157. *Studies in the Polyene Series. Part V. The Employment of* 3-(2′ : 6′ : 6′-*Tri-methyl*cyclo*hexenyl*)-1-*methylcrotonaldehyde for the Synthesis of Vitamin A and Analogues.*

By I. M. Heilbron, A. W. Johnson, E. R. H. Jones, and A. Spinks.

Previous work on the synthesis of vitamin A (I) is reviewed with particular reference to anomalies encountered in the use of β-ionone (III). A new scheme for the synthesis of vitamin A and analogues, based on the coupling of the aldehyde (V) with 3-ketobutanol through an acetylene molecule has been devised and this paper contains an account of preliminary work along these lines.

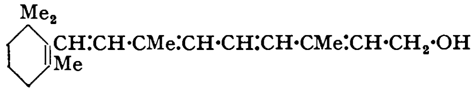
The preparation of *glycide* esters (VII, VIII, and IX) from β- and α-ionones and mesityl oxide is described. Light absorption data (Tables I and II) reveal that the epoxy-group in these compounds largely resembles an ethylenic linkage in absorptive properties. Decarboxylation of the glycide acids from β- and α-ionone yields isomeric αβ-unsaturated C_{14} *aldehydes* (V and X respectively), both of which have been characterised by the preparation of derivatives. Absorption spectra (Table III) of the latter and of the aldehydes themselves provide valuable constitutional evidence. The glycide acid (IX) from mesityl oxide on decarboxylation gives a mixture of 2 : 4-dimethylpentenals (XII and XIII), from which only derivatives of the αβ-unsaturated isomer (XII) are isolated.

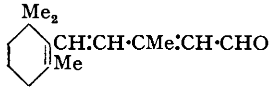
The aldehyde (V) condenses with acetone, yielding the *ketone* (XIV), the value of which for the synthesis of vitamin A analogues is pointed out. This is emphasised by the successful condensation of the ketone with ethylmagnesium bromide to a C_{19} *carbinol* (XVII).

Preliminary experiments on the reaction of αβ-unsaturated aldehydes with acetylene led to the preparation of 1-*ethinylgeraniol* (XVIII) (from citral) and the *ethinylcarbinol* of (V), and indications of the successful dehydration of (XVIII) have been obtained.

Whereas the structure of vitamin A (I) has been definitely established by degradation experiments (Karrer, Morf, and Schopp, *Helv. Chim. Acta*, 1931, **14**, 1036, 1431; Heilbron, Morton, and Webster, *Biochem. J.*, 1932, **26**, 1194) and also by the synthesis of the perhydro-vitamin (Karrer and Morf, *Helv. Chim. Acta*, 1933, **16**, 625), the only claim to have synthesised the vitamin itself is that of Kuhn and Morris (*Ber.*, 1937, **70**, 853). This synthesis is based on the condensation of 2-methylcrotonaldehyde with β-ionylideneacetaldehyde (II), the latter being prepared by reduction of the *o*-toluidide of the corresponding β-ionylideneacetic acid by the successive actions of phosphorus pentachloride and chromous chloride (von Braun and Rudolph, *Ber.*, 1934, **67**, 1735). The final product was claimed to contain 7·5% of vitamin A as estimated by the antimony trichloride colour reaction and also by biological tests. No subsequent publication on this synthesis has emanated from the Heidelberg laboratories and both Karrer and Ruegger (*Helv. Chim. Acta*, 1940, **23**, 284) and Krauze and Slobodin (*J. Gen. Chem. Russ.*, 1940, **10**, 907) have reported unfavourably on the Kuhn and Morris synthesis. We also have entirely failed to repeat this synthesis, not even obtaining the aldehyde (II), and in this connection it is noteworthy that von Braun and Kurtz (*Ber.*, 1937, **70**, 1009) were unable to prepare citrylideneacetaldehyde from the corresponding acid by the series of reactions employed by Kuhn and Morris. That these authors obtained a final product possessing growth-promoting properties cannot be denied in view of the published results, but it is doubtful whether their material contained vitamin A as isolated

(I.)





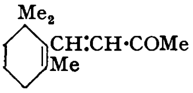
(II.)

from natural sources, and further, it is clear that, since the formation of this biologically active substance by the series of reactions employed is apparently fortuitous, the synthesis is of little practical value.

