198. *Experiments bearing on the Synthesis of Cortisone. Part I.*[*] *Some* cyclo*Pentenone Derivatives.*

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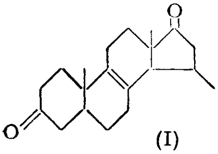
3-Methyl*cyclo*pent-2-enone has been prepared by the cyclisation of acetonylacetone. A reconsideration of Goss and Ingold's supposed bi*cyclo*pentane derivatives (*J.*, 1928, 1268) has suggested that these are *cyclo*pentadienes or *cyclo*pentenones and the assumption of a bridged ring is unnecessary. For example, in the case of 2-methyl-4-keto*cyclo*pent-2-ene-1-carboxylic acid, the monocyclic structure is the only one consistent with the chemical and physical evidence.

ALTHOUGH the total synthesis of cortisone has already been achieved by two distinct routes [(*a*) Cardwell, Cornforth, Duff, Holtermann, and Robinson, *Chem. and Ind.*, 1951, 389; Rosenkrantz, Pataki, and Djerassi, *J. Amer. Chem. Soc.*, 1951, **73**, 4057; (*b*) Woodward, Sondheimer, and Taub, *J. Amer. Chem. Soc.*, 1951, **73**, 4057], the methods adopted have been so tortuous that these accomplishments have only an indirect value in relation to the preparation of the hormone by a feasible practical synthesis. It is therefore still necessary to investigate all possible synthetic routes in the hope that the production of cortisone may thereby be facilitated.



(I)

Little use has so far been made of the Diels–Alder reaction in the synthesis of sterol derivatives from carbocyclic intermediates which later constitute the intact D-ring. The brilliant recent work of Woodward and his collaborators (*loc. cit.*) is excluded from this category by definition, since ring D as set up in the Diels–Alder reaction was later broken and then reconstituted in a different form. Experiments so far reported include the work of Dane and her collaborators (*Annalen*, 1939, **537**, 246, and earlier papers) on the addition of 2-methyl*cyclo*pent-2-ene-1 : 5-dione to 1 : 2-dihydro-7-methoxy-4-vinylnaphthalene, and that of Nazarov and Bergel'son (*Zhur. Obschei. Chim.*, 1950, **20**, 648; *Chem. Abs.*, 1950, **44**, 8913) who showed that 2 : 4-dimethyl*cyclo*pent-2-enone reacted with Δ^1-octahydro-6-keto-9-methyl-1-vinylnaphthalene to give a compound considered to be (I), although alternative structures were not excluded and one of these appears the more probable on theoretical grounds.

In this type of reaction it is desirable that the *cyclo*pentene derivative should be substituted in such a way that in the resulting tetracyclic molecule it will (*a*) provide the angular $C_{(13)}$-methyl group, (*b*) enable manipulation of substituents in the $C_{(17)}$-position to be carried out, and (*c*) facilitate the conversion of the *cis*-C–D-ring-junction produced in the reaction into a *trans*-linkage. The use of a substituted diene designed strongly to

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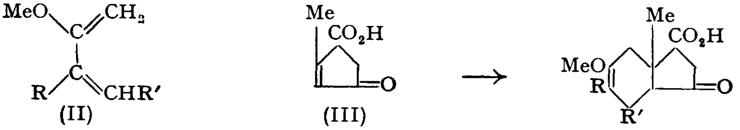
[*] A preliminary account of an investigation in this field, which it is hoped may later be published as a Part of the present series, has already appeared (Friedmann and Robinson, *Chem. and Ind.*, 1951, 777).

orient the dienophile during the reaction is also desirable. The reaction between methoxybutadienes of type (II) and 4-keto-2-methyl*cyclo*pent-2-ene-1-carboxylic acid (III), or a

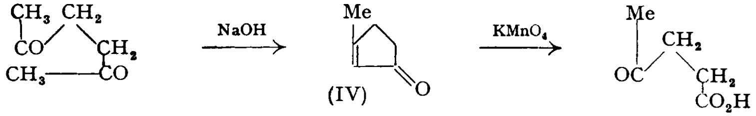


(II) (III)

derivative of the acid, which has the above desiderata for the dienophile, was therefore contemplated. As shown in the sequel it transpires that (III) is already known and we hope to use it for the purpose stated herein. It seems probable that the conjugation of the ring carbonyl group with the double bond will be paramount and will impede movement of the double bond towards the carboxyl (or ester) group. An example of the expected reaction is indicated in the formula below, given as a product from (III).

