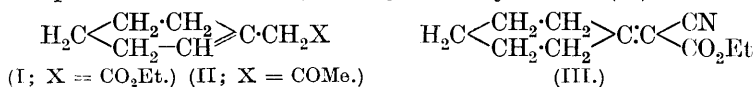CCCLXI.—*The Chemistry of the Three-carbon System. Part VII. Derivatives of Malonic Acid.*

By GEORGE ARMAND ROBERT KON and ERIC ALFRED SPEIGHT.

THE distinction between the mobility and the point of equilibrium of a tautomeric system has been emphasised by Kon and Linstead (J., 1925, **127**, 616). The mobility of the system appears to be principally connected with the efficiency of the activating group, usually known as the " enolising efficiency " when the term is applied to systems exhibiting keto-enol tautomerism; it must depend ultimately on the capacity of this group to cause the potentially mobile hydrogen atom to move towards one of the atoms constituting it, this movement being accompanied by a rearrangement of the multiple linkings which the group contains. For example, the carbethoxyl group, which has a low enolising efficiency according to Claisen's rule (compare Dieckmann, *Ber.*, 1922, **55**, 2470), has but little effect in promoting the mobility of a three-carbon system, whereas the more active acetyl group has a much greater effect; the difference is well exemplified by a comparison of the ester (I) with *cyclo*hexenylacetone (II).
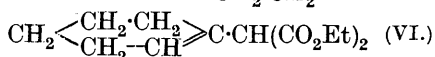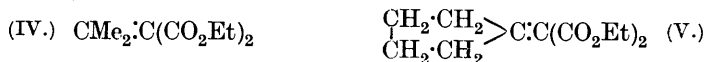
$$H_2C<{}^{CH_2 \cdot CH_2}_{CH_2-CH}>C \cdot CH_2X \qquad H_2C<{}^{CH_2 \cdot CH_2}_{CH_2 \cdot CH_2}>C{:}C<{}^{CN}_{CO_2Et}$$

(I; X = CO$_2$Et.) (II; X = COMe.) (III.)

The position of equilibrium, which is, of course, a measure of the relative stabilities of the two forms ($\alpha\beta$ * and $\beta\gamma$ in a three-carbon system), is the resultant of several effects. One of these is again due to the activating group, in virtue of the tendency of a double bond to become conjugated with the double or triple bond of the activating group. Another effect, which may operate in the same or in the opposite sense, can be due to the presence of a second unsaturated group (another activating group or phenyl) or to a structural condition capable of stabilising the double bond in a given position; an example of the latter type is the influence of the *cyclo*pentane or *cyclo*hexane ring or of a suitable *gem*-group in the β-position of a three-carbon system. It follows that the

* The carbon atom to which the activating group is attached is called a in all cases.

attachment of a second activating group to the α-carbon atom, reinforcing the first one, not only enhances the mobility of the system, but also tends to stabilise the αβ-phase of the compound, since the double bond in this position is doubly conjugated; these effects are apparent in ethyl α-cyano*cyclo*hexylideneacetate (III), which, unlike the compounds (I) and (II), normally occurs in the αβ-form.

In accordance with Claisen's rule, the introduction of a second carbethoxyl group into the ester (I) in the α-position should produce, both on the mobility of the system and on the point of equilibrium, effects similar to, but less pronounced than, those of the cyano-group. This view receives support from a study of several esters prepared by condensing ethyl malonate with appropriate ketones; the first member of the series, ethyl *iso*propylidenemalonate (IV), has already been prepared by Meyenberg (*Ber.*, 1895, **28**, 785).
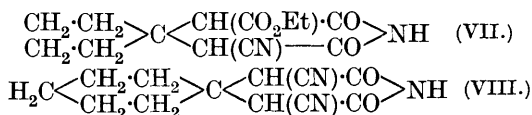
(IV.) $CMe_2:C(CO_2Et)_2$
$\begin{array}{c}CH_2 \cdot CH_2 \\ CH_2 \cdot CH_2\end{array}\!\!>\!\!C:C(CO_2Et)_2$ (V.)

