CCXIV.—*The Condensation of Ketones with Ethyl Acetoacetate.*

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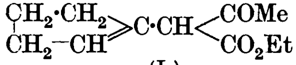
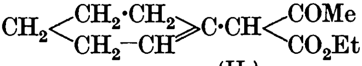
THE object of the present investigation was the preparation of esters such as (I) and (II) which should be of considerable interest



$$\begin{array}{l}CH_2\cdot CH_2\\ CH_2-CH\end{array}\!\!>C\cdot CH<\!\begin{array}{l}COMe\\ CO_2Et\end{array}$$

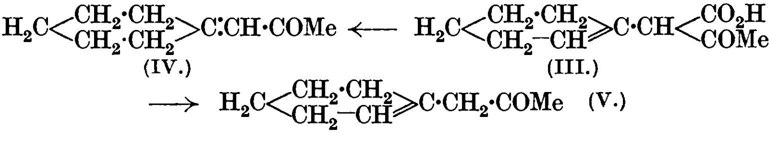
(I.)



$$CH_2<\!\begin{array}{l}CH_2\cdot CH_2\\ CH_2-CH\end{array}\!\!>C\cdot CH<\!\begin{array}{l}COMe\\ CO_2Et\end{array}$$

(II.)

from the point of view of three-carbon tautomerism. Ethyl *iso*propylideneacetoacetate, $CMe_2{:}C(COMe)\cdot CO_2Et$, had already been prepared by Merling and Welde (*Annalen*, 1909, **366**, 119) by condensing ethyl acetoacetate with acetone. Their method, however, fails when *cyclo*hexanone is used in place of acetone, *cyclo*hexenyl*cyclo*hexanone being the sole product. We therefore tried the action of *cyclo*hexanone on ethyl sodioacetoacetate and obtained evidence of a reaction in the desired direction, but the ester (II) was formed in insignificant amount and it was practically impossible to separate it from the large quantities of other products such as *cyclo*hexenyl*cyclo*hexanone. The acid portion of the reaction product contained a considerable quantity of the corresponding acid (III), which could be readily obtained pure. This acid cannot be esterified by ordinary methods, being either unattacked or converted into some compound formed by a secondary change. It is otherwise remarkably stable and can be kept unchanged for many months. It gives off carbon dioxide just above its melting point and yields a mixture of *cyclo*hexylideneacetone (IV) (Dickins, Hugh, and Kon, preceding paper) and *cyclo*hexenylacetone (V), the former predominating :



$$H_2C<\!\begin{array}{l}CH_2\cdot CH_2\\ CH_2\cdot CH_2\end{array}\!\!>C{:}CH\cdot COMe \longleftarrow H_2C<\!\begin{array}{l}CH_2\cdot CH_2\\ CH_2-CH\end{array}\!\!>C\cdot CH<\!\begin{array}{l}CO_2H\\ COMe\end{array}$$

(IV.) (III.)

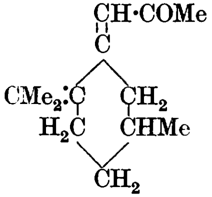
$$\longrightarrow H_2C<\!\begin{array}{l}CH_2\cdot CH_2\\ CH_2-CH\end{array}\!\!>C\cdot CH_2\cdot COMe$$

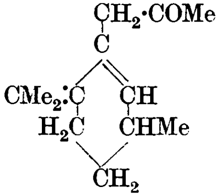
(V.)

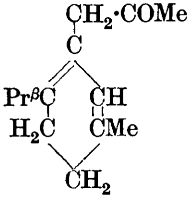
The preferential production of the $\alpha\beta$-ketone (IV), which is less stable than the $\beta\gamma$-ketone, from an acid having the $\beta\gamma$-structure is certainly remarkable and requires further investigation.