Kipping and Wild (*Chem. and Ind.*, 1939, **58**, 802) have reported a synthesis of vitamin A methyl ether by condensation of 6-methoxy-4-methylhexa-2 : 4-dienyl bromide with β-ionone of unspecified purity in the presence of lithium, followed by dehydration of the product. In the absence of any published criteria as to the nature of their final product (neither absorption spectra nor biological data are given) this claim can only be accepted with considerable reserve.

Although the most obvious starting material for the synthesis of vitamin A would appear to be β-ionone (III), apart from its normal Reformatsky reaction with ethyl bromoacetate and some evidence of normal reactions with vinylacetylenes, in general this ketone behaves anomalously (Gould and Thompson, *J. Amer. Chem. Soc.*, 1935, **57**, 340; Karrer, Salomon, Morf, and Walker, *Helv. Chim. Acta*, 1932, **15**, 878; Giacolone, *Gazzetta*, 1937, **67**, 464; Kipping and Wild, J., 1940, 1239), exhibiting a marked tendency towards the formation of 1 : 4-adducts. According to Kipping and Wild (J., 1940, 1239) β-ionone reacts normally with methyl-lithium and phenyl-lithium. Prior to their publication we had attempted reactions in the presence of lithium with more complex halides (*e.g.*, hexadienyl and octatrienyl bromides, bromoacetal, etc.) but in no case could homogeneous products exhibiting the expected light absorption be isolated. In contrast to the abnormal behaviour of β-ionone, the α-isomer undergoes essentially 1 : 2-addition and consequently statements in the literature concerning normal reactions of the former must be accepted with reserve unless supported by definite evidence of purity of the starting material such as is provided by light absorption data, refractive index, etc. In our experience, no commercial specimen should be employed without purification through a derivative and the essential constants should be indicated.

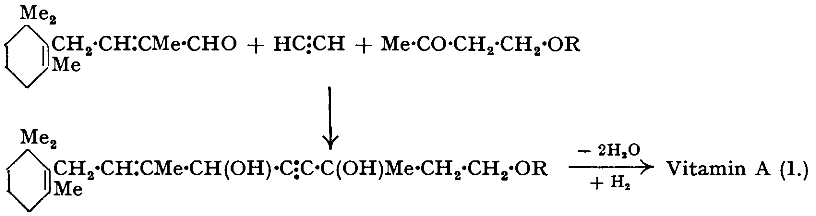
(III.)



(IV.)

In searching for routes to vitamin A or related compounds containing the necessary polyene system but not involving Grignard-type reactions with β-ionone, our attention became focused on the possibility of employing the aldehyde originally described by Ishikawa and Matsuura (*Sci. Rep. Tokyo Bunrika Daigaku, A*, 1937, **3**, 173; *Chem. Zentr.*, 1937, II, 3452) * and formulated by them as (IV) but now shown to be correctly represented by (V). This aldehyde is of especial interest, since it would be expected to react normally in all types of Grignard reaction and the broken conjugation readily lends itself to syntheses of polyenes involving acetylene condensations. Its value for vitamin A syntheses is clearly indicated in the following scheme :

(V.) (VI.)



It is obvious from the above that many alternative methods of effecting the completed project present themselves. Thus the glycol (VI) could be reached either (*a*) by the condensation of the ketonic portion with the ethinylcarbinol of (V) or alternatively (*b*) by the condensation of (V) with the ethinylcarbinol derived from an appropriate ketone. Further, the determination of the most suitable stage for the removal of water from the carbinols or glycols and for the semihydrogenation of the acetylenic bond leads to a multiplicity of permutations and combinations of the basic theme. The many implications of this scheme are in course of investigation in these laboratories and, as is inevitable, numerous new problems have arisen, the elucidation of which will form the subject of this and subsequent publications.

In the first place a more detailed study of the preparation and properties of the aldehyde prepared by Ishikawa and Matsuura (*loc. cit.*) appeared to be essential, as no evidence in support of its formulation as (IV) was provided. The Japanese authors condensed both α- and β-ionones (characterised only by their b. p.'s at different pressures) with ethyl chloroacetate and the glycide esters (obtained in 20% yields) were hydrolysed with alcoholic alkali to the glycide acids, which decomposed spontaneously on liberation from their salts, giving poor yields of the aldehydes. These were characterised as the thiosemicarbazones (m. p. 152° and 160° corr. respectively, but no mixed m. p. mentioned), which provided the only satisfactory analytical data in the paper. No other constants (*e.g.*, density and refractive index) were given to distinguish between the glycide esters and aldehydes from the α- and β-ionones and it seems highly probable, on the basis of our findings (*q.v.*), that the two aldehydes prepared by Ishikawa and Matsuura were identical, both being derived from α-ionone.