$CH_2\!\!<\!\!\begin{array}{c}CH_2 \cdot CH_2 \\ CH_2\!-\!CH\end{array}\!\!>\!\!C \cdot CH(CO_2Et)_2$ (VI.)

The most striking feature of this series is the point of equilibrium in the compounds (V) and (VI). The ester (V), like ethyl *iso*propylidenemalonate, has the αβ-unsaturated structure; it gives *cyclo*pentanone on oxidation and shows an exaltation of the molecular refraction. The *cyclo*hexane compound, on the other hand, has the βγ-unsaturated formula (VI) as shown by its optical properties; on oxidation with ozone it gives Δ^1-*cyclo*pentenyl methyl ketone, which can only be derived from a compound with a double bond in the ring. In addition, the acid corresponding to it gives Δ^1-*cyclo*hexenylacetic acid on heating.

Although such a difference had not previously been observed, it was clearly to be expected, since the *cyclo*hexane ring has a much greater tendency to acquire a double bond than the *cyclo*pentane ring (compare Dieckmann, *loc. cit.*) and therefore is capable of overcoming the attraction of the two carboxyl groups.

This observation is of considerable interest; there is little doubt that a relationship exists between the internal strain in a ring consequent upon the alteration of the normal tetrahedral angle and the tendency of the ring to acquire a double bond. A similar effect probably accounts for the tendency of the double bond to move towards the βγ-position in ββ-diethylacrylic acid (Kon and Linstead, *loc. cit.*). A more detailed discussion of this relationship is reserved for a future communication.
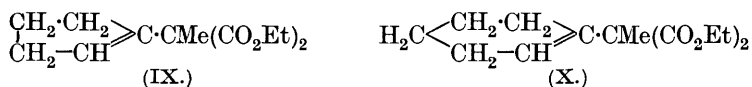
The mobility of the hydrogen atom in this series is somewhat difficult to gauge owing to certain peculiarities of the compounds.

For example, it is very difficult to demonstrate the existence of the αβ-phase by the usual addition reactions. Even the ester (V), which has unquestionably the αβ-structure, does not readily undergo the Michael reaction in presence of sodium, no doubt on account of the great tendency to form its own sodio-derivative; * we have, however, succeeded in obtaining an addition product with hydrogen cyanide and in condensing the ester (V) with ethyl cyanoacetate and ammonia, the compound (VII) being produced in poor yield.

$$\begin{matrix} CH_2 \cdot CH_2 \\ CH_2 \cdot CH_2 \end{matrix} \!\!>\!\! C \!\!<\!\! \begin{matrix} CH(CO_2Et) \cdot CO \\ CH(CN) \!-\! CO \end{matrix} \!\!>\!\! NH \quad \text{(VII.)}$$

$$H_2C \!\!<\!\! \begin{matrix} CH_2 \cdot CH_2 \\ CH_2 \cdot CH_2 \end{matrix} \!\!>\!\! C \!\!<\!\! \begin{matrix} CH(CN) \cdot CO \\ CH(CN) \cdot CO \end{matrix} \!\!>\!\! NH \quad \text{(VIII.)}$$

The ester (VI) did not yield a similar compound, the product being the well-known imide (VIII), the formation of which is best explained by assuming that the condensation product first formed undergoes fission, ethyl malonate being eliminated (compare Scheiber and Meisel, *Ber.*, 1915, **48**, 238) and a further molecule of ethyl cyanoacetate being then added on. This reaction was not observed if the ester had been prepared by the action of ethyl iodide on the silver salt of the pure solid acid, although both the ester prepared by direct condensation and that obtained by esterification of the acid by Fischer's method gave the same poor yield of the imide. The pure ester reacts with ethyl sodiocyanoacetate to a limited extent; the condensation product, however, again appears to undergo fission, eliminating ethyl malonate, for a nitrogenous fraction is isolated which readily condenses with ethyl cyanoacetate and ammonia to give the imide (VIII) and therefore probably consists of ethyl α-cyano*cyclo*hexylideneacetate (III). It would thus appear that the pure ester is non-mobile under the conditions of the Guareschi reaction and requires the presence of a powerful reagent to "equilibrate" it; we were, however, unable to effect such an equilibration even by the prolonged action of hot sodium ethoxide, perhaps for the reason above.