The ketones (IV) and (V) were present in quantity, approximately in the proportions of the equilibrium mixture (Dickins, Hugh, and Kon, *loc. cit.*), in the neutral products of the original condensation. The yield was increased at the expense of the acid (III) by adding water (1 mol.) to the reaction mixture after 24 hours and continuing the heating for a few hours longer—this constitutes the best method of preparing the equilibrium mixture in quantity. *cyclo*Pentenylacetone could not be prepared by a similar process, the only ketone produced in the condensation of *cyclo*pentanone with ethyl sodioacetoacetate being *cyclo*pentylidene*cyclo*pentanone; the ester (I) could not be isolated, although a minute quantity of the corresponding acid was obtained. The oxidation of this acid showed that, unlike the acid (III), it had an αβ-unsaturated structure; this difference is analogous to that already observed in the malonic acids (Kon and Speight, J., 1926, 2787).

Finally, pulegone and piperitone were condensed with ethyl acetoacetate. The principal compound obtained from the former is the ketone (VII) prepared by Barbier (*Compt. rend.*, 1898, **127**, 870). The structure of this compound was confirmed by oxidation, α-methylglutaric acid and acetone being obtained, showing that the formula (VII) and not the alternative one (VI), assumed by Barbier, is correct. A compound of formula (VI) should yield β-methyladipic acid under the same conditions. The ketone (VII) can, however, be condensed with ethyl sodiomalonate, giving a derivative of dihydroresorcinol; so it can react in the phase (VI). Like other similar ketones, it can be alkylated; the alkyl derivative gives the same oxidation products as the parent substance. The product obtained from piperitone has not been fully investigated, but by analogy it probably has the structure (VIII).


(VI.)


(VII.)


(VIII.)

EXPERIMENTAL.

Condensation of cyclo*Hexanone with Ethyl Sodioacetoacetate.*—Ethyl acetoacetate (260 g.) was added to a solution of 46 g. of sodium in 600 c.c. of alcohol, followed by 196 g. of *cyclo*hexanone; the mixture was heated under reflux for 24 hours. Water was added and the oil was taken up in ether, washed, dried, and distilled under reduced pressure (Neutral Oil A). The aqueous layer was strongly acidified with dilute sulphuric acid and again thoroughly extracted with ether; this extract on being dried and evaporated gave a solid (B).

The oil A gave on fractional distillation ethyl acetate, *cyclo*hexanone, a considerable fraction, b. p. 68—94°/17 mm., and a fraction boiling up to 120°/17 mm. The last two fractions on refractionation usually gave about 40 g., b. p. 84—88°/11 mm., and fractions, b. p. 79—83° and 89—95°. All these had the characteristic odour of *cyclo*hexenylacetone and gave a caseous semicarbazone from which the semicarbazone, m. p. 145° (Wallach, *Annalen*, 1913, **396**, 376; Dickins, Hugh, and Kon, *loc. cit.*) was isolated. Titration with iodine chloride (kindly carried out by Mr. W. E. Hugh) showed that the main fraction, $d_{4^{\circ}}^{17\cdot6^{\circ}}$ 0·94053, n_D 1·47555, had a composition closely approximating to that of the equilibrium mixture, namely, 70·5% of the $\beta\gamma$-form (72·7% addition) (Dickins, Hugh, and Kon, *loc. cit.*), and that there was a slight excess of the $\alpha\beta$-form in the highest fraction (53·5% $\beta\gamma$). The yield of equilibrium mixture can be considerably increased by adding water to the condensation product of *cyclo*hexanone and ethyl sodioacetoacetate and continuing the boiling for a further 6 hours. In one experiment, 21·5 g. of ketone (32%) were obtained from 65 g. of ethyl acetoacetate in this way.