A preliminary investigation of the reaction between 3-methyl*cyclo*pent-2-enone and 2-methoxybutadiene will be reported in a subsequent communication.

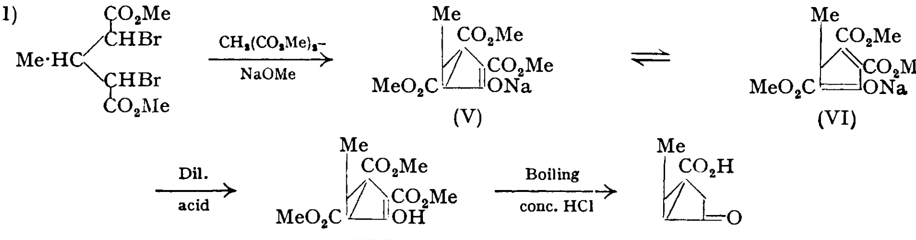
Experiments were first directed towards the synthesis of 3-methyl*cyclo*pent-2-enone (IV) and it was found that this compound could be prepared from acetonylacetone by boiling 1% aqueous sodium hydroxide. The conditions for this reaction are critical. Too little alkali gives a mixture of acetonylacetone and the *cyclo*pentenone which is difficult to separate, whereas prolonged boiling or too much alkali increases the production of tar. Blaise (*Compt. rend.*, 1914, **158**, 708) has stated that it is impossible to isolate any of the *cyclo*pentenone from this reaction, the product being a red resin, but the conditions he employed were probably too drastic. Similar cyclisations of unsymmetrical diketones, in which the carbonyl groups may react with either a CH_3 or a CH_2 group and appear to favour the latter course, have been reported by Hunsdiecker (U.S.P. 2 387 587; *Chem. Abs.*, 1946, **40**, 3131). The ketone (IV) was characterised as the oxime, semicarbazone,



(IV)

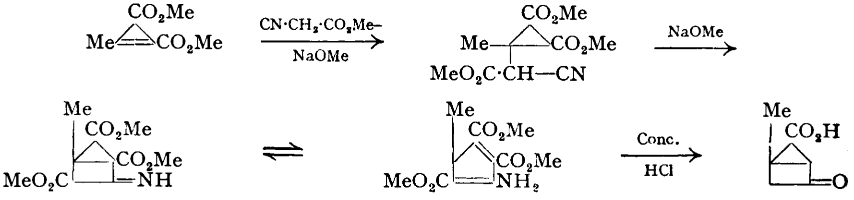
and 2 : 4-dinitrophenylhydrazone. Its structure was confirmed by oxidation to lævulic acid, isolated as the 2 : 4-dinitrophenylhydrazone.

(1)



(V) (VI) (VII) (VIII)

(2)

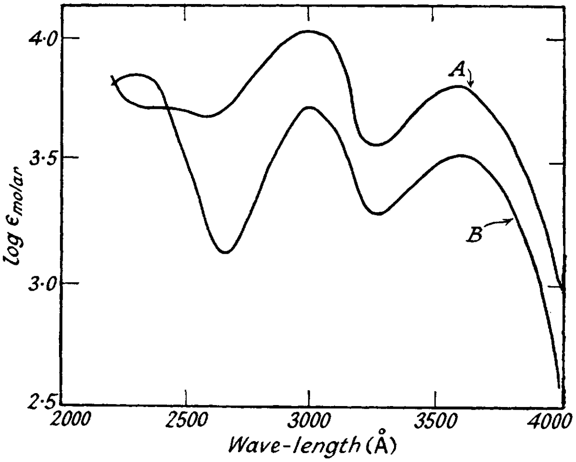


(IX) (X) (XI)

Godchot and Taboury (*Compt. rend.*, 1913, **156**, 1780) have reported the preparation of (IV) from 3-methyl*cyclo*pentanone by chlorination to 2-chloro-3-methyl*cyclo*pentanone followed by removal of hydrogen chloride. No analytical data were given, either for their ketone, the structure of which appeared to be supported by degradation experiments, or for its oxime, m. p. 127°, or semicarbazone, m. p. 230°. As the melting points of these derivatives do not agree with those reported here, and as the refractive index of authentic 3-methyl*cyclo*pent-2-enone (n_D^{20} 1·4893) is much higher than that of Godchot and Taboury's ketone (n_D^{26} 1·4714) it is probable that the latter material was a mixture, one constituent of which may have been 3-methyl*cyclo*pentanone.

