121. *Studies in the Synthesis of Vitamin-A. Part II.*

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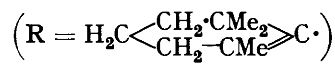
IN Part I (J., 1935, 584) the preparation of certain intermediates in the proposed synthesis of vitamin-*A* was described, notably α-aldehydo-δ-(2 : 2 : 6-trimethyl-Δ^6-*cyclo*hexenyl)-β-methyl-$\Delta^{\alpha\gamma}$-butadiene (I) and β-keto-δ-hydroxy-θ-(2 : 2 : 6-trimethyl-Δ^6-*cyclo*hexenyl)-ζ-methyl-$\Delta^{\epsilon\eta}$-octadiene (II). In view of the importance of these as key compounds in the development of the work, a number of additional derivatives have now been prepared. The synthesis itself has also been extended along the lines previously discussed.

(I.) $\mathrm{R{\cdot}CH{:}CH{\cdot}CMe{:}CH{\cdot}CHO}$ $\mathrm{R{\cdot}CH{:}CH{\cdot}CMe{:}CH{\cdot}CH(OH){\cdot}CH_2{\cdot}COMe}$ (II.)



$$\left(\mathrm{R} = \mathrm{H_2C}\!\begin{array}{l}\mathrm{<CH_2{\cdot}CMe_2>}\\ \mathrm{<CH_2{-}CMe\gg}\end{array}\!\mathrm{C{\cdot}}\right)$$

The conversion of (II) into β-keto-θ-(2 : 2 : 6-trimethyl-Δ^6-*cyclo*hexenyl)-ζ-methyl-$\Delta^{\gamma\epsilon\eta}$-octatriene (III) was difficult to effect owing to the exceptional ease of formation of resinous material under moderately acid conditions. Among the many dehydrating agents tried without success may be mentioned: (a) alcoholic sodium ethoxide (Cherbuliez and Hegar, *Helv. Chim. Acta*, 1932, **15**, 200); (b) distillation from aluminium phosphate (Kyriakides, *J. Amer. Chem. Soc.*, 1914, **36**, 533); (c) phosphorus tribromide; (d) distillation from aniline hydrobromide (Kyriakides, *ibid.*, p. 992); (e) heating the acetate with copper-bronze in an inert solvent (Meyer, *Helv. Chim. Acta*, 1935, **18**, 470). Dehydration was ultimately accomplished by means of anhydrous oxalic acid, but even here the reaction could only be carried out satisfactorily with small quantities of the hydroxy-ketone.

Condensation of (III) with ethyl bromoacetate gave *ethyl* θ-(2 : 2 : 6-*trimethyl*-Δ^6-cyclo*hexenyl*)-βζ-*dimethyl*-$\Delta^{\alpha\gamma\epsilon\eta}$-*octatetraene-α-carboxylate* (IV) as a viscous liquid, which, in contrast to ethyl δ-(2 : 2 : 6-trimethyl-Δ^6-*cyclo*hexenyl)-β-methyl-$\Delta^{\alpha\gamma}$-butadiene-α-carboxylate (Karrer, Salomon, Morf, and Walker, *Helv. Chim. Acta*, 1932, **15**, 878), was found to be exceedingly difficult to distil without extensive decomposition, even at a pressure of 0·1 mm. It was accordingly hydrolysed in the cold, but the resultant solid acid could not be obtained pure, since on attempted crystallisation it was partly converted into an alkali-insoluble material. This behaviour is paralleled by the tendency towards decarboxylation exhibited by δ-phenyl-β-methyl-$\Delta^{\alpha\gamma}$-butadiene-α-carboxylic acid (Kohler and Heritage, *Amer. Chem. J.*, 1910, **43**, 485) and the difficulty experienced in purifying $\Delta^{\alpha\gamma\epsilon\eta}$-decatetraenoic acid (Reichstein, Amman, and Trivelli, *Helv. Chim. Acta*, 1932, **15**, 263). For analysis a portion of the crude acid was converted into its *methyl* ester, which was purified by slow distillation at 2×10^{-4} mm., from a retort heated in an electrically controlled furnace.

Conversion of the barium salt of the acid from (IV) into the corresponding aldehyde by the method employed in the preparation of (I) is now under investigation.

