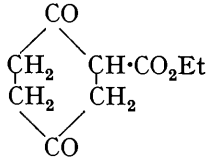
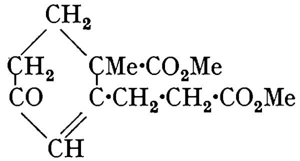
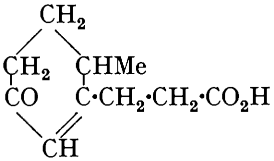
104. *Experiments on the Synthesis of Substances related to the Sterols. Part XXXVIII. Ethyl* cyclo*Hexane*-1 : 4-*dione-2-carboxylate and Other Intermediates.*

By Sir Robert Robinson and E. Seijo.

For several reasons a convenient synthesis of 2-keto-1 : 2 : 3 : 4-tetrahydrophenanthrenes and 2-keto-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydrophenanthrenes is required and one route would be to follow the method of Part III (J., 1935, 1288), replacing the dihydroresorcinol moiety of the molecule by *cyclo*hexane-1 : 4-dione. Attempts to introduce one β-arylethyl group into succinosuccinic ester were fruitless and therefore the substance (I) named in the title has been synthesised in the hope that it may prove more amenable to substitution processes.


(I.)

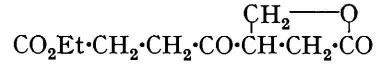

(II.)


(III.)

Condensation of methyl β-keto-α-methyladipate with δ-diethylaminobutan-β-one methiodide under the influence of sodium methoxide in pyridine solution afforded the *ester* (II) in small yield, but under slightly different conditions the product corresponded in composition to the *acid* (III).

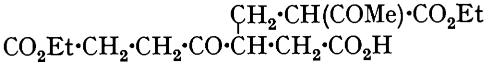
As already explained, we hope to extend the method of du Feu, McQuillin, and Robinson (J., 1937, 53) to 1-substituted 5-keto-8-methylhydrindanones, but have experienced difficulties in attempts to acquire suitable intermediates. An obvious alternative is to include the *cyclo*pentanone ring, not as such, but as the equivalent adipic acid structure. The unsaturated keto-ester (II) fulfils all requirements and would be a highly valuable starting point, but up to the present we have only succeeded in preparing it in about 8% yield and this is inadequate for the purpose in view. Although we have already covered a wide range of conditions, further attempts will be made to secure at least enough material to investigate the direction of condensation of its dihydro-derivative with α-diethylaminopentan-γ-one methiodide.

The Dieckmann ring-closure of γ-ketopimelic ester succeeded only when the keto-group was protected and we believe that *ethyl* cyclo*hexane*-1 : 4-*dione*-2-*carboxylate* (I) should prove a useful intermediate for several purposes. It is evident from preliminary work that the substance can be alkylated, but the best conditions have not yet been ascertained. The availability of γ-ketopimelic acid induced us to explore another line. Condensation of its ester with formaldehyde affords the *lactone* (IV), which is equivalent to a methylene ketone. It might condense with ethyl sodioacetoacetate, either through its carbonyl group or to give in the first instance the substance (V).



$$\begin{array}{l} \qquad\qquad\qquad\qquad\quad CH_2\text{——}O \\ CO_2Et\cdot CH_2\cdot CH_2\cdot CO\cdot CH\cdot CH_2\cdot CO \end{array}$$

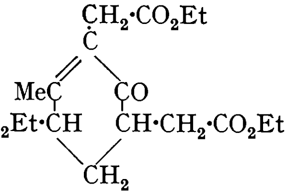
(IV.)



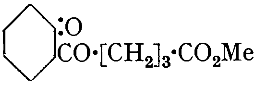
$$\begin{array}{l} \qquad\qquad\qquad\qquad\quad CH_2\cdot CH(COMe)\cdot CO_2Et \\ CO_2Et\cdot CH_2\cdot CH_2\cdot CO\cdot CH\cdot CH_2\cdot CO_2H \end{array}$$

(V.)

