359. *The Reactions of Ethyl* cyclo*Hexanone-2-carboxylate and Ethyl* cyclo*Pentanone-2-carboxylate with Unsaturated Methyl Ketones.*

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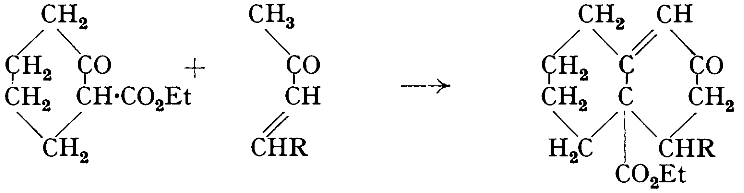
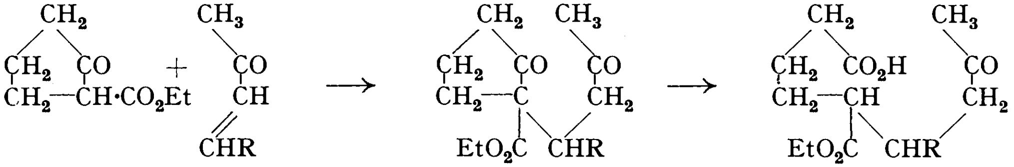
THE reactions of ethyl potassio*cyclo*hexanone-2-carboxylate with various unsaturated methyl ketones have followed the course which was to be expected from the analogous reactions of sodio*cyclo*hexanone with similar unsaturated ketones (Rapson and Robinson, J., 1935, 1285). For instance, it condenses with ethylideneacetone in dry alcoholic solution in the cold to yield (I, R = Me). Piperidine fails to effect the condensation. Under similar conditions styryl methyl ketone yields (I, R = C_6H_5), and *p*-methoxystyryl methyl ketone yields (I, R = C_6H_4·OMe). Both mesityl oxide and acetyl*cyclo*hexene failed to react. No saponification of the carbethoxy-group occurs during these condensations, the products, as might be expected from the tertiary nature of the ester group, being highly resistant to attack by both acids and alkalis.


(I.)


(II.) (III.).

With ethyl potassio*cyclo*pentanone-2-carboxylate, however, analogous condensations have not been effected. From reactions with both styryl methyl ketone and *p*-methoxystyryl methyl ketone in alcoholic solution, acidic products have been isolated, and from titrations and analyses, these are considered to be the *monoethyl* esters (III, R = C_6H_5 and C_6H_4·OMe respectively) : this view is supported by the preparation of the corresponding *methyl ethyl* esters and by the fact that on saponification a mixture of two stereoisomeric *acids* is produced, analyses and titrations of which indicate that they are the two possible racemic forms (III with H in place of Et).

Further, if the reaction with styryl methyl ketone is carried out in an inert medium such as benzene, in the cold, then little self-condensation of the styryl methyl ketone occurs, and both neutral and acidic products of reaction can be isolated. The acidic product is the same as that isolated from the reaction in alcoholic solution. Analyses of the neutral product indicate that it has the formula $C_{18}H_{22}O_4$, and since it yields the acidic product (III, R = C_6H_5) on treatment with alcoholic alkali, it is formulated as (II, R = C_6H_5). This reaction also confirms the position assigned to the ester group in (III). This abnormal ease of fission of the substance (II, R = C_6H_5) and its failure to undergo ring closure to a *cyclo*hexenone derivative are probably related phenomena.

Some difficulty is attached to explaining the production of acidic substances of the type (III) in the yields recorded, for despite precautions for the exclusion of moisture during the reactions, these substances are always produced. It is suggested that substances of type (II) are initially formed, and that they give rise to the acidic substances (III) on addition of water to the reaction mixture.

EXPERIMENTAL.

Ethylideneacetone was prepared by Hibbert's method (*J. Amer. Chem. Soc.*, 1915, **37**, 1755), a crystal of iodine being added to hydracetylacetone (40 g.) and the material then heated in an oil-bath at 155°. A mixture of ethylideneacetone and water slowly distilled. The product was salted out with potassium carbonate, dried with this agent, and distilled, the fraction, b. p. 119—125° (15 g.), being collected.

