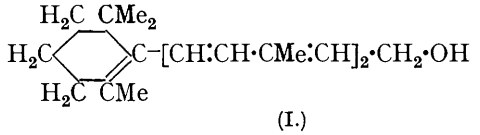
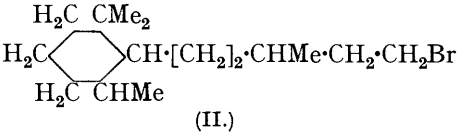
129. *Studies in the Synthesis of Vitamin-A. Part I.*

By W. H. Davies, I. M. Heilbron, W. E. Jones, and A. Lowe.

The synthesis of ι-(2 : 2 : 6-trimethyl*cyclo*hexyl)-γη-dimethyl-*n*-nonyl alcohol by Karrer, Morf, and Schöpp (*Helv. Chim. Acta*, 1933, **16**, 557; see also Karrer and Morf, *ibid.*, p. 625) and its identity with fully hydrogenated vitamin-*A* (perhydrovitamin-*A*) establish the structure (I) first proposed by Karrer, Morf, and Schöpp (*ibid.*, 1931, **14**, 1431) and supported by Heilbron, Morton, and Webster (*Biochem. J.*, 1932, **26**, 1199) for the vitamin.



(I.)



(II.)

Prior to the first publication by Karrer, Salomon, Morf, and Walker (*Helv. Chim. Acta*, 1932, **15**, 878) relating to the synthesis of perhydrovitamin-*A*, we, working on a similar projected synthesis, had prepared ε-(2 : 2 : 6-trimethyl*cyclo*hexyl)-γ-methyl-*n*-amyl bromide (II), but further work in this direction was then abandoned. Karrer and Morf (*loc. cit.*) succeeded in condensing the above bromide with sodiomalonic ester, but all our attempts to condense it with sodioacetoacetic ester gave an unsaturated *hydrocarbon*, $C_{15}H_{28}$, probably ε-(2 : 2 : 6-trimethyl*cyclo*hexyl)-γ-methyl-Δ^{α}-pentene.

In the projected synthesis of vitamin-*A* itself, our first objective was α-aldehydo-δ-(2 : 2 : 6-trimethyl-Δ^{6}-*cyclo*hexenyl)-β-methyl-$\Delta^{\alpha\gamma}$-butadiene (III). As shown by Rupe and Gassmann (*Helv. Chim. Acta*, 1929, **12**, 198), tertiary acetylene carbinols of the type RR'C(OH)·C:CH are capable in certain cases of rearrangement with formic acid to the isomeric αβ-ethylenic aldehydes (compare, however, Fischer and Löwenberg, *Annalen*, 1929, **475**, 186; Rupe and Hirschmann, *Helv. Chim. Acta*, 1931, **14**, 687). The *carbinol*

(IV) was therefore prepared by condensation of β-ionone with acetylene in presence of sodamide; * it reacted vigorously with formic acid or acetic anhydride, but no aldehyde could be detected among the products. The desired aldehyde was obtained from δ-(2 : 2 : 6-trimethyl-Δ^6-*cyclo*hexenyl)-β-methyl-$\Delta^{\alpha\gamma}$-butadiene-α-carboxylic acid (Karrer, Salomon, Morf, and Walker, *loc. cit.*) by an analogous method to that employed by Tiemann (*Ber.*, 1898, **31**, 826) for the preparation of citral from geranic acid : dry distillation of the barium salt of the acid with barium formate under reduced pressure gave a good yield of (III), characterised as its *phenylsemicarbazone*, m. p. 182—183°. Reduction of the aldehyde by the method of Reichstein, Ammann, and Trivelli (*Helv. Chim. Acta*, 1932, **15**, 264) gave the corresponding *alcohol*. This shows a broad inflexion in the ultra-violet absorption spectrum at about 270 mμ, but possesses no growth-promoting activity.

(III.) R·CH:CH·CMe:CH·CHO R·CH:CH·CMe:CH·CH:CH·COMe (V.)