Progressive refractionation of the higher fractions of the oil A gave a quantity of *cyclo*hexenyl*cyclo*hexanone (Wallach, *Annalen*, 1911, **381**, 95; Kon and Nutland, J., 1926, 3101), and a very small amount, seldom more than 1 g., of an oil, b. p. 135°/20 mm., giving an intense red-violet colour with alcoholic ferric chloride and consisting of the *ester* (II) (Found : C, 68·8; H, 8·6. $C_{12}H_{18}O_3$ requires C, 68·6; H, 8·6%). It was characterised by the *semicarbazone*, m. p. 141° (Found : C, 58·2; H, 8·0; N, 15·5. $C_{13}H_{21}O_3N_3$ requires C, 58·4; H, 7·9; N, 15·7%). It was not possible to isolate a sufficient quantity of the ester to confirm its constitution.

cyclo*Hexenylacetoacetic acid* (III). The solid acid B (45—60 g.), after recrystallisation from benzene–light petroleum, formed needles, m. p. 121° (decomp.), consisting of Δ^1-cyclo*hexenylacetoacetic acid.* The acid can also be recrystallised from dilute alcohol, but aqueous solvents should be avoided, as the acid readily loses carbon dioxide on boiling with water (Found : C, 65·9; H, 8·0. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·8%. Titration : Found, 19·8 c.c. NaOH; calc. for monobasic acid, 19·7 c.c.). The *semicarbazone*, m. p. 196°, crystallised from methyl alcohol (Found : C, 55·1; H, 7·2; N, 17·2. $C_{11}H_{17}O_3N_3$ requires C, 55·2; H, 7·2; N, 17·5%).

Oxidation. The acid, dissolved in an excess of aqueous sodium hydrogen carbonate, was treated with a slight excess of 3% aqueous potassium permanganate. The filtered solution gave to ether no neutral oxidation products, but after being acidified and re-extracted, it gave oxalic and adipic acids, which were separated by means of benzene. These two acids were also obtained when the acid (III) was oxidised with ozone in chloroform solution.

Action of heat. When heated under reduced pressure just above its melting point, the acid gave an almost theoretical yield of a ketone, b. p. 86—87°/13 mm., $d_{4^{\circ}}^{17 \cdot 8^{\circ}}$ 0·94250, $n_{D}^{17 \cdot 8^{\circ}}$ 1·48810, which was isolated from the distillate by means of ether. The iodine absorption of the ketone determined by Mr. Hugh was 41·3, corresponding to 74·3% of the αβ-form (IV). The semicarbazone obtained from it was caseous, but on repeated crystallisation from methyl alcohol gave the characteristic plates of *cyclo*hexylideneacetone-semicarbazone, m. p. 180°.

Attempts to esterify the acid (III). Methyl sulphate and sodium hydroxide had no action on the acid.

The silver salt, boiled over-night with an excess of methyl iodide in dry ether, gave an unsaturated substance, isomeric with (III), which did not give the expected colour with ferric chloride, was sparingly soluble in ether, and crystallised from dilute alcohol in plates, m. p. 177°; it did not effervesce with sodium hydrogen carbonate, although it dissolved in alkalis and was reprecipitated by acids (lactone ?) (Found : C, 65·5, 65·9; H, 7·9, 7·7. $C_{10}H_{14}O_3$ requires C, 65·7; H, 7·8%).

By the methyl-alcoholic hydrogen chloride method, from 5 g. of the acid were obtained 2 g. of an isomeric *substance* which crystallised from dilute methyl alcohol in long needles, m. p. 80° (Found : C, 65·8; H, 7·8%); it had no acid properties and gave a slight colour with ferric chloride (the liquid filtrate obtained from the original distillate gave a marked colour and had an odour of *cyclo*hexenylacetone). The same compound was produced when the acid (3 g.) was kept with methyl alcohol (10 c.c.) and concentrated sulphuric acid (3 c.c.) for 60 hours.