(III.) $\mathrm{R{\cdot}CH{:}CH{\cdot}CMe{:}CH{\cdot}CH{:}CH{\cdot}COMe}$
(IV.) $\mathrm{R{\cdot}CH{:}CH{\cdot}CMe{:}CH{\cdot}CH{:}CH{\cdot}CMe{:}CH{\cdot}CO_2Et}$
(V.) $\mathrm{R{\cdot}CH{:}CH{\cdot}CMe{:}CH{\cdot}CH(OH){\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CO_2Et}$
(VI.) $\mathrm{R{\cdot}CH{:}CH{\cdot}CMe(OH){\cdot}C{:}CH}$

The hydroxy-ketone (II) has been condensed with ethyl bromoacetate to *ethyl* δ-*hydroxy*-θ-(2 : 2 : 6-*trimethyl*-Δ^6-cyclo*hexenyl*)-βζ-*dimethyl*-$\Delta^{\alpha\epsilon\eta}$-*octatriene-α-carboxylate* (V), which was hydrolysed and converted into the barium salt in the usual manner. Distillation of the latter with barium formate at 2×10^{-4} mm. gave α-*aldehydo*-δ-*hydroxy*-θ-(2 : 2 : 6-*trimethyl*-Δ^6-cyclo*hexenyl*)-βζ-*dimethyl*-$\Delta^{\alpha\epsilon\eta}$-*octatriene* (*phenylsemicarbazone*, m. p. 181—182°) and not, as had been hoped, α-aldehydo-θ-(2 : 2 : 6-trimethyl-Δ^6-*cyclo*hexenyl)-βζ-dimethyl-$\Delta^{\alpha\gamma\epsilon\eta}$-octatetraene.

A further unsuccessful attempt has been made to convert ε-(2 : 2 : 6-trimethyl-Δ^6-*cyclo*hexenyl)-γ-methylpent-δ-en-α-yn-γ-ol (VI) (see Part I) into the aldehyde (I). Descriptions are given in French Patents 671,558 and 770,154 (*Chem. Zentr.*, 1930, II, 134; 1935, I,

632) for the preparation of vinyl acetate and ethylidene diacetate by the condensation of acetylene with acetic acid in the presence of the mercury salt of naphthalene-2 : 7-disulphonic acid. Treated in the same manner, (VI) gave a semi-solid product, probably a mixture of the mono- and the di-acetate, which distilled steadily over a wide range. The whole was accordingly hydrolysed directly with cold alkali, which theoretically could give rise to either (VII) or (VIII) depending on the mode of addition of the acetic acid at the acetylene linkage; whereas the former might be expected readily to dehydrate on heating, such is not possible with (VIII). The compound actually obtained was not the aldehyde (I) and the analysis of its *phenylsemicarbazone*, m. p. 176—178°, agrees with that required for the derivative of the hydroxy-ketone (VIII), although this does not completely eliminate the possibility of (VII).

(VII.) $R{\cdot}CH{:}CH{\cdot}CMe(OH){\cdot}CH_2{\cdot}CHO$ $R{\cdot}CH{:}CH{\cdot}CMe(OH){\cdot}COMe$ (VIII.)

EXPERIMENTAL.

α-Aldehydo-δ-(2 : 2 : *6-trimethyl-*Δ^6-cyclo*hexenyl*)*-β-methyl-*$\Delta^{\alpha\gamma}$*-butadiene* (I).—The following additional derivatives have been prepared: (a) the p-*tolylsemicarbazone* (method of Sah and Lei, *J. Chinese Chem. Soc.*, 1934, **2**, 168), fine needles from alcohol, m. p. 172—173° (Found: C, 75·9; H, 8·4; N, 11·8. $C_{23}H_{31}ON_3$ requires C, 75·6; H, 8·55; N, 11·6%); (b) the p-*chlorobenzoylhydrazone* (cf. Shih and Sah, *Sci. Reports Nat. Tsing Hua Univ.*, 1934, **2**, 354), plates from alcohol, m. p. 202—203° (Found: C, 71·0; H, 7·4; N, 7·7; Cl, 9·7. $C_{22}H_{27}ON_2Cl$ requires C, 71·2; H, 7·2; N, 7·6; Cl, 9·6%).