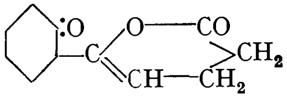
If this 1 : 5-diketone suffered cyclodehydration between the carbonyl of the pimelic acid chain and the methyl of the acetoacetate, the product would have been useful. A substance of the anticipated composition was obtained, but the resistance, to elimination by hydrolysis, offered by the carbethoxyl group of the acetoacetic ester component showed that the ring-closure went in the other possible direction, and the product, after esterification, was probably (VI).



(VI.)

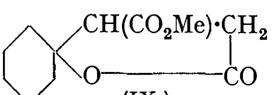


(VII.)



(VIII.)

The direction of condensation of *cyclo*hexanone with methyl glutarate differs from that with methyl succinate. In the former case a β-*diketone* (VII) is produced and this is converted by sulphuric acid into the *enol-lactone* (VIII). Our interest in the topic arose from the possibility of cyclodehydration of (VII) to a naphthalene derivative, but this has not been realised. Thinking that the hydrindane structure might be more readily produced in a similar fashion, we tried to prepare the lower homologue of (VII) by the use of methyl succinate. The product had the expected composition, appeared to solidify rather completely, and gave an intense ferric reaction. The purified solid, however, was not a β-diketone and on hydrolysis afforded cyclo*hexylidenesuccinic acid*. The diketone must be formed in small relative amount, but the main product in view of its neutrality and composition is the paraconic ester (IX) (cf. Stobbe, *J. pr. Chem.*, 1914, **89**, 329, 341, for the condensation of *cyclo*pentanone and active 3-methyl*cyclo*hexanone with ethyl succinate).



(IX.)

EXPERIMENTAL.

Ethyl cyclo*Hexane*-1 : 4-*dione*-2-*carboxylate* (I).—A mixture of ethyl γ-ketopimelate (46 g.) (Marckwald, *Ber.*, 1887, **20**, 2813; Volhard, *Annalen*, 1889, **253**, 235), ethyl orthoformate (32 g.), and acetyl chloride (2 c.c.) was kept for 12 hours, refluxed for 1 hour, and evaporated on the steam-bath under diminished pressure. The resulting keto-acetal could not be distilled without decomposition. It was dissolved in ether (50 c.c.), and dry sodium ethoxide (4·6 g. of sodium) gradually added with cooling and shaking; after 24 hours, ether and ice-cold dilute hydrochloric acid were added. The oil (32 g.) obtained from the ethereal layer had b. p. 119—125°/0·5 mm. and solidified on keeping. Analysis showed it to be a mixture of acetal and ketone (Found : C, 59·7; H, 7·3%). On shaking with water, isolation, and redistillation a colourless oil (25 g.), b. p. 116—120°/0·5 mm., was obtained and this did not crystallise (Found : C, 58·7; H, 7·0. $C_9H_{12}O_4$ requires C, 58·7; H, 6·6%). The substance gives an intense purple coloration with ferric chloride in alcoholic solution.

Alkylation experiments are still in progress. When β-phenylethyl bromide and alcoholic potassium ethoxide were used, a *product*, b. p. 175—185°/0·7 mm., was obtained (Found : C, 71·6; H, 7·0. $C_{17}H_{20}O_4$ requires C, 70·8; H, 7·0%). On hydrolysis this gave an acid forming colourless needles, m. p. 129—130° (1% low in carbon; equiv., 135). The methyl ester did not crystallise but afforded a 2 : 4-*dinitrophenylhydrazone*, which formed thick yellow prisms, m. p. 113—114°, from methyl alcohol (Found : N, 11·4. $C_{23}H_{26}O_8N_4$ requires N, 11·3%). Methylation yielded a product of comparable b. p. which gave a very feeble ferric reaction.

Hydrolysis. The keto-ester (10 g.) was heated in an autoclave with water (30 c.c.) at 190° for 8 hours. The filtered aqueous solution was saturated with ammonium sulphate and extracted with chloroform. The solid residue (4·5 g.), after evaporation of the solvent, was sublimed and afforded the pure 1 : 4-*cyclo*hexanedione. It crystallised from benzene–light petroleum in long, colourless needles, m. p. 77—78° (Found : C, 64·5; H, 7·3. Calc. for $C_6H_8O_2$: C, 64·3; H, 7·1%).