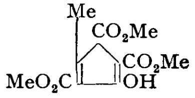
4-Keto-2-methyl*cyclo*pent-2-ene-1-carboxylic acid (III) was first prepared by Goss and Ingold (*J.*, 1928, 1268) although they failed to recognise, or at least to emphasise, its correct structure. It was obtained from two series of reactions, outlined on p. 1128 in the original formulation. Goss and Ingold found that the end products of both series of reactions, although formulated as (VIII) and (XI) respectively, were identical. Nevertheless the compound in question appears to be neither (VIII) nor (XI), but 4-keto-2-methyl*cyclo*pent-2-ene-1-carboxylic acid (III). The *cyclo*pentenone structure for this compound was certainly mentioned as an alternative in parentheses in the experimental section of Goss and Ingold's paper, but the possibility that most of the compounds were in fact *cyclo*pentenone derivatives was kept in the background and attention was focused on the bicyclic structure. The reported oxidation of (IX or X) with hydrogen peroxide in the presence of ferrous sulphate to α- and β-methylglutaconic acids and β-acetylacrylic acid can be explained on the *cyclo*pentadieneamine formulation (X) but a *cyclo*propane derivative might well have arisen from the oxidation of (IX).

Methyl αα′-dibromo-β-methylglutarate was found to react with methyl malonate in the presence of sodium methoxide as described by Goss and Ingold, to give the sodium salt of methyl 3-hydroxy-5-methyl*cyclo*pentadiene-1 : 2 : 4-tricarboxylate (sodium salt of XII or XIII). The free hydroxy-compound, prepared from the salt with cold dilute mineral acid, distilled to give a pale yellow oil. Its absorption spectrum in methanol and that of the aqueous sodium salt indicate conjugation of a high order resembling that of an aromatic system (cf. Fig.). This does not support structures (VII) and (V), which are unlikely in any case on stereochemical grounds, for these compounds. The similarity of two curves also indicates that the free acid consists largely of the hydroxy-compound (XII and/or XIII).

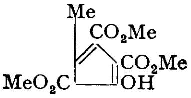


A, *The sodium salt of* (XII) *and/or* (XIII) *in water.*

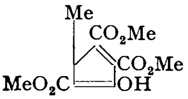
B, *Methyl* 3-*hydroxy*-5-*methyl*cyclo-*pentadiene*-1 : 2 : 4-*tricarboxylate* (XII *and/or* XIII) *in methanol.*



(XII)



(XIII)



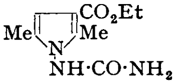
(XIV)

This is also in accord with the immediate deep blue coloration with ferric chloride, the non-formation of ketonic derivatives, and the vigorous reaction with aqueous potassium hydrogen carbonate. The infra-red absorption of the hydroxy-compound indicates the presence of a small amount of an αβ-unsaturated carbonyl group in a five-membered ring, with a large proportion of an unconjugated ester group. This suggests that the substance contains only small amounts of ketonic tautomers (in agreement with the ultra-violet absorption measurements) and of structure (XIV); the larger proportion of the material therefore consists of (XII) and/or (XIII).

Decomposition of the sodium salt with concentrated hydrochloric acid gave 4-keto-2-methyl*cyclo*pent-2-ene-1-carboxylic acid (III) characterised as the 2 : 4-dinitrophenylhydrazone. The ethyl ester was prepared from the acid with ethanolic hydrogen chloride and characterised as the semicarbazone and 2 : 4-dinitrophenylhydrazone.