(IV.) R·CH:CH·CMe(OH)·C:CH R·CH:CH·CMe:CH·CH(OH)·CH_2·COMe (VI.)

(VII.) R·CH:CH·CMe:CH·CH:CH·CH_2·OH R·CH:CH·CMe:CH·CH(OH)·CH_2·CO_2Et (VIII.)

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

The condensation of (III) with acetone by means of hot piperidine (cold sodium ethoxide having proved unsatisfactory) gave the *hydroxy-ketone* (VI) (*phenylsemicarbazone*, m. p. 171—172°). The dehydration of this to (V) and the possibility of adding two more carbon atoms by the further application of the methods outlined above are under investigation.

In an attempt to prepare the alcohol (VII) with the view of ascertaining whether it would be physiologically active, the aldehyde (III) was condensed with ethyl bromoacetate to give *ethyl* β-*hydroxy*-ζ-(2 : 2 : 6-*trimethyl*-Δ^6-cyclo*hexenyl*)-δ-*methyl*-$\Delta^{\gamma\epsilon}$-*hexadiene*-α-*carboxylate* (VIII). As dehydration of this ester could not be effected under suitably mild conditions, it was hydrolysed, and the acid converted into the barium salt. This, when distilled with barium formate under reduced pressure, gave the original C_{15}-aldehyde (III), scission of the chain at the hydroxylated β-carbon atom evidently having occurred. This reaction is being further studied.

Experimental.

ε-(2 : 2 : 6-*Trimethyl*cyclo*hexyl*)-γ-*methyl*-n-*amyl Bromide* (II).—Our method of preparation (compare Karrer, Salomon, Morf, and Walker, *loc. cit.*) consisted in the condensation of tetrahydroionone with ethyl bromoacetate to ethyl β-hydroxy-δ-(2 : 2 : 6-trimethyl*cyclo*hexyl)-β-methylvalerate, which, as observed by the above investigators also, could not readily be dehydrated. It was therefore converted into the corresponding β-bromo-ester which was reduced with zinc dust and hydrogen chloride in acetic acid to ethyl δ-(2 : 2 : 6-trimethyl*cyclo*hexyl)-β-methylvalerate. Reduction of this with sodium and amyl alcohol gave ε-(2 : 2 : 6-trimethyl-*cyclo*hexyl)-γ-methyl-*n*-amyl alcohol as a slightly viscous oil, b. p. 136°/1·5 mm. (Karrer, Salomon, Morf, and Walker, *loc. cit.*, give b. p. 150—156°/7 mm.).

The bromide (II) was prepared by slowly adding a solution of the alcohol (16·5 g.) in dry petroleum (b. p. 80—100°; 40 c.c.) to phosphorus tribromide (10 g.) in the same solvent (40 c.c.). The whole was refluxed for 3 hours and, after cooling, poured into ice-water. The bromide was isolated by ether extraction and obtained as a pale yellow oil (15·5 g.), b. p. 140—145°/4 mm. (Found : C, 62·7; H, 10·0; Br, 27·5. Calc. for $C_{15}H_{29}Br$: C, 62·3; H, 10·1; Br, 27·7%).

Condensation of ε-(2 : 2 : 6-*Trimethyl*cyclo*hexyl*)-γ-*methyl*-n-*amyl Bromide* (II) *with Acetoacetic Ester.*—Alcoholic sodioacetoacetic ester (prepared from 10 g. of ethyl acetoacetate) was treated at 0° with the freshly distilled bromide (15·2 g. in 30 g. of alcohol). After remaining at this temperature for 2 hours, the mixture was refluxed for 12 hours and cooled. Ether extracted an oil which gave on distillation a pale yellow, mobile liquid (8 g.) with a pleasant terpene-like odour, b. p. 112—115°/2 mm. (Found : C, 86·2; H, 13·1. $C_{15}H_{28}$ requires C,

* Since this synthesis was carried out, Gould and Thompson (*J. Amer. Chem. Soc.*, 1935, **57**, 340) also have prepared this compound. They used potassium *tert.*-amyloxide as condensing agent, having, contrary to our findings, failed to achieve reaction with sodamide.