β-(β'-*Carbethoxypropionyl*)*butyrolactone* (IV).—A mixture of ethyl γ-ketopimelate (46 g.), paraformaldehyde (15 g.), concentrated hydrochloric acid (140 c.c.), and water (60 c.c.) was kept for 12 hours and then heated on the steam-bath for 8 hours. Evaporation under diminished pressure left a brown syrup, which was esterified by boiling with alcoholic sulphuric acid. On distillation ethyl ketopimelate (14 g., b. p. 140—150°/0·5 mm.) was recovered, followed by a fraction, b. p. 178—190°/0·5 mm.; redistilled, b. p. 179—183°/0·5 mm. (16 g.) (Found : C, 55·3, 55·7; H, 6·7, 6·8. $C_{10}H_{14}O_5$ requires C, 56·0; H, 6·5%). A much higher boiling fraction (decomp.) was not investigated.

The *semicarbazone* crystallised from aqueous alcohol in small colourless prisms, m. p. 171—173° (Found : N, 15·8. $C_{11}H_{17}O_5N_3$ requires N, 15·5%).

The 2 : 4-*dinitrophenylhydrazone* showed little tendency to crystallise but was eventually obtained in yellow needles, m. p. 148—152°, from ethyl acetate (Found : N, 14·5. $C_{16}H_{18}O_8N_4$ requires N, 14·2%). When methyl-alcoholic sulphuric acid was used for the esterification, the product had b. p. 166—170°/0·7 mm.

Ethyl 4-*Carbethoxy*-3-*methyl*-Δ^2-cyclo*hexen*-1-*one*-2 : 6-*diacetate* (VI).—A mixture of carbethoxypropionylbutyrolactone (21·4 g.), ethyl acetoacetate (15 g.), and alcoholic sodium ethoxide (2·4 g. of sodium in 50 c.c.) was refluxed for 2½ hours. The product, isolated in the known manner, was a hygroscopic mass that could not be distilled. It was hydrolysed by boiling with concentrated hydrochloric acid for 4 hours, the solution evaporated under diminished pressure, and the residue esterified with alcoholic sulphuric acid. On distillation two main fractions were obtained : (i) a colourless liquid, b. p. 145—180°/0·2 mm., with a marked odour of *cyclo*hexanone type. Redistillation gave (*a*) a colourless mobile liquid, b. p. 150—151°/0·2 mm., possessing an intense odour (Found : C, 62·2; H, 7·7%), (*b*) a colourless liquid with a faint odour, b. p. 155—156°/0·2 mm. (Found : C, 62·0; H, 7·6%), (*c*) a yellowish liquid with a faint odour, b. p. 161—163°/0·2 mm. (Found : C, 61·6; H, 7·5%).

The second main fraction (ii) was a thick, yellowish oil, b. p. 180—199°/0·2 mm. Redistilled, it had b. p. 189—191°/0·15 mm. (Found : C, 61·0; H, 7·2. $C_{18}H_{26}O_7$ requires C, 61·0; H, 7·3%). There was a considerable undistillable residue. It is clear from the b. p.'s of the products that condensation has occurred and from the analyses that the three carbethoxyl groups of the components are intact. The linking of ethyl acetoacetate and ethyl ketopimelate by means of one methylene group gives $C_{18}H_{28}O_8$ and therefore we have assumed cyclodehydration in such a manner as to explain the retention of the carbethoxyl group of the ethyl acetoacetate. Various combinations of condensations and elimination of groups such as carbethoxyl, ethyl, and acetyl fail to supply an alternative explanation. The lower-boiling component may, however, be derived from $C_{18}H_{28}O_8$ by loss of an acetyl group and dehydration ($C_{16}H_{24}O_6$ requires C, 61·5; H, 7·7%). A structure conforming with this hypothesis is, for example, ethyl γ-carboxymethylene-β-methylenepimelate, or an isomeride with a different position of one of the double bonds.

