones outlined above may enter into the problem relating to the formation of ester (and allied) addition products.

It was shown by Bechert (*J. pr. Chem.*, 1894, **50**, 13) and Hinrichsen (*Annalen*, 1904, **336**, 339) that cinnamaldehyde reacts with cyanoacetic ester and with malononitrile in the presence of a few drops of alcoholic sodium ethoxide to yield cinnamylidenecyanoacetic ester, $Ph\cdot CH{:}CH\cdot CH{:}C(CN)\cdot CO_2R$, and cinnamylidenemalononitrile, $Ph\cdot CH{:}CH\cdot CH{:}C(CN)_2$, respectively; later it was shown by Meerwein (*Annalen*, 1908, **358**, 71) that cinnamaldehyde condenses with methyl malonate in the presence of a molecular proportion of sodium methoxide to yield a saturated trimalono-compound which could reasonably be represented as the double-addition

$Ph\cdot CHX\cdot CH_2\cdot CHX\cdot CH(CO_2R)_2$ (I.)

$Ph\cdot CH{:}CH\cdot CHX\cdot CH(CO_2R)_2$ (II.)

$Ph\cdot CHX\cdot CH{:}CH\cdot CH(CO_2R)_2$ (III.)

$[X = CH(CO_2Et)_2]$

$Ph\cdot CH(CH_2\cdot CO_2H)\cdot CH(CH_2\cdot CO_2H)\cdot CH_2\cdot CO_2H$ (IV.)

$CH_2<\begin{matrix}CHPh\text{—}CH_2\\ CO\text{——}CH_2\end{matrix}>CH\cdot CH_2\cdot CO_2H$ (V.)

$Ph\cdot CH_2\cdot CHX\cdot CHX\cdot CH(CO_2Et)_2$ (VI.)

product (I) of cinnamylidenemalonic ester, $Ph\cdot CH{:}CH\cdot CH{:}C(CO_2R)_2$. The tendency to the formation of this compound was so great that even when strictly molecular amounts of the reactants were employed

it still appeared—mixed with unchanged cinnamaldehyde but unaccompanied by isolable amounts of cinnamylidenemalonic ester or either of the simple addition products thereof (II and III). The constitution assigned to the saturated addition product rested on its hydrolysis to a tribasic acid represented as (IV), which in turn was convertible by the action of sodium on its ester, followed by hydrolysis, into a cyclic keto-acid represented as (V).

Now the formation of a double-addition product of this kind could be explained by assuming the steps : (1) the formation of cinnamylidenemalonic ester, (2) the formation of an αδ-addition product (III) which subsequently suffered βγ, αβ-double bond displacement, and (3) the addition of another molecule of malonic ester at the αβ-double bond of the resulting compound (compare Meerwein, *loc. cit.*, p. 338). The correctness of this view was, however, at least open to doubt, for although a simple ester-addition product of cinnamylidenemalonic ester had never been obtained * (consequently the possibility of realising the postulated αδ-addition had not been tested), yet there was evidence to show that in the parallel reaction with potassium cyanide the same conjugated ester yielded first an αβ-addition product, $Ph{\cdot}CH{:}CH{\cdot}CH(CN){\cdot}CH(CO_2Et)_2$, and then a saturated double-addition product representable as

$$Ph{\cdot}CH(CN){\cdot}CH_2{\cdot}CH(CN){\cdot}CH(CO_2Et)_2$$

(Thiele and Meisenheimer, *Annalen*, 1899, **306**, 252). If the mono-addition product in the latter instance were indeed wholly of αβ-type, then the representation of additive mode as determined by mobile ion tautomerism (of either type) in the simple manner envisaged above would become impossible of acceptance so far as ester addition is concerned. Although it is by no means certain from the published evidence that the αβ-hydrocyanide referred to was unaccompanied by an isomeric αδ-product, or that the corresponding double-addition product was unaccompanied by one or both forms of the mono-addition product, there was, however, another possibility to consider, *viz.*, that the formula reasonably assigned to the double-addition product was incorrect and ought to be replaced by the only alternative formula (VI) which could correspond with Meerwein's observations. A substance of this formula would of course give *cyclo*pentanone- instead of *cyclo*hexanone-derivatives on cyclisation, but its formation would be dependent on the occurrence of rearrangement of the first-formed αβ-addition product whereby the malonic ester group became transferred to the γ-carbon atom.