Other attempts to prepare the ester (II). (1) Ethyl *cyclo*hexenylmalonate (48 g.), prepared from the pure acid (Kon and Speight, *loc. cit.*), was added to 4·6 g. of " molecular " sodium in benzene, together with two drops of alcohol to start the reaction; 16 g. of acetyl chloride were added after an hour and the mixture was heated for 2 hours. Water was then added and the benzene solution was washed, dried, and evaporated; on distillation, 8 g. of *ethyl* Δ^1-cyclo*hexenylacetylmalonate*, b. p. 181°/19 mm., were obtained (Found : C, 63·8; H, 7·8%) and characterised by its *semicarbazone*, m. p. 178° (Found : C, 56·6; H, 7·6; N, 12·2. $C_{16}H_{25}O_5N_3$ requires C, 56·6;

H, 7·4; N, 12·4%). When the new ester was warmed with an excess of sodium ethoxide for 4 hours, ethyl *cyclo*hexenylmalonate and ethyl acetate were produced.

(2) Ethyl chloroformate failed to condense with the sodio-derivative of *cyclo*hexenylacetone in dry benzene.

(3) Ethyl *cyclo*hexenylmalonate (120 g.) was heated for 4 hours with 28 g. of potassium hydroxide in 500 c.c. of alcohol. The neutral solution was diluted with water, extracted with ether, acidified, and re-extracted. The crude acid-ester obtained was treated with an excess of thionyl chloride and distilled, giving 46 g. of an acid-chloride-ester, b. p. 151°/19 mm., and 15 g. of a high fraction probably containing the diacid chloride. The acid-chloride-ester, when treated with an excess of zinc methyl iodide (Blaise and Maire, *Ann. Chim. Phys.*, 1908, **15**, 556), was apparently reconverted into the acid-ester and the desired ketonic ester was not obtained.

When *cyclo*hexanone was condensed with ethyl acetoacetate in presence of zinc chloride and acetic anhydride, *cyclo*hexenylacetone was obtained. With dry sodium ethoxide or sodium methoxide prepared by Komppa's method (*Annalen*, 1909, **368**, 137), the products were the same as with alcoholic sodium ethoxide, and " molecular " sodium in benzene gave no measurable quantity of the ester (II) and a poor yield of the other products.

Condensation of cyclo*Pentanone with Ethyl Sodioacetoacetate.*—The reaction was carried out as described on p. 1639 with half-molecular quantities. No *cyclo*pentenylacetone was isolated from the neutral fraction, *cyclo*pentylidene*cyclo*pentanone (Wallach, *Ber.*, 1896, **29**, 2963; Kon and Nutland, *loc. cit.*) was obtained in quantity, but none of the desired ester appeared to be formed. The acid product consisted of cyclo*pentylideneacetoacetic acid* (1·5 g.), which crystallised from dilute alcohol in needles, m. p. 137° (decomp.) (Found: C, 64·0; H, 7·2. $C_9H_{12}O_3$ requires C, 64·2; H, 7·2%. Titration: Found, 20·4 c.c. $N/10$-NaOH; calc., 20·6 c.c.). The acid in chloroform solution was oxidised with ozone and the ozonide decomposed with water as usual; *cyclo*pentanone and oxalic acid were isolated.

Ethyl iso*Propylideneacetoacetate.*—This ester was prepared as described by Merling and Welde (*loc. cit.*) in order to study its behaviour on alkylation. The ester had b. p. 103°/18 mm., $d_{4°}^{21·0°}$ 0·96308, $n_D^{21·0°}$ 1·45583, whence $[R_L]_D = 46·52$ (calc., 44·96). The *semicarbazone* melted at 247° after crystallisation from alcohol (Found: C, 52·8; H, 7·8; N, 18·2. $C_{10}H_{17}O_3N_3$ requires C, 52·8; H, 7·6; N, 18·5%). All attempts to methylate the ester with the aid of " molecular " sodium in solvents failed, and in the presence of alcohol the methylated ester immediately underwent fission, as already observed by Merling and Welde, giving ethyl trimethylacrylate, $d_{4^{\circ}}^{21\cdot0^{\circ}}$ 0·97812, $n_{\mathrm{D}}^{21\cdot0^{\circ}}$ 1·45802, whence $[R_L]_{\mathrm{D}} = 41{\cdot}02$ (calc., 40·33). The structure of this ester was confirmed by oxidation with ozone, acetone being obtained.