By interaction of β-ionone (regenerated from its crystalline semicarbazone) with ethyl chloroacetate in the presence of sodium methoxide at — 60° rather than at 0° (cf. Yarnall and Wallis, *J. Org. Chem.*, 1939, **4**,

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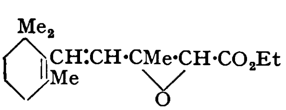
* The authors are indebted to Dr. W. E. Jones for drawing their attention to this paper.

270) a 60% yield of the *glycide* ester (VII) was obtained. Hydrolysis with alcoholic alkali furnished a crude acid which gave a small yield of a crystalline *glycide acid,* m. p. 132° (decomp.), yielding the *methyl* ester on treatment with diazomethane. All three substances exhibit high intensity absorption at 2860 A. (Table I) which, at first sight, is not readily reconcilable with the formulation (VII). We have been unable to obtain evidence that the acid or its esters exist in the isomeric keto-form, *i.e.*, absence of coloration with ferric chloride, no evolution of methane with methylmagnesium iodide, and failure to exhibit ketonic reactions, and there is no escape from the hypothesis that the epoxy-group in compounds such as (VII) largely resembles, insofar as light absorption properties are concerned, an ethenoid linkage. Thus, whereas octatrienic acid, containing three double bonds conjugated with the carboxyl group, absorbs, in alcoholic solution, at 2960 A., sorbic acid absorbs only at 2540 A. in the same solvent (Smakula, *Angew. Chem.*, 1934, **47**, 657).

TABLE I.

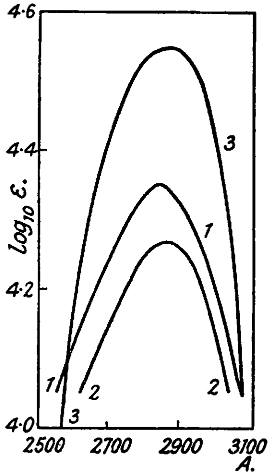
From β-Ionone.	λ max., A.	log ε.
Glycide acid (m. p. 132°) (Fig. 1)	2870	4·49
Ethyl ester (Fig. 1)	2860	4·25
Methyl ester	2860	4·56



(VII.)

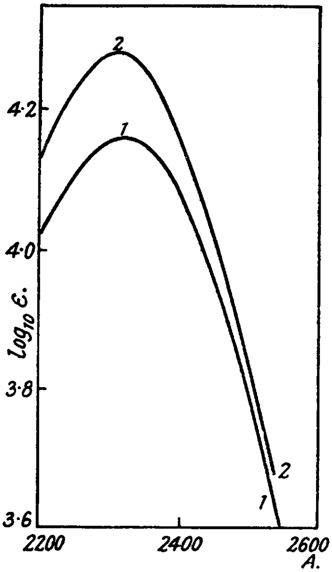
Although all three compounds listed in Table I were analytically pure, a marked difference in the intensities of the absorption at 2860 A. is apparent between the ethyl ester obtained directly from the condensation on the one hand, and the crystalline acid and the methyl ester derived from it on the other, a difference which is also clearly reflected in the divergent refractive indices of the two esters (see Experimental). A similar behaviour is also apparent in the case of the glycide esters from mesityl oxide (see Table II). These variations in the physical constants of analytically pure materials can only be ascribed to the existence of stereoisomeric forms of the glycide acid. Such marked intensity variations with stereoisomers are not unusual. Smakula and Wassermann (*Z. physikal. Chem.*, 1931, **155**, 353) observed more than 100% differences in intensity between the *cis*- and the *trans*-forms of both stilbene and cinnamic acid.

FIG. 1.



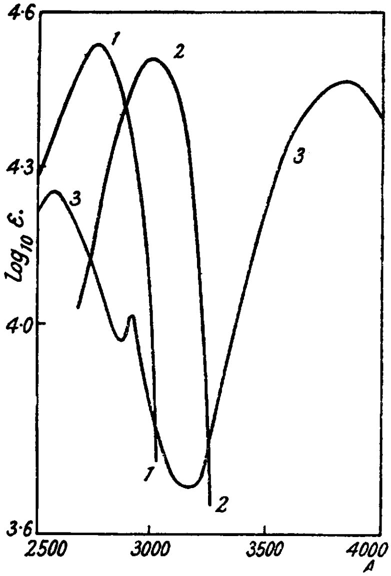
1. *Ketone* (XIV).
2. *Glycide ester* (VII).
3. *Acid corresponding to* (VII).