* There is little doubt that Knoevenagel and Herz's alleged cinnamylidene-*di*malonic ester, prepared by condensation of cinnamaldehyde and malonic ester in the presence of piperidine (*Ber.*, 1904, **37**, 4483), was actually cinnamylidenemalonic ester (Meerwein, *loc. cit.*, p. 336).

As the manner of hydrogen cyanide addition to cinnamylidenemalonic ester and other conjugated compounds was already under investigation in connexion with another series of experiments, the authors thought it advisable to examine the reactivity of crotonaldehyde towards malonic ester. The formation of crotonylidenemalonic ester under the condensing action of piperidine had been effected by Meerwein (*loc. cit.*), but the preparation of crotonylidene-*di*malonic ester (VII) had not been accomplished. Farmer and Healey had unsuccessfully attempted to prepare the latter compound and the corresponding cyanoacetic ester addition product by addition to crotonylidenemalonic ester (J., 1927, 1065), and the present authors in renewing these attempts have found that, although some condensation can be effected between crotonaldehyde and malonic ester in the presence of a few drops of sodium ethoxide solution, the product is complex and cannot be satisfactorily fractionated; on the other hand, they have found that the interaction of the two substances in the presence of a molecular proportion of sodium ethoxide yields very readily an analogue (VIII) of Meerwein's double-addition compound (I). The behaviour of this substance (which appeared to be quite free from crotonylidene-*di*malonic ester or its $\alpha\delta$-isomeride) paralleled that of Meerwein's compound. It yielded by hydrolysis a tribasic acid (IX), and to some extent a cyclised derivative thereof. The latter compound (X) was also obtained by submitting the ester of (VIII) to the Dieckmann reaction and hydrolysing the solid ketonic ester so obtained, to which one of the formulæ (XI) and (XII) should apply.

$CH_3\cdot CH{:}CH\cdot CHX\cdot CH(CO_2Et)_2$ (VII.)

$CH_3\cdot CHX\cdot CH_2\cdot CHX\cdot CH(CO_2Et)_2$ (VIII.)

$CH_3\cdot CH(CH_2\cdot CO_2H)\cdot CH_2\cdot CH(CH_2\cdot CO_2H)\cdot CH_2\cdot CO_2H$ (IX.)

$CH_2<CHMe\cdot CH_2>CO\cdot CH_2>CH\cdot CH_2\cdot CO_2H$ (X.)

(XI.) $CHMe<CH_2\cdot CO\cdot CH(CH_2\cdot CO_2Et)>CH\cdot CO_2Et$ $\xrightarrow{KMnO_4}$ $CHMe<CH_2\cdot CO_2H\cdot CH(CH_2\cdot CO_2Et)>CO\cdot CO_2Et$

(XII.) $CHMe<EtO_2C\cdot CH\cdot CO\cdot CH(CH_2\cdot CO_2Et)>CH_2$

[X = $CH(CO_2Et)_2$]

Actually the former formula was correct, since the Dieckmann reaction product gave β-methylglutaric acid and oxalic acid as the final products of oxidation with permanganate; it followed also from the fact that β-methylglutaric acid was obtained that the formula (VI), as representing the original double-addition product, was finally confirmed, since the Dieckmann reaction product from (VII) should have yielded ethylsuccinic acid.

The formation of the saturated double-addition compound from crotonaldehyde and malonic ester thus constitutes the third known example of this type of additive reaction. Preliminary experiments on the addition of malonic ester to sorbic ester in the presence of a molecular proportion of sodium ethoxide indicate that a saturated double-addition compound is formed in this example also. It seems clear, therefore, that although reaction can proceed direct from aldehyde to double-addition product in one operation, it need not necessarily do so, but can start from the butadiene ester; in all cases, however, the employment of the sodium enolate of the addendum is necessary. It is a remarkable fact that in the formation of double-addition compounds from both cinnamylidene- and crotonylidene-malonic ester it has not been possible to arrest reaction at the stage intermediate between the formation of the butadiene ester and the double-addition compound. (In all of the numerous additions to butadiene esters under " catalytic " conditions which have been studied, reaction appears to cease at the stage of simple addition.)