An attempt to make the semicarbazone of the acid in hot aqueous solution caused decarboxylation, and 3-methyl*cyclo*pent-2-enone semicarbazone was isolated from the reaction. Decarboxylation of the acid to the free ketone, identified by its physical constants and conversion into its 2 : 4-dinitrophenylhydrazone, was also effected by hot alcoholic potassium hydroxide (cf. Stork and Burgstahler, *J. Amer. Chem. Soc.*, 1951, **73**, 3544). These experiments show conclusively that the acid has a *cyclo*pentenone structure. As the compound gives no colour with ferric chloride and is so stable to acid, the carboxyl group, considered as a substituent into the methyl*cyclo*pentenone, is unlikely to be present at position 2 or 5, and is therefore probably at position 4. This is supported by the infra-red absorption spectra of the acid and the ethyl ester, which are not consistent with any other structure. The infra-red absorption of the latter ester is also very similar to that of Hagemann's ethyl 4-keto-2-methyl*cyclo*hex-2-ene-1-carboxylate (*Ber.*, 1893, **26**, 879; cf. Schwenk and Bloch, *J. Amer. Chem. Soc.*, 1942, **64**, 3050), which was examined for comparison (Experimental section). The ultra-violet absorption of the *cyclo*pentanonecarboxylic ester in methanol showed $\lambda_{\text{max.}}$ 2300 (ε 12 150) and this confirms the *cyclo*-2-enone structure. It is very similar to the spectrum of Hagemann's ester in methanol ($\lambda_{\text{max.}}$ 2300; ε 12 900).

Various attempts were made to synthesise 4-keto-2-methyl*cyclo*pent-2-ene-1-carboxylic acid or ester from ethyl α-acetyl-lævulate, which was best prepared from bromoacetone and ethyl sodio-acetoacetate by Stevenson and Johnson's method (*J. Amer. Chem. Soc.*, 1937, **59**, 2525). Goldberg and Muller (*Helv. Chim. Acta*, 1938, **21**, 1699) report that ethyl α-acetyl-β-methyl-lævulate cyclised to ethyl 4-keto-2 : 5-dimethyl*cyclo*pent-2-ene-1-carboxylate when kept with warm water for 3 weeks. Ethyl α-acetyl-lævulate was recovered largely unchanged from this operation, and also from treatment with hot piperidine acetate, piperidine and pyridine in boiling benzene, or with ethereal *N*-ethylanilinomagnesium bromide which was apparently decomposed by the enolic form of the ester. Cold aqueous calcium chloride likewise had no effect, but boiling aqueous sodium acetate caused slow hydrolysis to acetonylacetone. Aqueous sodium hydroxide under a variety of conditions, including those used for the cyclisation of acetonylacetone, merely caused hydrolysis to the latter compound which subsequently cyclised to 3-methyl*cyclo*pent-2-enone if the conditions were vigorous enough. Hot ethanolic sodium ethoxide also gave some acetonylacetone as well as much ethyl lævulate produced by "acid hydrolysis" of the β-keto-ester (cf. Hunsdiecker, *Ber.*, 1942, **75**, 455). Cold ethanolic sodium ethoxide however gave an excellent yield of ethyl 2 : 5-dimethylfuran-3-carboxylate, the identity of which was confirmed by hydrolysis to the crystalline carboxylic acid. In this connexion it is of interest that Willstätter and Clarke (*Ber.*, 1914, **47**, 291) found that in the reaction of methyl iodide and sodium ethoxide with ethyl α-acetyl-lævulate there were indications of some cyclisation to a *cyclo*pentenone derivative.



(XV)

Ethyl α-acetyl-lævulate is reported by Borsche and Spannagel (*Annalen*, 1903, **331**, 315) to react with semicarbazide to give a colourless solid, which they considered to be a pyridiazine. The ultra-violet absorption spectrum of this compound is stated to be inconsistent with this formulation by Korschun and Roll (*Bull. Soc. chim.*, 1923, [iv], **33**, 59) who suggested that the compound was (XV). They did not mention that it might also be the isomeric 4- or 5-carbethoxy-derivative of 3-methyl*cyclo*pent-2-enone semicarbazones. The latter structures have now been excluded. The compound is not identical with the semicarbazone of ethyl 4-keto-2-methyl*cyclo*pent-2-ene-1-carboxylate. It was not decomposed by pyruvic acid in boiling aqueous acetic acid and did not give any indication of the formation of 3-methyl*cyclo*pent-2-enone or of 2-methylbut-1-ene-1 : 4-dicarboxylic acid on decomposition with hot concentrated hydrochloric acid. The pyrrole structure (XV) is supported by the observations that the compound gives a red Ehrlich reaction, has an infra-red absorption spectrum very similar to that of ethyl 2 : 5-dimethylfuran-3-carboxylate in the 11—12-μ region, and gives a *C*-methyl value in the Kuhn–Roth determination which suggests the presence of more than two *C*-methyl groups in the molecule.