FIG. 2.



1. *Aldehyde* (X).
2. *Aldehyde* (V).

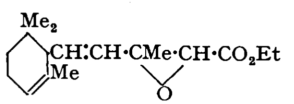
FIG. 3.

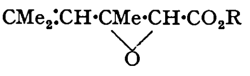


1. *Phenylsemicarbazone of aldehyde* (V).
2. *Thiosemicarbazone* ,, ,,
3. 2 : 4-*Dinitrophenylhydrazone* ,,

In order to obtain further spectrographic values for unsaturated glycide esters and also to study the aldehydes obtained on decarboxylation of the corresponding glycide acids, condensations of both α-ionone and mesityl oxide with ethyl chloroacetate have been carried out. The *glycide* ester (VIII) from α-ionone was obtained in 30% yield but in this case the glycide acid failed to crystallise. Mesityl oxide gave a *glycide* ester (IX) (a mixture of methyl and ethyl esters was obtained, due to some alcoholysis with the sodium

(VIII.)





$$\mathrm{CMe_2{:}CH{\cdot}CMe{\cdot}\underset{O}{\underbrace{CH}}{\cdot}CO_2R}$$

(IX.)

methoxide employed as condensing agent) in 55% yield, which on hydrolysis yielded a small amount of a crystalline *glycide acid*, m. p. 72°, the latter furnishing a *methyl* ester on treatment with diazomethane. The light absorption data for these compounds are in Table II, from which two main facts emerge. The epoxy-group in compounds of the type of (VIII) and (IX) again resembles an ethylenic linkage, as has already been suggested by the data in Table I. Secondly, in the case of the methyl ester of the acid corresponding to (IX) there is again apparent a very definite difference in the intensities of absorption of otherwise analytically pure samples.

TABLE II.

	From α-ionone.			From mesityl oxide.	
	λ max., A.	log ε.		λ max., A.	log ε.
Glycide acid (crude) ...	2340	4·00	(m. p. 72°)	2345	4·025
			(crude)	2345	3·87
Ethyl ester	2340	4·06		2340	3·95
Methyl ester	—	—	(from cryst. acid)	2345	4·01
			(crude)	2345	3·91

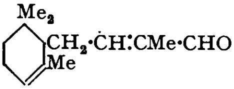
Numerous methods of decarboxylating the above glycide acids have been examined and heating with copper powder in a vacuum at about 130° produced the most satisfactory results. Under these conditions the crude acid corresponding to (VII) gave a 30% yield of the aldehyde (V), *i.e.*, 3-(2′ : 6′ : 6′-*trimethyl*cyclo*hexenyl*)-1-*methylcrotonaldehyde*, the αβ-unsaturated nature of which is illustrated by its absorption spectrum and also by similar data (Table III) for the *thiosemicarbazone* (from which the pure aldehyde was regenerated), *phenylsemicarbazone*, and 2 : 4-*dinitrophenylhydrazone*.

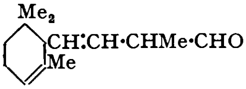
TABLE III.

	λ max., A.	log ε.
1. Aldehyde (V) (from thiosemicarbazone) (Fig. 2)	2300	4·25
2. Aldehyde (X) (from thiosemicarbazone) (Fig. 2)	2325	4·16
3. Aldehyde (XII + XIII) (crude) ...	2270	3·69
4. Citral (commercial sample distilled)	2320	4·05
5. Phenylsemicarbazone of 1 (Fig. 3)	2780	4·57
	2370	4·34
6. ,, ,, 2	2775	4·53
	2370	4·30
7. ,, ,, (XII)	2750	4·50
	2380	4·30
8. ,, ,, 4	2850	4·64
	2390	4·30
9. Thiosemicarbazone of 1 (Fig. 3)	2990	4·59
10. ,, ,, 2	3030	4·53
11. ,, ,, 4	3030	4·66
12. 2 : 4-Dinitrophenylhydrazone of 1 (Fig. 3)	3830	4·46
	2580	4·25
13. 2 : 4-Dinitrophenylhydrazone of 2 ...	3840	4·46
	2600	4·26
14. 2 : 4-Dinitrophenylhydrazone of (XII)	3820	4·49
	2540	4·26
15. 2 : 4-Dinitrophenylhydrazone of 4	3840	4·52
	2550	4·35