The conditions and manner of formation of double-addition compounds will be further investigated, but there is little doubt that *radical-migration plays no part* in their production. Therefore, since there is no appearance that the proportions in which αβ- and αδ-addition products are formed are purely fortuitous, the experimental evidence in favour of butadienoid polarisation of a conjugative type is strengthened in direct proportion as the evidence of an anionotropic relationship between isomeric addition products is weakened.

EXPERIMENTAL.

Condensation of Ethyl Malonate with Crotonaldehyde.—(a) *With a fractional molecular proportion of sodium ethoxide at* 0°. Condensation under these conditions proceeded to some extent, but the condensation product was obviously not homogeneous and could not satisfactorily be resolved into its component compounds by fractional distillation.

(b) *With a molecular proportion of sodium ethoxide.* Freshly distilled crotonaldehyde (28 g.; 1 mol.) and ethyl malonate (192 g.; 3 mols.) were mixed and cooled in a freezing-mixture. A solution of sodium ethoxide (9·2 g. of sodium in 140 c.c. of absolute alcohol)

was gradually added during 1 hour, the temperature not being allowed to rise. The solution, which had become yellow and viscous, was kept for 3 hours at room temperature and then diluted with a large quantity of water. The alkaline liquor was extracted with ether to remove the neutral products of reaction : these consisted of unchanged ethyl malonate and a very small quantity (too small to allow of identification) of an oil, b. p. 140—150°/13 mm. The mother-liquor, after acidification with the calculated quantity of hydrochloric acid, yielded an acidic reaction product on extraction with ether. This substance, obtained as a colourless viscous liquid, was immediately hydrolysed by boiling with 35% hydrochloric acid for 30 hours. The acid obtained by extracting the product with ether was a thick viscous oil which began to solidify after standing for some days in a vacuum desiccator and became completely solid after being kept for 3 months with occasional scratching of the containing vessel and trituration with common organic solvents. In later experiments it was found advantageous to esterify the hydrolysed product directly by dissolving it in alcohol and saturating the solution with dry hydrogen chloride; the oily product obtained could then be easily separated into two compounds, (i) a colourless oil, b. p. 140°/11 mm., and (ii) a colourless oil, b. p. 187—188°/11 mm. The former of these was *ethyl* 1-*methyl*cyclo*hexan*-3-*one*-5-*acetate*, which was later obtained (see below) in a different way; it yielded a *semicarbazone* (colourless prisms, m. p. 152°, from ethyl acetate. Found : C, 56·3; H, 8·2. $C_{12}H_{21}O_3N_3$ requires C, 56·4; H, 8·3%). The latter compound was *ethyl* β-*methylpimelate*-β′-*acetate* (Found : C, 61·0; H, 8·7. $C_{16}H_{28}O_6$ requires C, 60·7; H, 8·9%), which yielded on hydrolysis with hydrochloric acid pure β-*methylpimelic*-β′-*acetic acid* in almost quantitative yield. The acid was obtained in colourless cubes, m. p. 130°, after crystallising in turn from ether–petroleum and acetone–chloroform (Found : equiv., 77. Calc. : equiv., 77·3), and from the acid the corresponding crude anhydride was obtained as a non-solidifiable liquid by boiling with acetyl chloride. By saturating an alcoholic solution of the acid with hydrogen chloride at 0°, ethyl β-methylpimelate-β′-acetate was regenerated in very pure condition (Found : C, 60·5; H, 8·7%).