86·5; H, 13·5%). The same product was obtained when the sodioacetoacetic ester was prepared in benzene, and the condensation carried out in this solvent.

Condensation of β-Ionone with Acetylene.—A solution of β-ionone (90 g.) in dry ether (150 c.c.) was added during ½ hour with stirring to a suspension of fresh sodamide (45 g.) in dry ether (220 c.c.), the whole being maintained at 0° for, in all, 2½ hours; acetylene was then rapidly passed into the viscous mass during 20 hours. The deep red mixture was poured on ice and ether-extracted. Removal of the solvent from the washed (dilute sulphuric acid) and dried extract, and distillation, yielded ε-(2 : 2 : 6-*trimethyl*-Δ^6-cyclo*hexenyl*)-*γ-methylpent*-δ-*en*-α-*yn*-*γ-ol* (IV) as a viscous yellowish oil (58 g.), b. p. 112—115°/3 mm., which gave an intense blue colour with chloroformic antimony trichloride, and readily formed a white silver salt (Found: C, 82·4; H, 10·2. $C_{15}H_{22}O$ requires C, 82·6; H, 10·1%).

α-*Aldehydo*-δ-(2 : 2 : 6-*trimethyl*-Δ^6-cyclo*hexenyl*)-β-*methyl*-$\Delta^{\alpha\gamma}$-*butadiene* (III).—Undistilled δ-(2 : 2 : 6-trimethyl-Δ^6-*cyclo*hexenyl)-β-methyl-$\Delta^{\alpha\gamma}$-butadiene-α-carboxylic acid (46 g.), prepared as described by Karrer, Salomon, Morf, and Walker (*loc. cit.*), was converted into the potassium salt with aqueous potassium hydroxide (11·6 g. in 100 c.c. of water), and a solution of barium chloride (21·6 g. in 120 c.c. of water) slowly added with stirring. The precipitated barium salt was washed with water and dried by distilling its suspension in benzene under reduced pressure. A finely sieved mixture of the dry salt (29 g.) and barium formate (24 g.) was diluted with an equal bulk of silver sand and heated first for 1 hour (oil-bath temp. 150°) under 2 mm. pressure, and then directly by a luminous flame, until no more oil distilled over (about 1½ hours; wt. of distillate, 14·6 g.). The aldehyde was obtained after repeated fractionation as a pale yellow, mobile oil (11·7 g.), b. p. 92—93°/1·8 mm. It was volatile in steam, reduced Tollens's reagent, and rapidly formed a semi-solid semicarbazone and a red 2 : 4-dinitrophenylhydrazone, neither of which was suitable for characterisation, the former owing to excessive solubility and the latter because it could not be crystallised unchanged. The *phenylsemicarbazone*, prepared in the usual manner, separated from alcohol in needles, m. p. 182—183° (Found: C, 75·2; H, 8·2; N, 12·1. $C_{22}H_{29}ON_3$ requires C, 75·2; H, 8·3; N, 11·9%). The aldehyde, regenerated on treatment with oxalic acid and steam-distilled, showed a broad inflexion between 280—310 mμ, and gave a red-brown colour with antimony trichloride showing a band near 467 mμ and strong absorption in the violet region.

ε-(2 : 2 : 6-*Trimethyl*-Δ^6-cyclo*hexenyl*)-*γ-methyl*-$\Delta^{\beta\delta}$-*pentadien*-α-*ol*.—A solution of the above aldehyde (12 g.) and aluminium *iso*propoxide (12 g.) in absolute *iso*propyl alcohol (150 c.c.) was refluxed for 50 hours, the solvent removed, and the residue steam-distilled in a current of nitrogen. An ethereal extract of the distillate yielded an oil, which was treated with phenylsemicarbazide acetate to remove unchanged aldehyde and again steam-distilled in nitrogen after 12 hours. The oily distillate was fractionally distilled, giving the *alcohol* as a pale yellow oil (8·5 g.), b. p. 99—100°/2 mm. [Found: C, 81·5; H, 10·7. $C_{15}H_{24}O$ requires C, 81·8; H, 10·9%. Found, active hydrogen atoms, 0·98 (Zerewitinov)]. Chloroformic antimony trichloride and a few drops of acetic anhydride gave a red colour, slowly changing to blue-violet. No solid derivative of the alcohol has so far been obtained.