Δ^1-*Pulegenylacetone* (VII).—This ketone, b. p. 149—153°/21 mm., m. p. 73°, was prepared either by condensing pulegone with ethyl sodioacetoacetate or by the process used by Barbier (*loc. cit.*), the former giving 29 g. and the latter 55 g. of ketone from 1 g.-mol. of pulegone. The corresponding keto-ester or acid was not isolated in either preparation. The *semicarbazone*, m. p. 187°, crystallised from benzene (Found: C, 67·2; H, 9·4. $C_{14}H_{23}ON_3$ requires C, 67·4; H, 9·3%). The ketone in chloroform was oxidised with ozone, and the ozonide decomposed with dilute sulphuric acid; acetone and α-methylglutaric acid were isolated and identified as usual, the constitution now assigned to the ketone thus being confirmed.

α-*Methyl*-α-Δ^1-*pulegenylacetone*.—Pulegenylacetone (19·2 g.) was added to " molecular " sodium (2·3 g.) in dry ether (50 c.c.) and when the vigorous reaction had subsided an excess of methyl iodide was introduced; the mixture was finally refluxed for 2 hours. The ketone was isolated in the usual way and the fraction, b. p. 149—154°/20 mm., was treated with semicarbazide; the *semicarbazone* melted at 191° after crystallisation and depressed the melting point of the semicarbazone of pulegenylacetone (Found: C, 68·4; H, 9·4. $C_{15}H_{25}ON_3$ requires C, 68·4; H, 9·6%). The *ketone* regenerated from it by means of oxalic acid in a current of steam had b. p. 150°/21 mm., $d_{4^{\circ}}^{21\cdot2^{\circ}}$ 0·94694, $n_{\mathrm{D}}^{21\cdot2^{\circ}}$ 1·49347, whence $[R_L]_{\mathrm{D}} = 64{\cdot}39$ (calc., 63·73). The new ketone gave on oxidation with ozone the same products as the parent substance.

Condensation of Pulegenylacetone with Ethyl Sodiomalonate.—The ketone (19·2 g.) was added to a mixture of ethyl malonate (16 g.) and sodium (2·3 g.) dissolved in alcohol (40 c.c.) and the whole was heated on the steam-bath for 2 hours. Water was then added and the solution was extracted with ether to remove neutral impurities, acidified, and re-extracted. The crude keto-ester obtained was hydrolysed by boiling for 20 hours with 90 g. of barium hydroxide in 720 c.c. of water. The hot solution was acidified and filtered, then an excess of concentrated hydrochloric acid was added and the solution again boiled for 15 minutes. On cooling, the *dihydroresorcinol* derivative separated (2·5 g.); it crystallised from alcohol in needles, m. p. 130°, and gave a reddish-violet colour with ferric chloride (Found: C, 76·7; H, 9·6. $C_{15}H_{22}O_2$ requires C, 76·9; H, 9·5%).

Condensation of Piperitone with Ethyl Acetoacetate.—Piperitone (from eucalyptus oil) was condensed with ethyl acetoacetate in the same way as pulegone; the yields of ketone $C_{13}H_{20}O$ were about 10% by Barbier's method and 6% in presence of sodium ethoxide. No keto-ester appeared to be formed. The ketone was isolated in the form of *semicarbazone*, m. p. 217° after crystallisation from alcohol (Found: C, 67·5; H, 9·3. $C_{14}H_{23}ON_3$ requires C, 67·4; H, 9·3%). The *ketone* regenerated from it had b. p. 155°/20 mm., $d_{4^\circ}^{21·8^\circ}$ 0·95821, $n_D^{21·8^\circ}$ 1·49610, whence $[R_L]_D = 60·59$. The properties of this substance have not yet been fully investigated.

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