Both esters (V and VI) very readily yield sodio-derivatives by the action of sodium in methyl- or ethyl-alcoholic solution. By the action of methyl iodide on these the corresponding α-methyl derivatives (IX and X) were produced in good yield; the reaction involves the passage of the compound (V) into the βγ-form.

$$\begin{matrix} CH_2 \cdot CH_2 \\ CH_2 \!-\! CH \end{matrix} \!\!>\!\! C \cdot CMe(CO_2Et)_2 \qquad H_2C \!\!<\!\! \begin{matrix} CH_2 \cdot CH_2 \\ CH_2 \!-\! CH \end{matrix} \!\!>\!\! C \cdot CMe(CO_2Et)_2$$
$$\text{(IX.)} \hspace{5cm} \text{(X.)}$$

* It is presumably for a similar reason that ethyl acetonedicarboxylate cannot be condensed with ethyl cyanoacetate either by Michael's or by Gaureschi's method (unpublished observation).

Ethyl *iso*propylidenemalonate also can be alkylated with comparative ease, giving the *ester*, $CH_2:CMe \cdot CMe(CO_2Et)_2$: the production of a terminal methylene group by the movement of a hydrogen atom away from a *gem*-dimethyl group usually occurs with some difficulty. The *acid* corresponding to this ester loses carbon dioxide on heating and passes into a liquid *acid* which must have the formula $CH_2:CMe \cdot CHMe \cdot CO_2H$; this is not identical with trimethylacrylic acid (Perkin, J., 1896, **69**, 1480) but passes into it on boiling with strong alkalis. It is proposed to investigate this change at a later date.

EXPERIMENTAL.

Methylation of Ethyl iso*Propylidenemalonate* (IV).—To a solution of 2·3 g. of sodium in 30 c.c. of ethyl alcohol was added the ester (Meyenberg, *loc. cit.*) (0·1 g.-mol.), followed slowly by an excess of methyl iodide. The deep orange colour of the liquid faded and the reaction was complete after 2 hours' warming. Water and dilute hydrochloric acid were added and the oil was taken up in ether and washed with sodium carbonate, which removed some acid material. The extract was washed, dried, and evaporated, and after two methylations an *ester* was obtained, b. p. 124°/18 mm., $d_4^{24 \cdot 6°}$ 1·01159, $n_D^{24 \cdot 6°}$ 1·44020, $[R_L]_D$ 55·81 (calc., 55·84). We have not yet succeeded in oxidising this ester.

The methylated ester was hydrolysed by 64% aqueous potassium hydroxide and a little alcohol in ½ hour. The *acid*, isolated by means of ether, readily solidified. It contained a little of the parent acid (m. p. 170—171°) which, being almost insoluble in chloroform, was removed by extracting the mixture with this solvent. Addition of petroleum to the solution gave a substance from which, after several crystallisations from chloroform–petroleum and finally from hydrochloric acid, the new acid was obtained in flattened needles, m. p. 135° (decomp.) (Found : C, 53·3; H, 6·3. $C_7H_{10}O_4$ requires C, 53·2; H, 6·2%).

The acid was heated under reduced pressure until no more carbon dioxide was evolved. The residue, on distillation, gave a colourless, mobile oil, b. p. 108°/25 mm., having the characteristic odour of the acrylic acids. It was converted into the *anilide*, which crystallised from dilute alcohol or, better, from petroleum (b. p. 60—80°) in fine needles, m. p. 88° (Found : C, 76·0; H, 8·2. $C_{12}H_{15}ON$ requires C, 76·2; H, 8·0%).

The *anilide* of αββ-trimethylacrylic acid, prepared for comparison, was similar in appearance but had m. p. 94°; a mixture of the two melted at 78—80°.

The oil produced by boiling the liquid acid with 64% aqueous potassium hydroxide for a few minutes and acidifying the cooled solution solidified slowly and was identified as αββ-trimethylacrylic acid by direct comparison with a genuine specimen.