Although there is no doubt that the derivatives are those of an αβ-unsaturated aldehyde, the possibility that the aldehyde itself has the structure (IV) cannot be entirely excluded on the spectrographic evidence, since (IV) contains a diene system which would exhibit light absorption similar to that recorded in Table III. We do not attach much importance to this possibility, but in order to provide more complete evidence for formulation (V) we have examined the decarboxylation of the isomeric glycide acid from α-ionone. This gave a 65% yield of an aldehyde, which we formulate as 3-(2′ : 6′ : 6′-*trimethyl*-Δ$^{2'}$-cyclo*hexenyl*)-1-*methylcrotonaldehyde* (X), and this has been characterised by the preparation and analysis of the *thiosemicarbazone* (from which the pure aldehyde was regenerated), *phenylsemicarbazone*, and the 2 : 4-*dinitrophenylhydrazone*. The light absorption data for this aldehyde and its derivatives (Table III) proved to be strictly analogous to those obtained for the isomeric aldehyde (V) from β-ionone and, since the only alternative formulation (XI) contains no conjugated system, there is no doubt that the aldehydes obtained from β- and α-ionone are correctly represented by (V) and (X) respectively.

(X.)



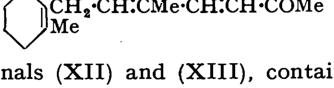


(XI.)

On heating the acid (IX, R = H) at 145°/760 mm. in the presence of copper powder an aldehyde was obtained in 35% yield. The molecular extinction coefficient (ε) of this aldehyde at its maximum is considerably lower than that observed for citral (see Table III) and this, together with the fact that, although crystalline aldehydic derivatives are readily formed, their purification is extremely tedious, suggests that this aldehyde is a mixture of the two 2 : 4-dimethylpentenals (XII) and (XIII), containing approximately 25% of the former. The *semicarbazone*, *phenylsemicarbazone*, and 2 : 4-*dinitrophenylhydrazone* must, from

(XII.) $CHMe_2·CH{:}CMe·CHO$

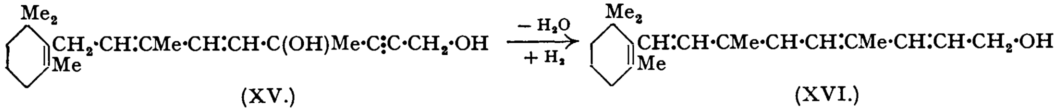
(XIII.) $CMe_2{:}CH·CHMe·CHO$



(XIV.)

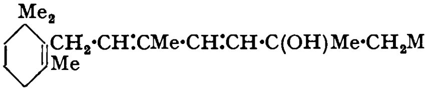
their absorption spectra (Table III), be derivatives of the αβ-unsaturated aldehyde (XII), *i.e.*, 2 : 4-dimethylpent-2-enal. An aldehyde of this constitution was described by Kohn (*Monatsh.*, 1901, **22**, 21), but no data were given whereby a direct comparison could be made. Regeneration from the partially purified semicarbazone gave an analytically pure aldehyde mixture richer in (XII) (maximum, 2270 A.; log ε = 3·94).

Condensation of the C_{14} aldehyde (V) with acetone has been effected in the presence of sodium ethoxide, or preferably aluminium *tert.*-butoxide, yielding a C_{17} ketone to which the constitution 7-(2′ : 6′ : 6′-*trimethyl*cyclo*hexenyl*)-5-*methylhepta*-3 : 5-*dien*-2-*one* (XIV) is ascribed. The ketone, purified through the crystalline *semicarbazone*, exhibited a single well-defined absorption maximum (Fig. 1) at 2850 A. (log ε = 4·35) comparing satisfactorily with that of ψ-ionone (max. 2930 A., log ε = 4·37), which contains the same chromophoric group. This ketone (XIV) is of potential importance for the synthesis of polyenes of the vitamin A type. Thus condensation with propargyl alcohol or one of its derivatives by the Grignard or other method would furnish a primary-tertiary glycol (XV) which, on partial dehydration and semihydrogenation of the acetylenic bond, would yield an alcohol (XVI) differing from the vitamin only in the position of one of the side-chain methyl groups. In order to ascertain the practicability or otherwise of the initial condensation involved in this scheme the ketone has been treated with ethylmagnesium bromide; the carbinol, 8-(2′ : 6′ : 6′-*trimethyl*cyclo*hexenyl*)-3 : 6-*dimethylocta*-4 : 6-*dien*-3-*ol* (XVII), was then obtained, as shown by its absorption band at 2370 A. (log ε = 4·08) and the presence of one active hydrogen atom, as indicated by a Zerewitinoff determination. We are now engaged on a study of the condensation of (XIV) with propargyl alcohol and analogues.