β-Keto-δ-hydroxy-θ-(2 : 2 : *6-trimethyl-*Δ^6-cyclo*hexenyl*)*-ζ-methyl-*$\Delta^{\epsilon\eta}$*-octadiene* (II).—This compound, prepared as described in Part I, yields a p-*tolylsemicarbazone* crystallising from alcohol in short needles, m. p. 168—169° (Found: C, 74·0; H, 8·6; N, 10·2. $C_{26}H_{37}O_2N_3$ requires C, 73·8; H, 8·8; N, 10·0%), and a p-*chlorobenzoylhydrazone*, which separates from alcohol in pearly plates with a greenish reflex, m. p. 204° (Found: C, 69·8; H, 7·5; N, 6·8; Cl, 8·6. $C_{25}H_{33}O_2N_2Cl$ requires C, 70·0; H, 7·75; N, 6·5; Cl, 8·3%).

The *o*-chlorobenzoylhydrazones of both (I) and (II) were unsuitable for characterisation owing to their excessive solubilities.

β-Keto-θ-(2 : 2 : *6-trimethyl-*Δ^6-cyclo*hexenyl*)*-ζ-methyl-*$\Delta^{\gamma\epsilon\eta}$*-octatriene* (III).—β-Keto-δ-hydroxy-θ-(2 : 2 : 6-trimethyl-Δ^6-*cyclo*hexenyl)-ζ-methyl-$\Delta^{\epsilon\eta}$-octadiene (II) (2 g.) was heated at 160° (oil-bath temperature) with freshly dehydrated oxalic acid (5 g.) for 1½ hours and the whole was then steam-distilled in nitrogen, whereby unchanged hydroxy-ketone was removed. The residual solid was extracted with ether, the extract dried over sodium sulphate, and the major portion of the solvent removed. Alcohol was then added, and the *ketone* precipitated by cooling in solid carbon dioxide–acetone. After repeated crystallisation from alcohol at − 50° it was obtained as a pale yellow solid softening at 138° and melting completely at 144°; it gave a violet-red colour with chloroformic antimony trichloride (Found: C, 83·8; H, 10·4. $C_{18}H_{26}O$ requires C, 83·7; H, 10·1%).

Ethyl θ-(2 : 2 : *6-Trimethyl-*Δ^6-cyclo*hexenyl*)*-βζ-dimethyl-*$\Delta^{\alpha\gamma\epsilon\eta}$*-octatetraene-α-carboxylate* (IV).—A solution of the above ketone (5 g.) and ethyl bromoacetate (3·3 g.) in benzene (40 c.c.) was added rapidly to zinc needles (1·3 g.) covered with boiling benzene (20 c.c.), and the reaction completed by refluxing for 3 hours in an atmosphere of nitrogen. After being filtered rapidly in a stream of nitrogen (the product at this state is extremely sensitive towards oxidation), the solution was decomposed by shaking with 10% acetic acid (50 c.c.), and the whole extracted with light petroleum (b. p. 40—60°). The washed extract was dried over sodium sulphate and after removal of solvent the dark semi-solid residue was heated for 20 minutes at 180°/20 mm. to effect dehydration of the β-hydroxy-ester. Distillation of a portion of the product at 2×10^{-4} mm. gave two fractions: (a) a small quantity of a yellow oil, b. p. *ca.* 150°, consisting of almost pure *ester* (IV) (Found: C, 81·3; H, 10·1. $C_{22}H_{32}O_2$ requires C, 80·5; H, 9·9%); and (b) an orange-red oil, b. p. *ca.* 180°, which set to a hard resin on standing (Found: C, 85·5; H, 10·4%). The main portion of the crude undistilled ester (5 g.), dissolved in the minimum quantity of ether, was added to 10% alcoholic potassium hydroxide (20 c.c.), and the mixture rendered homogeneous by gradual addition of ether. After standing for 24 hours at room temperature, the red solution was diluted with water and thoroughly extracted with ether. The aqueous layer was rendered slightly acid with dilute phosphoric acid and extracted with ether, and the extract washed and dried over sodium sulphate. The solid acid obtained on evaporation of the solvent could not be obtained sufficiently pure for analysis.