Ethyl cyclo*Pentylidenemalonate* (V).—Attempts to condense ethyl malonate with *cyclo*pentanone by means of tertiary bases were unsuccessful. With sodium ethoxide, a small amount of the corresponding acid was produced (see below).

Ethyl malonate (80 g.), 42 g. of *cyclo*pentanone, 50 c.c. of acetic anhydride, and 30 g. of zinc chloride were heated together on the steam-bath for 70—80 hours. The black mixture was poured into water and extracted with ether, and the extract was washed until the washings were colourless. The dried extract was evaporated and distilled, some 11 g. boiling at 136—144°/10 mm.; this fraction gave with ferric chloride a slight coloration, due to the presence of an impurity which could be removed by extraction with 15% aqueous potassium hydroxide. The purified ester, b. p. 140°/10 mm., consisted of *ethyl* cyclo*pentylidenemalonate* (Found: C, 63·4; H, 8·1. $C_{12}H_{18}O_4$ requires C, 63·7; H, 8·1%).

A much better yield of the ester was obtained by using the double compound of aniline and zinc chloride in the place of zinc chloride : 60 c.c. of aniline were gradually added to 150 g. of powdered zinc chloride and the mixture was well stirred; the solid was then added to 480 c.c. of ethyl malonate, 264 c.c. of *cyclo*pentanone, and 360 c.c. of acetic anhydride, and the whole heated and worked up as before. On distillation, the highest fraction contained a quantity of acetanilide which could be removed by the addition of light petroleum; the final yield was 195 g., b. p. 145—160°/20 mm. With zinc chloride–aniline alone, very little condensation takes place. An attempt was made to synthesise the ester from 1-chloro-Δ^1-*cyclo*pentene and ethyl sodiomalonate, but no reaction took place.

The ester was hydrolysed by 30% aqueous potassium hydroxide and a few drops of alcohol. cyclo*Pentylidenemalonic acid*, isolated in the usual way, readily solidified and crystallised from ethyl acetate–petroleum in rectangular prisms and from hydrochloric acid in plates, m. p. 169° (decomp.) (Found : C, 56·4; H, 5·9. $C_8H_{10}O_4$ requires C, 56·4; H, 5·9%). Titration : Found, 20·2 c.c. of $N/20$-NaOH. Calc. for a dibasic acid, 20·15 c.c.).

Oxidation. cycloPentylidenemalonic acid was dissolved in sodium hydrogen carbonate solution, and a slight excess of 1% potassium permanganate solution added. The acid products were isolated in the usual way and converted into their calcium salts; calcium oxalate then separated. From the filtrate, strongly acidified with

hydrochloric acid, ether extracted glutaric acid, which was identified by comparison with a genuine specimen.

The pure acid (2·8 g.) was dissolved in chloroform and treated with ozone. The ozonide was decomposed by dilute sulphuric acid, and distillation in steam then gave *cyclo*pentanone, which was isolated in the form of its semicarbazone (1 g.); the residue contained a considerable amount of oxalic acid. *cyclo*Pentanone was also obtained by decomposing the ozonide of the ester.

A pure specimen of ethyl *cyclo*pentylidenemalonate was prepared by the action of ethyl iodide on the silver salt of the acid suspended in ether. It boiled at 139—141°/10 mm. and had $d_{4°}^{19·8°}$ 1·06164, $n_D^{19·8°}$ 1·47241, $[R_L]_D$ 59·59 (calc., 58·02). On ozonisation and subsequent decomposition it gave *cyclo*pentanone; it had, therefore, the same structure as the ester obtained by direct condensation.

Methylation. The ester was twice treated with sodium methoxide and methyl iodide under the usual conditions. The ester isolated was hydrolysed to the *acid*, which solidified at once and crystallised from ethyl acetate and benzene in clusters of needles, m. p. 136·5° (decomp.), and from water in plates (Found : C, 58·6; H, 6·6. $C_9H_{12}O_4$ requires C, 58·7; H, 6·6%. Titration : Found, 19·1 c.c. of $N/20$-NaOH. Calc. for a dibasic acid, 19·1 c.c.). The acid was re-esterified through the silver salt, the *ester* (IX) having b. p. 150°/20 mm., $d_{4°}^{22·0°}$ 1·03457, $n_D^{22·0°}$ 1·45853, $[R_L]_D$ 63·24 (calc., 62·64) (Found : C, 64·8; H, 8·4. $C_{13}H_{20}O$ requires C, 65·0; H, 8·4%).