EXPERIMENTAL

3-*Methyl*cyclo*pent*-2-*enone* (IV).—Acetonylacetone (120 g.) was rapidly added to a boiling solution of sodium hydroxide (10 g.) in water (1 l.). After refluxing for 15 minutes the dark brown solution was quickly cooled to room temperature, saturated with salt, and extracted three times with ether (500, 250, and 250 c.c.). The extracts were washed with water (3 × 15 c.c.), dried, and evaporated. On distillation the residual dark brown oil gave the ketone (42·4 g., 42%) as a colourless liquid, b. p. 74—76°/16 mm., n_D^{20} 1·4818. The ketone could not be obtained analytically pure by repeated distillation but was purified *via* the oxime or semicarbazone, both of which were decomposed by pyruvic acid in aqueous acetic acid under the conditions of Hershberg (*J. Org. Chem.*, 1948, **13**, 542). The *ketone* thus obtained had b. p. 74°/15 mm., n_D^{20} 1·4893, and $\lambda_{max.}$ 2250 (ε 18 150) in methanol (Found : C, 74·4; H, 8·2; *C*-Me, 12·6. C_6H_8O requires C, 75·0; H, 8·3; *C*-Me, 15·6%). It is miscible with water. The *oxime* crystallised from ethanol–water (2 : 3 by volume) in colourless prisms, m. p. 144° (Found : C, 65·1; H, 8·0; N, 12·4. C_6H_9ON requires C, 64·9; H, 8·1; N, 12·6%). The m. p. of the 2 : 4-*dinitrophenylhydrazone*, m. p. 180—181° (Found : N, 20·0. $C_{12}H_{12}O_4N_4$ requires N, 20·3%), and semicarbazone, m. p. 220—221°, were unchanged by the addition of authentic samples prepared from ethyl α-acetyl-lævulate.

Oxidation. The ketone (0·24 g.) was added to a cold solution of potassium permanganate (0·83 g.) in water (23 c.c.), causing a vigorous reaction. The mixture was strongly cooled and after the addition of excess of permanganate was clarified by sulphur dioxide. The excess of sulphur dioxide was removed on a stream of air, and the solution treated with a hot solution of 2 : 4-dinitrophenylhydrazine (0·5 g.) in 2N-sulphuric acid (70 c.c.). A yellow precipitate 0·57 g., 77%) of lævulic acid 2 : 4-dinitrophenylhydrazone immediately formed. After one crystallisation from methanol it had m. p. 203—204°, alone or mixed with an authentic specimen.

Methyl 3-*Hydroxy*-5-*methyl*cyclo*pentadiene*-1 : 2 : 4-*tricarboxylate* (XII or XIII).—The sodium salt of this compound was prepared according to Goss and Ingold (*loc. cit.*) and crystallised from methanol in pale yellow needles m. p. 265° (decomp.) (Found : Na, 7·85. Calc. for $C_{12}H_{13}O_7Na$: Na 7·9%). On treatment with cold dilute sulphuric acid this salt gave the free hydroxy-ester (XII or XIII) which was collected with ether and distilled as a pale yellow oil, b. p. 175—180°/2 mm., n_D^{17} 1·4892 (Found : C, 53·7; H, 5·5; OMe, 33·2; *C*-Me, 4·7%; *M*, cryoscopic in camphor, 206. Calc. for $C_{12}H_{14}O_7$: C, 53·3; H, 5·2; 3OMe, 34·4; *C*-Me, 5·6%; *M*, 270). The infra-red absorption spectrum (film) showed maxima at 2·75 (OH), 2·89 (OH), 5·75 (unconjugated CO_2Me), 5·79 (conjugated CO_2Me), and 6·12 μ (conjugated C=C). There was a shoulder in the curve at 5·94 μ indicating the presence of a small amount of an αβ-unsaturated five-membered-ring carbonyl compound.