Methyl θ-(2 : 2 : *6-Trimethyl-*Δ^6-cyclo*hexenyl*)-*βζ-dimethyl-*$\Delta^{\alpha\gamma\epsilon\eta}$*-octatetraene-α-carboxylate.*—A solution of the above acid (1 g.) in aqueous potassium hydroxide (0·2 g. in 100 c.c. of water) was treated with methyl sulphate (0·3 g.), and the whole shaken for 2 hours in an atmosphere of nitrogen. Further quantities of potassium hydroxide solution (0·2 g. in 5 c.c. of water) and methyl sulphate (0·3 g.) were added after 2 and 4 hours and shaking was continued for a further 12 hours. The suspension was then thoroughly extracted with light petroleum (b. p. 60—80°) and filtered from a small quantity of semi-solid material, and the filtrate dried over sodium sulphate. The oil obtained after removal of the solvent was distilled at 2 × 10^{-4} mm., giving the *methyl* ester as a pale yellow, viscous oil, b. p. 135—140° (Found : C, 80·1; H, 9·7. $C_{21}H_{30}O_2$ requires C, 80·2; H, 9·6%).

Ethyl δ-Hydroxy-θ-(2 : 2 : *6-trimethyl-*Δ^6-cyclo*hexenyl*)*-βζ-dimethyl-*$\Delta^{\alpha\epsilon\eta}$*-octatriene-α-carboxylate* (V).—β-Keto-δ-hydroxy-θ-(2 : 2 : 6-trimethyl-Δ^6-*cyclo*hexenyl)-ζ-methyl-$\Delta^{\epsilon\eta}$-octadiene (II) (10 g.) was condensed with ethyl bromoacetate (6 g.) as described in Part I for the similar reaction with β-ionone. The product was a yellow oil, b. p. 90—150°/4 mm., which on redistillation was separated into two fractions : (a) 2·5 g., b. p. 95—130°/4 mm., consisting mainly of unchanged hydroxy-ketone; (b) 8·0 g., b. p. 135—145°/4 mm. Redistillation of the latter gave the pure *hydroxy-ester* (V) as a pale yellow oil, b. p. 140—142°/4 mm. (Found : C, 76·0; H, 10·0. $C_{22}H_{34}O_3$ requires C, 76·3; H, 9·9%).

α-Aldehydo-δ-hydroxy-θ-(2 : 2 : *6-trimethyl-*Δ^6-cyclo*hexenyl*)*-βζ-dimethyl-*$\Delta^{\alpha\epsilon\eta}$*-octatriene.*—The above ester was converted into the barium salt of the corresponding acid as described in Part I for ethyl δ-(2 : 2 : 6-trimethyl-Δ^6-*cyclo*hexenyl)-β-methyl-$\Delta^{\alpha\gamma}$-butadiene-α-carboxylate. A finely sieved mixture of the dry barium salt (2·5 g.) and barium formate (2·3 g.) was evenly diluted with an equal bulk of silver sand, and the whole distilled in the apparatus mentioned in the theoretical section (temperature 180°, pressure 2 × 10^{-4} mm.). The aldehyde, an orange-yellow, fairly mobile oil, was converted into its *phenylsemicarbazone*, which crystallised from alcohol in needles, m. p. 181—182° (Found : C, 74·2; H, 8·5; N, 10·0. $C_{27}H_{37}O_2N_3$ requires C, 74·4; H, 8·5; N, 9·7%).

Action of Acetic Acid on ε-(2 : 2 : *6-Trimethyl-*Δ^6-cyclo*hexenyl*)*-γ-methylpent-δ-en-α-yn-γ-ol* (VI).—A solution of (VI) (8 g.), prepared as previously described (see Part I), in glacial acetic acid (50 c.c.) was added during ½ hour to a well-stirred suspension of mercuric oxide (0·5 g.) and naphthalene-2 : 7-disulphonic acid (5 g.) in glacial acetic acid (50 c.c.) at 30—40°. After 2 hours the temperature was raised to 70—80° for a further 2 hours; the reaction mixture was then cooled, poured into water, and neutralised with sodium carbonate. The resultant brown oil, which was extracted with ether and worked up in the usual manner, distilled steadily over a range (120—140°/5 mm.). The total distillate was hydrolysed by treatment at room temperature with 5% alcoholic potassium hydroxide (100 c.c.); after dilution with water, the whole was ether-extracted, and the extract dried over sodium sulphate. Removal of the solvent gave an oil, which was first heated at 150°/20 mm. for ½ hour and then distilled, yielding a yellowish-orange mobile oil, b. p. 90—100°/2 mm., giving a *phenylsemicarbazone*, which crystallised from alcohol in needles, m. p. 176—178° (Found : C, 71·9; H, 8·4; N, 11·4. $C_{22}H_{31}O_2N_3$ requires C, 71·6; H, 8·4; N, 11·4%).

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