Ethyl 2-Keto-4-methyl-$\Delta^{1:9}$-octalin-10-carboxylate (I, R = Me).—A mixture of ethylideneacetone (10·5 g.) and ethyl *cyclo*hexanone-2-carboxylate (21 g.) was gradually added to an ice-cooled solution of potassium (4·6 g.) in dry alcohol (40 c.c.). After 12 hours, the mixture was diluted with water, acidified, and extracted with ether. The ether was evaporated from the dried neutral extracts, and the residue distilled in a vacuum. Ethyl *cyclo*hexanonecarboxylate (9·5 g.) was recovered, and a fraction, b. p. 150—190°/1 mm., collected. On redistillation, this yielded a fraction (10 g.), b. p. 165—170°/1 mm., which crystallised gradually but not completely. The crystals were separated and recrystallised from light petroleum (b. p. 40—60°), forming colourless needles, m. p. 76° (Found : C, 71·1; H, 8·6; OEt, 19·1. $C_{14}H_{20}O_3$ requires C, 71·2; H, 8·5; OEt, 19·4%).

Ethyl 2-Keto-4-phenyl-$\Delta^{1:9}$-octalin-10-carboxylate (I, R = C_6H_5).—Ethyl *cyclo*hexanonecarboxylate (25 g.; 1·5 mols.) was added gradually to an ice-cold solution of potassium (3·9 g.; 1 atom) in dry alcohol (50 c.c.). To the resulting solution was then added, drop by drop, a solution of styryl methyl ketone (14·6 g.; 1 mol.) in alcohol (15 c.c.). After 12 hours, ether was added to the reaction mixture, the whole shaken with dilute sulphuric acid, and the ethereal layer separated, washed with alkali, and dried. After evaporation of the ether, the residue was distilled in a vacuum. Besides recovered ethyl *cyclo*hexanonecarboxylate (12 g.), there was obtained a yellow distillate (20 g.), b. p. 215—220°/1 mm. A residue of polymerised styryl methyl ketone remained in the flask, and its quantity was not diminished by variation of the above procedure. The product crystallised on treatment with light petroleum and, recrystallised from this solvent or from alcohol, formed colourless elongated prisms (15 g.), m. p. 150° (Found : C, 76·7; H, 7·4. $C_{19}H_{22}O_3$ requires C, 76·5; H, 7·4%).

*Ethyl 2-Keto-4-*p*-methoxyphenyl-$\Delta^{1:9}$-octalin-10-carboxylate* (I, R = $C_6H_4{\cdot}OMe$).—Under analogous conditions to the above, anisylideneacetone and ethyl *cyclo*hexanonecarboxylate yielded this material as a viscous distillate, b. p. 235—240°/6 mm. It crystallised from light petroleum and from methyl alcohol in colourless needles, m. p. 112—113° (Found : C, 73·2; H, 7·2. $C_{20}H_{24}O_4$ requires C, 73·4; H, 7·3%). Neither this substance nor the preceding one was attacked by concentrated alkali or by concentrated hydrochloric acid on long boiling. Even sulphuric acid–acetic acid mixtures failed to effect hydrolysis. The usual ketonic reagents failed to yield ketonic derivatives.

*Condensation of Ethyl Potassio*cyclo*pentanone-2-carboxylate with Styryl Methyl Ketone in Alcoholic Solution.*—Styryl methyl ketone (35 g.) was allowed to react with ethyl potassio*cyclo*pentanone-2-carboxylate, prepared from the keto-ester (36 g.) and potassium (8 g.) in dry alcohol (150 c.c.), in the manner described for the above preparations. The reaction mixture was acidified after 12 hours and extracted with ether. From the ethereal extracts, sodium bicarbonate solution extracted an acid, which was isolated by acidification of the extracts and extraction with ether. On evaporation of the ether, the residue (29 g.) slowly solidified. It was very soluble in benzene and insoluble in light petroleum. Purification was best effected by dissolving the substance in methyl alcohol and cooling the solution in ice; the *acid ethyl* ester then separated in white needles, m. p. 126·5—127·5° (Found : C, 67·5; H, 7·5; equiv., 322. $C_{18}H_{24}O_5$ requires C, 67·5; H, 7·5%; equiv., 320). On crystallisation from acetic acid a second crystalline form, m. p. 110—111°, was obtained. The two forms are interconvertible. This substance is considered to be (III, R = C_6H_5). It yielded no ketonic derivatives, but gave a positive iodoform reaction.