(XV.) (XVI.)

(XVII.)

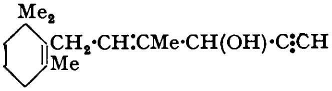


The possibility of preparing an ethinylcarbinol from the aldehyde (V) had also to be investigated. Ethinylcarbinols have been prepared from carbonyl compounds and acetylene in the presence of a variety of condensing agents such as sodamide, alkali-metal alkoxides or potassium hydroxide in ethereal solutions, or alkali metals or their amides in liquid ammonia. With substituted acetylenes, the Grignard method is often preferable, although not so convenient with acetylene itself owing to the difficulty of obtaining the pure monomagnesium bromide. There are but few references in the literature to the utilisation of unsaturated aldehydes in this type of condensation. Lespieau and Lombard (*Bull. Soc. chim.*, 1935, **2**, 369) and Teterin and Ivanov (*J. Gen. Chem. Russ.*, 1937, **7**, 1629) prepared ethinylcarbinols from crotonaldehyde and acraldehyde and their halogen substitution products in poor yield by the Grignard method and I.G. Farbenindustrie (B.P. 508,062) have condensed crotonaldehyde and acetylene under pressure in the presence of copper acetylide. Sodamide in liquid ammonia has been employed for the preparation of ethinylcarbinols from 1-methylacraldehyde and 2-ethylhexenal (Kreimeier, U.S.P. 2,106,181) and furfural (Macullum, U.S.P. 2,125,384).

Owing to the relative inaccessibility of (V) the condensation of citral with acetylene was examined in the first instance as a test case. 1-*Ethinylgeraniol* (XVIII) was prepared in 70% yield by reaction of the aldehyde with sodium acetylide (from sodium and not sodamide) in liquid ammonia and on treatment with acetic anhydride and pyridine at 100° readily yielded the *acetyl* derivative. Prolonged treatment of (XVIII) with acetic anhydride at 110°, followed by chromatographic analysis on alumina, gave a product which, according to its absorption spectrum (maximum at 2630 A.; $E^{1\%}_{1\,\text{cm.}}$ 900), a Zerewitinoff determination (0·9 active hydrogen atom), and a quantitative hydrogenation (4·6 molecules of hydrogen absorbed), consisted mainly of the hydrocarbon (XIX).

(XVIII.) $CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CH(OH){\cdot}C{\vdots}CH$

(XIX.) $CMe_2{:}CH{\cdot}CH_2{\cdot}CH{:}CMe{\cdot}CH{:}CH{\cdot}C{\vdots}CH$



(XX.)

A similar condensation with the aldehyde (V) gave the ethinylcarbinol (XX) [6-(2′ : 6′ : 6′-*trimethyl*cyclo*hexenyl*)-4-*methylhex*-4-*en*-1-*yn*-2-*ol*], but, as was observed with 1-ethinylgeraniol, no solid derivatives could be obtained. The carbinol exhibited end absorption at 2190 A. (log ε = 4·08), similar to that of 1-ethinylgeraniol and consistent with its formulation as (XX). Acetylation with acetic anhydride and pyridine at 100° gave the *acetyl* derivative, which showed a maximum light absorption at 2370 A. (log ε = 4·04), indicating that this process is accompanied by a double bond migration resulting in the formation of a conjugated diene system. This isomerisation takes place to some extent in the carbinol itself, since with some specimens of (XX) absorption of low intensity ($E^{1\%}_{1\,\text{cm.}}$ 300—400) at 2300 A. has occasionally been observed.

EXPERIMENTAL.

The spectrographic data are for alcoholic solutions except that 2 : 4-dinitrophenylhydrazones were examined in chloroform.