4-*Keto*-2-*methyl*cyclo*pent*-2-*ene*-1-*carboxylic Acid* (III).—The sodium derivative of methyl 3-hydroxy-5-methyl*cyclo*pentadiene-1 : 2 : 4-tricarboxylate (17·2 g.) was refluxed with concentrated hydrochloric acid (85 c.c.; *d* 1·16) for 1 hour. Much carbon dioxide was evolved and, after cooling, the brown solution was repeatedly extracted with ether (8 × 50 c.c.). The extracts were washed with saturated aqueous sodium chloride and dried. On evaporation the acid was obtained as a pale brown crystalline mass (4·6 g., 49%). The *monohydrate* separated from ether or light petroleum (b. p. 100—120°) in almost colourless needles, m. p. 60° (Found : C, 53·6; H, 6·3; *C*-Me, 6·9%; equiv., 160. $C_7H_8O_3,H_2O$ requires C, 53·2; H, 6·3; *C*-Me, 9·5%; equiv., 158). Goss and Ingold (*loc. cit.*) report m. p. 60° and analytical data for the anhydrous acid, but complete dehydration of our monohydrate was not effected by drying at 56° *in vacuo* over phosphoric anhydride. The infra-red absorption spectrum showed maxima at 2·86 (OH), 2·94 (OH), 3·88 (bonded OH), 5·85 (conjugated CO_2H), 5·95 (αβ-unsaturated five-membered-ring carbonyl) and 6·19 μ (conjugated C=C). The 2 : 4-*dinitrophenylhydrazone*, which was soluble in aqueous potassium hydrogen carbonate, was prepared from the acid and a cold solution of the reagent. It separated from dioxan in very dark yellow prisms, m. p. 227—229° (decomp., with darkening *ca.* 215°) (Found : C, 49·1; H, 3·4. $C_{13}H_{12}O_6N_4$ requires C, 48·7; H, 3·7%).

Ethyl ester. A refluxing solution of the acid (III) (0·5 g.) in dry ethanol (20 c.c.) was saturated with hydrogen chloride. Boiling was continued for 3·5 hours after which most of the solvent was removed *in vacuo.* The residual oil was treated with excess of aqueous potassium hydrogen carbonate (20%) and the *ester* collected with ether. It was a pale yellow oil (0·35 g., 66%), b. p. 127—130° (bath-temp.)/1 mm., n_D^{18} 1·4952 (Found: C, 64·1; H, 7·2. $C_9H_{12}O_3$ requires C, 64·2; H, 7·1%). It was soluble in water and gave no colour with ferric chloride. The infra-red absorption spectrum (film) showed maxima at 2·78 (OH), 2·83 (OH), 5·74 (unconjugated CO_2Et), 5·83 (αβ-unsaturated five-membered-ring ketone and at 6·13 μ (conjugated C=C). There was no band between 10·2 and 10·5 μ. The infra-red absorption spectrum (film) of Hagemann's ester was very similar and showed maxima at 2·90 (OH), 3·00 (OH), 5·77 (unconjugated CO_2Et), 5·97 (αβ-unsaturated six-membered-ring ketone), and 6·12 (conjugated C=C). We are obliged to Mr. C. A. Finch for a specimen of Hagemann's ester. The *semicarbazone* crystallised from water containing a little ethanol in colourless prisms, m. p. 220° (decomp.) (Found: C, 53·7; H, 6·7; N, 18·7. $C_{10}H_{15}O_3N_3$ requires C, 53·3; H, 6·7; N, 18·7%). The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in orange red needles, m. p. 186° (Found: C, 51·5; H, 4·6; N, 15·8. $C_{15}H_{16}O_6N_4$ requires C, 51·7; H, 4·6; N, 16·1%).