Ethyl 1-*Methyl*cyclo*hexan*-3-*one*-4-*carboxylate*-5-*acetate*.—Sodium (6·2 g.) was pulverised under xylene, and the xylene replaced by benzene. To the suspension, ethyl β-methylpimelate-β′-acetate (42 g.) was added, and the mixture heated to 90° in an oil-bath. A vigorous reaction ensued which was completed by heating the product for 5 hours at 100°. The jelly-like sodium derivative was decomposed with ice-cold 10% sulphuric acid, and the derived ester extracted with ether. The ether–benzene liquor, freed from a small

amount of acidic material by shaking with sodium carbonate, was dried and distilled. It yielded pure *ethyl* 1-*methyl*cyclo*hexan*-3-*one*-4-*carboxylate*-5-*acetate* as a colourless oil, b. p. 170—172°/11 mm., which solidified after several days and gave colourless needles, m. p. 47°, on recrystallisation from light petroleum (Found: C, 62·1; H, 8·3. $C_{14}H_{22}O_5$ requires C, 62·2; H, 8·2%). Yield, 75%. No semicarbazone of this strongly enolic substance could be obtained; the *phenylhydrazone* crystallised from alcohol in long needles, m. p. 111° (Found: C, 66·5; H, 7·8. $C_{20}H_{28}O_4N_2$ requires C, 66·6; H, 7·8%), but decomposed on keeping.

1-*Methyl*cyclo*hexan*-3-*one*-5-*acetic Acid*.—Ethyl 1-methyl*cyclo*hexan-3-one-4-carboxylate-5-acetate was boiled with equal volumes of alcohol, hydrochloric acid, and water for 3 hours, the free alcohol was then expelled, and hydrolysis continued for 12 hours. The product was neutralised and traces of residual neutral material were removed by extraction with ether. From the alkaline liquor an oil was isolated which solidified after distillation (b. p. 185°/9 mm.). This crystallised in long colourless needles, m. p. 77°, from petroleum (Found: C, 63·7; H, 8·1. $C_9H_{14}O_3$ requires C, 63·5; H, 8·2%). The corresponding *silver* salt was obtained as a white powder (Found: Ag, 39·1. $C_9H_{13}O_3Ag$ requires Ag, 39·0%); the *semicarbazone* separated from methyl alcohol as a white crystalline powder, m. p. 218° (Found: C, 52·6; H, 7·5. $C_{10}H_{17}O_3N_3$ requires C, 52·8; H, 7·5%); the ester obtained by warming the silver salt with alcoholic ethyl iodide was a colourless oil, b. p. 144°/13 mm., obviously identical with the above-described ethyl 1-methyl*cyclo*hexan-3-one-5-acetate (Found: C, 66·5; H, 9·1. $C_{11}H_{18}O_3$ requires C, 66·6; H, 9·15%), since it yielded a semicarbazone, m. p. 152°, identical with that previously obtained (Found: C, 56·3; H, 8·3%).

Oxidation of Ethyl 1-*Methyl*cyclo*hexan*-3-*one*-4-*carboxylate*-5-*acetate*.—To an ice-cold suspension of the ester in very dilute aqueous caustic potash, 3% permanganate solution equivalent to 7 atoms of oxygen was slowly added, with rapid stirring. The solution was kept over-night and then the small amount of residual permanganate was reduced by addition of a little hydrogen peroxide. After removal of the manganese mud, the solution was concentrated, acidified, and extracted with ether; the residue left on evaporation of the mother-liquor to dryness was also extracted with ether. The first ethereal extract yielded a water-soluble oily acid, partial solidification of which set in after inoculation with a crystal of β-methylglutaric acid. This solid portion was drained on a porous tile, and the dry solid extracted in turn with benzene, chloroform, and ether. The benzene extract yielded crystals of β-methylglutaric acid which after recrystallising in turn from benzene and ether–

petroleum melted at 87°, and did not depress the melting point of an authentic sample of the acid. The chloroform contained an acid which was extremely difficult to recrystallise, but this on further oxidation with permanganate yielded β-methylglutaric acid. The ethereal extract on concentration deposited crystals of oxalic acid, but a much larger quantity of the same acid was obtained on evaporating the ethereal extract of the solid residue (above). It was found that chromic acid yielded gummy oxidation products differing greatly from those here described.

The authors desire to thank the Government Grant Committee of the Royal Society and the Chemical Society for grants which have defrayed a portion of the cost of the investigation.

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
LONDON, S.W. 7. [*Received, June 6th,* 1931.]