β-Ionone.—The finely powdered semicarbazone (125 g., needles from 75% methyl alcohol, m. p. 142—144°), suspended in a mixture of light petroleum (500 c.c., b. p. 40—60°) and 2N-sulphuric acid (1200 c.c.), was shaken at 20° for 3 days (cf. Kon, J., 1930, 1616). After filtration the petroleum layer yielded β-ionone (79·5 g.), b. p. 82°/10^{-2} mm., $n_{\mathrm{D}}^{19^\circ}$ 1·5178. *Light absorption :* Maximum, 2930 A.; log $\epsilon = 4{\cdot}11$ (Ruzicka, Seidel, and Firmenich, *Helv. Chim. Acta*, 1941, **24**, 1434, give max. 2980 A.; log $\epsilon = 3{\cdot}95$. Burawoy, J., 1941, 20, gives max. 2935 A.; log $\epsilon = 3{\cdot}94$).

Condensation of β-Ionone with Ethyl Chloroacetate.—A solution of β-ionone (75 g., regenerated from the semicarbazone as above) and ethyl chloroacetate (96 g.) in light petroleum (150 c.c., b. p. 40—60°) was stirred vigorously in an atmosphere of nitrogen at − 60° while finely powdered sodium methoxide (36 g.) was added in small portions during 4 hours. The mixture, which had become orange-red and viscous, was stirred at − 60° for a further hour, and finally at 20° for 18 hours. After refluxing for 6 hours, the whole was cooled, treated with ice (200 g.), and acidified with 6N-acetic acid. The dark-coloured oil which separated was extracted with ether, and the extract washed with water and 2N-sodium bicarbonate. After drying and removal of solvent the residue was fractionally distilled, first at 20 mm. and finally at 0·2 mm., the portion (60 g.), b. p. 135—155°, $n_{\mathrm{D}}^{21^\circ}$ 1·5307, being retained. A middle cut from this fraction was twice distilled, yielding the *glycide* ester, b. p. 55° (bath temp.)/10^{-3} mm. (Found : C, 73·1; H, 9·15. $C_{17}H_{26}O_3$ requires C, 73·4; H, 9·35%). *Light absorption :* see Table I.

The Glycide Acid.—The ester (60 g.) was dissolved in alcoholic potassium hydroxide (250 c.c.; 10%) and kept at 20° for 24 hours. The mixture was diluted with water (1 l.) and, after the neutral portion had been removed with ether, the acid was liberated with 4N-phosphoric acid and isolated by means of ether as a red viscous oil (34 g.). The crude acid was treated with an equal volume of light petroleum (b. p. 40—60°) and kept at 0° over-night. The separated solid was washed with light petroleum (b. p. 40—60°) and on crystallisation from chloroform–light petroleum yielded the *glycide acid* (7·3 g.) in leaflets, m. p. 132° (decomp.), stable under nitrogen in the dark but rapidly becoming yellow and sticky on exposure to air and light. The acid is readily soluble in alcohol and methyl alcohol, hot chloroform and benzene and sparingly soluble in light petroleum (Found : C, 72·05; H, 8·8. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·85%). The *methyl* ester, prepared from the solid acid with diazomethane, had b. p. 70—80° (bath temp.)/10^{-4} mm., $n_{\mathrm{D}}^{22^\circ}$ 1·5540 (Found : C, 72·8; H, 8·9. $C_{16}H_{24}O_3$ requires C, 72·7; H, 9·1%).

Condensation of α-Ionone with Ethyl Chloroacetate.—A condensation with α-ionone (65 g.; $E_{1\,\mathrm{cm.}}^{1\%}$ at 2265 A. = 610; $n_{\mathrm{D}}^{25^\circ}$ 1·4984), ethyl chloroacetate (83 g.), sodium methoxide (23 g.), and ether (100 c.c.) was carried out as described above. The resulting *glycide* ester (31·5 g.) had b. p. 135—145°/0·2 mm., 70° (bath temp.)/10^{-4} mm., $n_{\mathrm{D}}^{24^\circ}$ 1·4996 (Found : C, 73·4; H, 9·45. $C_{17}H_{26}O_3$ requires C, 73·4; H, 9·35%). The ester was hydrolysed as previously described but in this case the acid failed to crystallise.