The *methyl ethyl* ester separated readily when the sodium salt of the above monoethyl ester was shaken with methyl sulphate in aqueous methyl-alcoholic solution. It crystallised from aqueous methyl alcohol in shining plates, m. p. 103—104° (Found : C, 68·1; H, 7·7. $C_{19}H_{26}O_5$ requires C, 68·2; H, 7·8%).

*α-(γ'-Keto-α'-phenyl-*n*-butyl)adipic Acid* (III, R = C_6H_5; H for Et).—Saponification of either of the above esters with caustic alkali led to a mixture of two substances, which was separated only with the greatest difficulty by fractional crystallisation from dilute acetic acid and aqueous alcohol. The less soluble product crystallised ultimately in prisms of hexagonal outline, m. p. 173—174° (Found : C, 65·6; H, 6·8; equiv., 145. $C_{16}H_{20}O_5$ requires C, 65·6; H, 6·8%; equiv., 146). The more soluble portion was finally isolated as colourless prisms, m. p. 231—232° with evolution of gas (Found : C, 65·3; H, 7·1%; equiv., 145).

*Ethyl Hydrogen α-(γ'-Keto-α'-*p*-methoxyphenyl-*n*-butyl)adipate* (III, R = $C_6H_4{\cdot}OMe$).—Anisylideneacetone (9 g.) and ethyl *cyclo*pentanone-2-carboxylate (8 g.) gave, under conditions analogous to those above, a product from which sodium bicarbonate solution extracted acidic material (11 g.). This, recrystallised either from methyl alcohol or from light petroleum, separated in colourless matted needles, m. p. 121—122° (Found : C, 64·9; H, 7·4. $C_{19}H_{28}O_6$ requires C, 65·0; H, 7·4%). It was saponified to a mixture of isomerides as was the above analogue, but the mixture was not separated. In this condensation, as in that with styryl methyl ketone, the neutral portion of the product consisted of unchanged keto-ester, together with material of high and indefinite b. p., so contaminated with the polymerised ketone that nothing crystalline could be induced to separate.

*Condensation of Ethyl Potassio*cyclo*pentanone-2-carboxylate with Styryl Methyl Ketone in Benzene Medium.*—The potassio-derivative was prepared from potassium (8 g.) and ethyl *cyclo*pentanone-2-carboxylate (44 g.; 1·4 mols.) in benzene (150 c.c.), and to it was added, with ice-cooling, a solution of styryl methyl ketone (29 g.) in benzene (100 c.c.). The reaction mixture was left for 2 days in the cold, during which time the potassio-derivative went largely into solution, and then poured into dilute hydrochloric acid. The benzene layer was washed with sodium bicarbonate solution and an acidic substance (9 g.) was obtained which proved identical with that obtained by carrying out the reaction in alcoholic medium. The neutral benzene layer was dried, the benzene evaporated, and the residue distilled in a vacuum. There resulted a mixture of *cyclo*pentanonecarboxylic ester and styryl methyl ketone (43 g.) and a higher-boiling fraction which on redistillation gave a distillate (7 g.), b. p. 210—215°/4 mm. A very small residue of polymerised styryl methyl ketone remained in the flask. The higher-boiling material was treated with light petroleum and frozen for 12 hours at − 15°. Oil separated, but no crystallisation occurred. Partial crystallisation was induced, however, by adding a trace of benzene, when oily material dissolved. The crystals were collected and recrystallised from light petroleum (b. p. 75—95°), from which they separated again in prisms of rectangular outline, m. p. 88—89·5° (Found : C, 71·3; H, 7·3. $C_{18}H_{22}O_4$ requires C, 71·5; H, 7·6%).

A quantity (0·1 g.) of the pure crystals was dissolved in alcohol, a few drops of aqueous sodium hydroxide added, and the whole left over-night. On acidification with dilute hydrochloric acid, an acid separated, which was recrystallised from dilute acetic acid and proved (mixed m. p.) to be identical with the lower-melting form of (III, $R = C_6H_5$).

The author thanks Prof. R. Robinson, F.R.S., for his interest in this work.

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[*Received, August* 31*st*, 1936.]