β-(β'-*Carboxyethyl*)*butyrolactone*.—The lactone of γ-hydroxypimelic acid has been obtained by Willstätter (*Ber*., 1898, **31**, 1551) from piperylenedicarboxylic acid and by Leuchs and Nagel (*Ber*., 1922, **55**, 3950) by malonic ester synthesis from δ-chloro-γ-valerolactone. It does not appear to have been made by the simpler direct method.

Sodium amalgam (200 g. of 2%) was gradually added to γ-ketopimelic acid (4 g.) and water (30 c.c.). When the evolution of hydrogen ceased, the solution was acidified with hydrochloric acid and concentrated under diminished pressure until salt separated; it was then extracted with chloroform. The residue after removal of the solvent was crystallised from benzene, giving 2 g. of m. p. 79—82° (Found : C, 53·4; H, 6·4. Calc. for $C_7H_{10}O_4$: C, 53·2; H, 6·3%).

Methyl δ : 2-*Diketo*-δ-cyclo*hexylvalerate* (VII).—The following experiment was carried out by Dr. F. Litvan. A vigorous reaction occurred between *cyclo*hexanone (25 g.), methyl glutarate

(32 g.), and sodium powder (7·8 g.) in ice-cold benzene (50 c.c.). After 3 hours in the cooling bath, the mixture was kept for 18 hours at room temperature and finally refluxed for 2 hours. Water, dilute acid, and ether were added, and the product isolated from the ethereal solution. After a fraction, b. p. 138—160°/2 mm., the main product distilled at 160—170°/2 mm. (14·8 g. of a thick yellow oil); redistilled, b. p. 132—143°/0·2 mm., $n_D^{18°}$ 1·4900 (11·8 g.) (Found : C, 63·2; H, 8·1. $C_{12}H_{18}O_4$ requires C, 63·7; H, 7·9%). The *diketone* gave a purple coloration with alcoholic ferric chloride. The condensation product with 2 : 4-dinitrophenylhydrazine crystallised from toluene in orange-yellow needles, m. p. 242°, raised to 247° by recrystallisation from dioxan (Found : N, 21·4, 21·5 in a specimen carefully freed from dinitrophenylhydrazine. The theory for the bisdinitrophenylhydrazone is N, 19·4%). The action of sulphuric acid on the diketone at — 10° gave a neutral substance, b. p. 134—144°/0·27 mm., $n_D^{18°}$ 1·4990. The 2 : 4-dinitrophenylhydrazone had m. p. 189° (Found : N, 14·5%).

Enol Lactone of δ : 2-*Diketo*-δ-cyclo*hexylvaleric Acid* (VIII).—The preliminary observation last mentioned was reinvestigated in order to determine whether ring-closure to a naphthalene derivative had occurred. Methyl diketo*cyclo*hexylvalerate (10 g.) was slowly added to concentrated sulphuric acid (15 c.c.) cooled in ice. After 15 minutes the solution was gently heated on the steam-bath until a faint odour of sulphur dioxide was perceptible. The mixture was cooled and added to ice, and the neutral product isolated by means of ether. It was obtained as a colourless liquid (4 g.), b. p. 120—123°/0·1 mm. (Found : C, 67·5, 67·6; H, 7·5, 7·2. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·2%). This *substance* gave a reddish-brown coloration with alcoholic ferric chloride. On boiling with aqueous sodium hydroxide it gave *cyclo*hexanone as one of the products of hydrolysis.