Decarboxylation. (i) A solution of the acid (0·5 g.) and potassium hydroxide (0·4 g.) in ethanol (10 c.c.) was refluxed for 17 hours. Most of the ethanol was then removed *in vacuo* and the residual liquid diluted with water. After saturation with salt the mixture was repeatedly extracted with ether. Distillation of the dried extract gave 3-methyl*cyclo*pent-2-enone as a colourless oil, b. p. 74—80° (bath-temp.)/16 mm., n_D^{20} 1·4884. It was characterised as the 2 : 4-dinitrophenylhydrazone which after one crystallisation from *n*-propanol had m. p. 181° unchanged by the addition of an authentic specimen (Found: C, 51·8; H, 4·3; N, 20·4%).

(ii) Carbon dioxide was evolved when an attempt was made to convert the keto*cyclo*pentenecarboxylic acid into its semicarbazone with hot aqueous sodium acetate and semicarbazide hydrochloride. After the mixture had cooled the white precipitate of 3-methyl*cyclo*pent-2-enone semicarbazone was collected. It did not react with aqueous potassium hydrogen carbonate and crystallised from ethanol in almost colourless plates, m. p. 217° alone or mixed with an authentic specimen (Found: C, 55·0; H, 7·0%).

The Hydrolysis and Cyclisation Reactions of Ethyl α-Acetyl-lævulate.—(i) *With sodium acetate.* The ester (15·0 g.) was refluxed with a solution of sodium acetate (20 g.) in water (100 c.c.) for 16 hours. After cooling, the solution was repeatedly extracted with ether, the extracts being washed with brine and dried. No keto*cyclo*pentenecarboxylic acid could be isolated from the aqueous layer. On distillation the ethereal solution gave acetonylacetone (5·25 g., 57%), b. p. 77—85°/14 mm., identified as the bis-2 : 4-dinitrophenylhydrazone, m. p. 258° (decomp.), and unchanged ester (2·8 g., 19%), b. p. 128—130°/14 mm.

(ii) *With semicarbazide.* A white precipitate of ethyl 2 : 5-dimethyl-1-ureidopyrrole-3-carboxylate was immediately formed when ethyl α-acetyl-lævulate (10·0 g.) was added to a hot solution of semicarbazide hydrochloride (12·0 g.) and sodium acetate (9·0 g.) in water (100 c.c.). After 20 minutes on a steam-bath the mixture was cooled and the pyrrole (10·3 g., 85%) collected, washed with water, and dried. It crystallised from aqueous ethanol in colourless needles, m. p. 229—230° (Found: C, 53·5; H, 6·8; N, 18·5; OEt, 21·8; *C*-Me, 14·0. Calc. for $C_{10}H_{15}O_3N_3$: C, 53·3; H, 6·7; N, 18·7; OEt, 20·0; 3*C*-Me, 20·0%). Borsche and Spannagel (*loc. cit.*) give m. p. 230°. An unstable crystalline modification, m. p. 220°, occasionally separated in short, colourless prisms from the same solvent (Found: C, 53·1; H, 6·8; N, 18·6; OEt, 19·3%); it had the same infra-red spectrum as the higher-melting material, and a mixture of the two melted sharply at 228°. Admixture with ethyl 4-keto-2-methyl*cyclo*pent-2-ene-1-carboxylate semicarbazone depressed the m. p. to 195—200°.

(iii) *With aqueous sodium hydroxide.* (*a*) The ester (5·0 g.) was refluxed with a solution of sodium hydroxide (2·0 g.) in water (50 c.c.) for 12 hours. After cooling, the solution was repeatedly extracted with ether. No acidic material could be isolated from the aqueous layer. The ethereal extracts were washed with water, dried, and distilled, giving 3-methyl*cyclo*pent-2-enone (0·7 g., 27%) as a colourless oil, b. p. 83—85° (bath-temp.)/18 mm., n_D^{20} 1·4878. The 2 : 4-dinitrophenylhydrazone separated from ethyl acetate or *n*-propanol in orange-red needles, m. p. 181° (Found: C, 52·4; H, 4·3; N, 20·1. $C_{12}H_{12}O_4N_4$ requires C, 52·2; H, 4·3; N, 20·3%). The *semicarbazone* separated from ethanol in colourless plates, m. p. 220—221° (Found: C, 54·9; H, 6·9. $C_7H_{11}ON_3$ requires C, 54·9; H, 7·2%).