The methylated ester was ozonised in moist chloroform solution, and the ozonide decomposed with dilute sulphuric acid; no products volatile in steam were obtained. The thick oil remaining after steam distillation had the properties both of an aldehyde and of an acid, giving a semicarbazone, m. p. 165° after crystallisation from alcohol; it gave glutaric acid on further oxidation, even by air, and therefore was the semialdehyde of glutaric acid.

The methylated ester (7 g.) was kept at 35° with an excess of alcoholic sodium ethoxide for several hours. Water was then added, the oil extracted with ether, and the extract distilled. A low fraction was obtained, consisting of ethyl carbonate; 1·5 g. of a middle fraction, b. p. 95—105°/10 mm., which was somewhat impure ethyl α-Δ^1-*cyclo*pentenylpropionate (Found : C, 72·7; H, 9·6. Calc. : C, 71·4; H, 9·5%); and a high fraction of unchanged ester, which was identified by hydrolysis to the acid.

The ester (V) was treated in the same way, but was recovered unchanged.

Addition of hydrogen cyanide, ethyl acetoacetate, and ethyl cyanoacetate. The pure ester (V) (22·6 g.) was kept for 10 days with 15 g. of potassium cyanide in 60 c.c. of water and 125 c.c. of alcohol.

The solution was filtered from a small amount of solid, diluted with water, acidified with hydrochloric acid, and extracted with ether. The extract yielded a viscous oil which gave scarcely any low fraction on distillation; 10 g. were obtained boiling at 200—210°/10 mm. This product was hydrolysed by 20 c.c. of sulphuric acid and 8 c.c. of water. Much charring occurred, but a quantity of 1-carboxy*cyclo*pentane-1-acetic acid, m. p. 156°, was isolated; it was identified by comparison with a genuine specimen.

The ester (V) did not condense with ethyl sodioacetoacetate. It was treated with ethyl cyanoacetate and alcoholic ammonia (Kon and Thorpe, J., 1919, **115**, 686). After 3 days the product was worked up as usual and the *imide* (VII), forming small prisms, m. p. 163°, from alcohol, was obtained in 42% yield (Found : C, 58·9; H, 6·2; N, 10·8. $C_{13}H_{16}O_4N_2$ requires C, 59·1; H, 6·1; N, 10·6%). The imide was hydrolysed by 70% sulphuric acid, giving a good yield of *cyclo*pentane-1 : 1-diacetic acid, m. p. 176—177°.

Ethyl Δ^1-cyclo*Hexenylmalonate* (VI).—This substance was prepared from *cyclo*hexanone by the method used for the preparation of (V). The yield was about the same in the two cases. The ester so obtained gave high figures for carbon on analysis and could not be completely purified by distillation. It was therefore hydrolysed by potassium hydroxide (see p. 2731) to the *acid*, which was readily obtained solid and crystallised in prisms, m. p. 150° (decomp.), from ethyl acetate and petroleum or from hot water (Found : C, 58·7; H, 6·7. $C_{19}H_{12}O_4$ requires C, 58·7; H, 6·6%. Found for the silver salt : Ag, 54·5. $C_{19}H_{10}O_4Ag_2$ requires Ag, 54·2%). When the acid was melted and the residue distilled under reduced pressure, Δ^1-cyclohexenylacetic acid was produced.