Condensation of cyclo*Hexanone with Methyl Succinate*.—This was carried out in ice-cold methyl-alcoholic solution by the use of equimolecular proportions of the components and of sodium methoxide. After 2 days the mixture was acidified, and the product isolated by means of ether. Although it was certainly a mixture, a large part of the viscid, dark-coloured oil crystallised. On distillation it was obtained as a colourless, viscid liquid, b. p. 145—150°/0·5 mm. (145°/0·5 mm. on redistillation), that slowly solidified (Found : C, 62·4; H, 7·4. $C_{11}H_{16}O_4$ requires C, 62·3; H, 7·6%). The crystals, freed from oil, separated from light petroleum (b. p. 60—80°) in colourless needles, m. p. 73·5—74·5°. The crystallised product gave no ferric reaction but the distilled material, never quite free from oil, gave an intense purple coloration with alcoholic ferric chloride. We consider that the distilled material contains methyl γ : 2-diketo-γ-*cyclo*hexylbutyrate (analogous β-diketone to that obtained from methyl glutarate) and that the solid part is the isomeric *methyl pentamethyleneparaconate* (IX). This is the γ-lactone corresponding to the unsaturated acid, methyl hydrogen *cyclo*hexylidenesuccinate.

When the alcoholic solution of the distilled product, containing a drop of ferric chloride, was kept, crystals separated. The substance crystallised from light petroleum in colourless needles, m. p. 99—101° (Found : C, 62·6; H, 7·3%). The titration (equiv., 196) of a very small specimen showed this to be the above-mentioned monocarboxylic *acid*. Hydrolysis of the distilled product with aqueous sodium hydroxide or cold concentrated hydrochloric acid afforded cyclo*hexylidenesuccinic acid* in colourless prisms, m. p. 186—187° (Found : C, 60·6; H, 7·1. $C_{10}H_{14}O_4$ requires C, 60·6; H, 7·1%). The equivalent (96) showed the acid to be dibasic (calc., 99). All the substances mentioned in this section afforded *cyclo*hexanone on oxidation with alkaline permanganate. Before the real direction of the condensation was understood, attempts were made to convert the product into a lactone analogous to (VIII), but without success.

Condensation of Methyl β-*Keto*-α-*methyladipate with* δ-*Diethylaminobutan*-β-*one Methiodide*.—Bardhan's method (J., 1936, 1848) for the preparation of methyl β-ketoadipate was adapted by the use of methyl sodio-α-acetylpropionate. The condensation of the latter with β-carbomethoxypropionyl chloride in ethereal solution gave a 60—65% yield of methyl β-keto-α-acetyl-α-methyladipate (b. p. 135—137°/0·5 mm.). Hydrolysis with dry ammonia in ether gave an excellent yield of methyl β-keto-α-methyladipate, b. p. 106—108°/0·3 mm.

Methyl ketomethyladipate (20·2 g.) and then (slowly) diethylaminobutanone methiodide (28 g.) in pyridine (20 c.c.) were added to an ice-cooled solution of anhydrous sodium methoxide (2·5 g. of sodium) in pyridine (30 c.c.). After 2 hours in the cooling bath, the mixture was gently heated on the steam-bath for 2 hours, cooled, and added to ice-cold dilute hydrochloric acid, and the product isolated by means of ether. Fractionation gave unchanged keto-ester and 2·5 g. of a pale yellow oil, b. p. 164°/0·3 mm. (Found : C, 61·3; H, 7·3. $C_{13}H_{18}O_5$ requires C, 61·4; H, 7·1%). The substance gave no ferric reaction and was doubtless the expected product, namely, 3-β-*carbomethoxyethyl*-4-*carbomethoxy*-4-*methyl*-Δ^2-cyclo*hexen*-1-*one* (II). Many efforts to improve the yield of this important intermediate were made but without success.

When the reaction mixture as above was refluxed for 8 hours, the carbomethoxy-group in position 4 was eliminated and the remaining ester group was hydrolysed. The product (2·4 g.) had b. p. 150—155°/0·5 mm. and partly crystallised. The drained solid crystallised from light petroleum in colourless, irregular prisms, m. p. 80—83° (Found: C, 65·7; H, 7·6. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·7%). The substance dissolved to some extent in water and was freely soluble in aqueous alkaline solutions. It is probably 3-β-*carboxyethyl*-4-*methyl*-Δ^2-cyclo*hexen*-1-*one* (III).

Attempts to use β-chloroethyl methyl ketone in the above type of process and to prepare a Mannich base from the ketoester were abandoned in view of the very poor yields obtained.

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