(*b*) The ester (10·0 g.) was added to a boiling solution of sodium hydroxide (1·0 g.) in water (100 c.c.) and refluxing was continued for 15 minutes. The solution was rapidly cooled, acidified (much carbon dioxide was evolved), and rapidly extracted with ether. No acidic material could be isolated from the aqueous layer. The ether contained unchanged ester (2·0 g., 20%), and acetonylacetone (2·76 g., 45%) identified as the bis-2 : 4-dinitrophenylhydrazone m. p. 256—258° (decomp.) alone or mixed with an authentic specimen.

(*c*) The ester (10·0 g.) was added to a cold solution of sodium hydroxide (4·4 g.) in water (100 c.c.). After 14 hours the solution was acidified and extracted with ether. Distillation of the extract gave a colourless liquid, b. p. 72—80°/15 mm., n_D^{18} 1·4620, which contained *ca.* 60% of 3-methyl*cyclo*pent-2-enone and *ca.* 40% of acetonylacetone estimated as their derivatives with 2 : 4-dinitrophenylhydrazine.

(iv) *With sodium ethoxide.* (*a*) The ester was recovered unchanged after being kept in a cold solution of sodium ethoxide (0·5% of sodium) in absolute ethanol for 72 hours.

(*b*) The ester (10·0 g.) was added to a cold solution of sodium (1·35 g.) in absolute ethanol (200 c.c.). After 18 hours at room temperature the solution was accurately neutralised with concentrated hydrochloric acid (6·0 c.c.; *d* 1·16), sodium chloride being precipitated. Anhydrous magnesium sulphate was then added, and after a short time the mixture was filtered. Distillation of the filtrate gave ethyl 2 : 5-dimethylfuran-3-carboxylate as a colourless oil (7·5 g., 83%), b. p. 90—94°/15 mm., n_D^{23} 1·4693. On hydrolysis with alcoholic potassium hydroxide this ester gave a quantitative yield of 2 : 5-dimethylfuran-3-carboxylic acid, which separated from light petroleum (b. p. 80—100°) in colourless prisms, m. p. 135° (Found : C, 60·3; H, 5·7. Calc. for $C_7H_8O_3$: C, 60·0; H, 5·7%). Scott and Johnson (*J. Amer. Chem. Soc.*, 1932, **54**, 2549) give b. p. 99—101°/14 mm. and n_D^{20} 1·46897 for the ester, and m. p. 135° for the furancarboxylic acid.

(*c*) The ester (10·0 g.) was refluxed with a solution of sodium (0·5 g.) in dry ethanol (100 c.c.) for 2 hours. After cooling, the solution was accurately neutralised with concentrated hydrochloric acid (1·3 c.c.; *d* 1·16), dried, and evaporated. The residual brown oil was dissolved in ether, the solution was extracted with 5% aqueous sodium hydroxide, and the extracts were retained. On distillation the dried ethereal solution gave ethyl lævulate (2·7 g., 35%) as a colourless oil, b. p. 101—102°/22 mm., n_D^{20} 1·4238 (Found : C, 58·4; H, 8·6. Calc. for $C_7H_{12}O_3$: C, 58·3; H, 8·3%). The 2 : 4-dinitrophenylhydrazone separated from methanol in yellow prisms, m. p. 107° (Found : C, 48·4; H, 5·0; N, 17·6. Calc. for $C_{13}H_{16}O_6N_4$: C, 48·1; H, 4·9; N, 17·3%). Auwers (*Ber.*, 1911, **44**, 3533) gives b. p. 95°/15 mm. and n_D^{16} 1·4242 for the ester. Cowley and Schuette (*J. Amer. Chem. Soc.*, 1933, **55**, 3644) report m. p. 101° for the 2 : 4-dinitrophenylhydrazone. The aqueous sodium hydroxide was acidified and extracted repeatedly with ether. Evaporation of the dried extract gave a brown oil (1·2 g.) from which only acetonylacetone, identified as the bis-2 : 4-dinitrophenylhydrazone, m. p. 258° (decomp.) alone or mixed with an authentic specimen, and ethyl α-acetyl-lævulate, identified as ethyl 2 : 5-dimethyl-1-ureidopyrrole-3-carboxylate, m. p. 228° (Found : C, 53·4; H, 6·5; N, 18·7%), could be isolated.

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