The acid, m. p. 150°, was esterified through the silver salt and pure *ethyl* Δ^1-cyclo*hexenylmalonate* was thus readily obtained, b. p. 160°/20 mm., $d_4^{22 \cdot 5°}$ 1·04419, $n_D^{22 \cdot 5°}$ 1·46470, $[R_L]_D$ 63·42 * (calc., 62·64). The esterification was also carried out in the cold by means of alcohol and sulphuric acid, but a large fraction of low b. p., evidently ethyl *cyclo*hexenylacetate, was obtained, the yield of ester (VI) being only 40%; this boiled at 160°/20 mm. on redistillation (Found : C, 64·9; H, 8·5. $C_{13}H_{20}O_4$ requires C, 65·0; H, 8·4%) and had $[R_L]_D$ 63·27. Esterification by boiling the acid with alcohol saturated with hydrogen chloride gave an 80% yield of ester with 20% of low fraction.

Attempts to prepare the ester (VI) by other methods. The condensation of ethyl sodiomalonate with 1-chloro*cyclo*hexene was unsuccessful. Ethyl α-bromo*cyclo*hexylmalonate (Hope and Perkin,

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* The value is practically identical with that for ethyl α-methyl-α-Δ^1-*cyclo*pentenylmalonate (p. 2732).

J., 1909, **95**, 1363) was boiled with diethylaniline and with pyridine, but the product in each case was ethyl *cyclo*hexylmalonate, which was readily identified by hydrolysis to the corresponding acid, m. p. 176°; with diethylamine, a part of the bromo-ester remained unchanged. Attempts to remove bromine from α-bromo*cyclo*hexylmalonic acid, and to hydrolyse α-cyano*cyclo*hexylideneacetic acid (Harding, Haworth, and Perkin, J., 1908, **93**, 1949) to the dicarboxylic acid by means of sulphuric acid, were unsuccessful.

Oxidation of the ester (VI). The pure ester was ozonised in chloroform, the ozonide boiled with dilute sulphuric acid, and the product distilled in steam; Δ^1-*cyclo*pentenyl methyl ketone (Harding, Haworth, and Perkin, *loc. cit.*) was obtained in considerable quantity and characterised by its semicarbazone, m. p. 203—204° (Found : C, 57·5; H, 8·2. Calc. : C, 57·5; H, 7·8%); no trace of *cyclo*hexanone appeared to be produced. Ozonisation of the acid and of the ester obtained by direct condensation gave the same result, and oxidation of the acid by permanganate yielded adipic acid.

Methylation. The ester (VI) was methylated twice in the same way as the ester (V). The *ester* (X), obtained in 80% yield, was hydrolysed to the *acid*, which crystallised from ethyl acetate and benzene in clusters of needles, m. p. 155° (decomp.) (Found : C, 60·9; H, 7·2. $C_{10}H_{14}O_4$ requires C, 60·6; H, 7·1. Titration : Found, 18·95 c.c. of $N/20$-NaOH. Calc. for a dibasic acid, 18·85 c.c.). On re-esterifying the acid through its silver salt, the pure ester (X) was obtained, b. p. 152—154°/16 mm., $d_4^{19·8°}$ 1·03723, $n_D^{19·8°}$ 1·46748, $[R_L]_D$ 68·06 (calc., 67·26) (Found: C, 66·1; H, 8·9. $C_{14}H_{22}O_4$ requires C, 66·1; H, 8·7%). The methylated ester was treated with sodium ethoxide as described on p. 2732, but, like the parent ester, was recovered unchanged.

Addition of hydrogen cyanide, ethyl acetoacetate, and ethyl cyanoacetate. No condensation products could be obtained with the first two reagents. With ethyl cyanoacetate and ammonia, no condensation occurred when the pure ester, prepared through the silver salt, was employed. With all other samples of the ester, a poor yield (about 10%) of the ω-imide of αα'-dicyano*cyclo*hexane-1 : 1-diacetic acid was obtained (Guareschi, *Atti R. Accad. Sci. Torino*, 1911, **46**, 662). The unchanged ester recovered from the condensation could not be condensed again. Attempts were also made to condense the ester with ethyl sodiocyanoacetate, but no recognisable products could be isolated, although the higher-boiling fractions of the neutral oil appeared to consist of ethyl α-cyano*cyclo*hexylideneacetate; they contained nitrogen and readily condensed with ethyl cyanoacetate and ammonia.