Ethyl β-*Hydroxy*-ζ-(2 : 2 : 6-*trimethyl*-Δ^6-cyclo*hexenyl*)-δ-*methyl*-$\Delta^{\gamma\epsilon}$-*hexadiene*-α-*carboxylate* (VIII).—A solution of the aldehyde (10 g.) and ethyl bromoacetate (9 g.) in dry benzene (30 c.c.) was added during ½ hour to zinc needles (4·0 g.) covered with boiling benzene (30 c.c.). The mixture was refluxed for 3 hours, and the filtered solution decomposed by shaking with 10% acetic acid (50 c.c.) for 2 hours. The whole was extracted with light petroleum (b. p. 40—60°) and the extract dried over sodium sulphate. The oily residue after removal of the solvent was distilled under reduced pressure, and the *ester* collected as a pale yellow oil (7·5 g.), b. p. 138—140°/2 mm. (Found: C, 74·2; H, 10·1. $C_{19}H_{30}O_3$ requires C, 74·5; H, 9·8%).

The ester (20 g.) was hydrolysed in the cold with alcoholic potassium hydroxide (5 g. in 75 c.c. of alcohol) and the red solution after dilution with water was thoroughly extracted with ether. The aqueous layer was rendered slightly acid with dilute phosphoric acid and extracted with ether, the extract washed and dried over sodium sulphate, and solvent removed. The oily acid was without further purification converted into its barium salt (yield, 14 g.), and heated with barium formate exactly as described under (III). The orange-yellow distillate was redistilled and yielded a pale yellow oil, b. p. 95—97/2 mm., which was proved to be identical with α-aldehydo-δ-(2 : 2 : 6-trimethyl-Δ^6-*cyclo*hexenyl)-β-methyl-$\Delta^{\alpha\gamma}$-butadiene by conversion into the phenylsemicarbazone (feathery needles from alcohol), m. p. 182—183° alone or mixed with the phenylsemicarbazone of (III) (Found: N, 11·9. Calc. for $C_{22}H_{29}ON_3$: N, 11·9%).

β-*Keto*-δ-*hydroxy*-θ-(2 : 2 : 6-*trimethyl*-Δ^6-cyclo*hexenyl*)-ζ-*methyl*-$\Delta^{\epsilon\eta}$-*octadiene* (VI).—A solution of the aldehyde (III) (11 g.) in a mixture of dry acetone (50 c.c.) and freshly distilled

piperidine (25 c.c.) was refluxed for 100 hours, a further quantity of piperidine (10 c.c.) being added after 40 hours. The excess of acetone and the piperidine were distilled off and the residue was steam-distilled in nitrogen. The distillate was extracted with ether; the washed and dried extract on distillation yielded an orange-yellow oil, b. p. 90—115°/2 mm., which was further separated into two fractions: (i) 3 g., b. p. 90—105°/2 mm., containing unchanged aldehyde, and (ii) 5 g., b. p. 109—111°/2 mm. Analysis of the latter after refractionation (b. p. 104—105°/1·5 mm.) proved it to be the *hydroxy-ketone* (Found: C, 78·0; H, 10·1. $C_{18}H_{28}O_2$ requires C, 78·2; H, 10·1%). The *phenylsemicarbazone* crystallised from alcohol in fine needles, m. p. 171—172° (Found: C, 73·4, 73·45; H, 8·4, 8·4; N, 10·5, 10·5. $C_{25}H_{35}O_2N_3$ requires C, 73·4; H, 8·5; N, 10·3%).

One of us (A. L.) thanks Imperial Chemical Industries Ltd. (Dyestuffs Group) for a scholarship.

UNIVERSITIES OF LIVERPOOL AND MANCHESTER. [*Received, March 16th*, 1935.]