Condensation of Mesityl Oxide with Ethyl Chloroacetate.—Starting from mesityl oxide (98 g.), ethyl chloroacetate (245 g.), sodium methoxide (108 g.), and ether (200 c.c.), the main reaction product (103 g.) had b. p 115—140°/20 mm., $n_{\mathrm{D}}^{22^\circ}$ 1·4624. On redistillation through a Widmer column the following fractions were collected : (1) B. p. 52—55°/1 mm. (31 g.), $n_{\mathrm{D}}^{24^\circ}$ 1·4552; (2) b. p. 58—63°/1 mm. (35 g.), $n_{\mathrm{D}}^{24^\circ}$ 1·4658; (3) b. p. 69—72°/1 mm. (18·5 g.), $n_{\mathrm{D}}^{24^\circ}$ 1·4661; (4) b. p. 80—90°/1 mm. (10 g.), $n_{\mathrm{D}}^{24^\circ}$ 1·4560. Redistillation of (1) indicated that it was not homogeneous and the upper fraction was consequently combined with (2) and refractionated : (2*a*) B. p. up to 58°/1 mm. (8 g.), $n_{\mathrm{D}}^{22^\circ}$ 1·4620; (2*b*) b. p. 59—61°/1 mm. (20 g.), $n_{\mathrm{D}}^{24^\circ}$ 1·4673. A middle cut from (2*b*) was redistilled, b. p. 60°/1 mm., $n_{\mathrm{D}}^{24^\circ}$ 1·4689 [Found : C, 63·6; H, 8·3. $C_9H_{14}O_3$ (Me ester) requires C, 63·5; H, 8·2%]. *Light absorption :* see Table II.

Fraction (3) was fractionated twice more; a middle cut had b. p. 65°/1 mm., $n_{\mathrm{D}}^{24^\circ}$ 1·4695 [Found : C, 64·5; H, 8·8. $C_{10}H_{16}O_3$ (Et ester) requires C, 65·2; H, 8·7%]. *Light absorption :* see Table II.

Hydrolysis of the mixed ester (20 g.) as described above gave a gum which partly crystallised in the presence of light petroleum (b. p. 40—60°) and a little chloroform. Recrystallisation of this solid (2·5 g.) from the same solvent mixture gave the *glycide acid* in needles, m. p. 72° (Found : C, 61·7; H, 7·6. $C_8H_{12}O_3$ requires C, 61·5; H, 7·7%). The methyl ester, prepared with diazomethane, had $n_{\mathrm{D}}^{21^\circ}$ 1·4791. *Light absorption :* see Table II.

3-(2′ : 6′ : 6′-*Trimethyl*cyclo*hexenyl*)-1-*methylcrotonaldehyde* (V).—The β-ionone glycide acid (crude, 65 g.) was treated with copper powder (0·2 g.) and heated in an oil-bath at 130°/15 mm. until decarboxylation appeared complete (about 1½ hours). The residue was distilled up to 180°/0·1 mm., and the distillate diluted with ether and dried. After removal of solvent the oil was fractionated through a Widmer column, yielding two fractions, (1) b. p. 80—90°/0·1 mm. (7 g.), which did not yield any ketonic derivatives, was inert towards sodium, and was not investigated further, and (2) b. p. 105—115°/0·1 mm. (14 g.), $n_{\mathrm{D}}^{24^\circ}$ 1·5059. *Thiosemicarbazone :* needles from methyl alcohol, m. p. 192° (Found : C, 64·5; H, 9·0; N, 14·75. $C_{15}H_{25}N_3S$ requires C, 64·5; H, 9·0; N, 15·05%). *Phenylsemicarbazone :* needles from methyl alcohol, m. p. 182° (Found : C, 74·5; H, 8·5; N, 12·4. $C_{21}H_{29}ON_3$ requires C, 74·3; H, 8·6; N, 12·4%). 2 : 4-*Dinitrophenylhydrazone :* red plates from alcohol, m. p. 164·5° (Found : C, 62·2; H, 6·7. $C_{20}H_{26}O_4N_4$ requires C, 62·0; H, 7·0%). The thiosemicarbazone (0·5 g.) and phthalic anhydride (3 g.) were steam-distilled for 20 hours in nitrogen; the oily distillate, after isolation by means of ether, yielded pure 3-(2′ : 6′ : 6′-*trimethyl*cyclo*hexenyl*)-1-*methylcrotonaldehyde* (0·4 g.), b. p. 45° (bath temp.)/10^{-4} mm., $n_{\mathrm{D}}^{24^\circ}$ 1·5067 (Found : C, 81·5; H, 10·95. $C_{14}H_{22}O$ requires C, 81·6; H, 10·7%). Treatment of this regenerated aldehyde with thiosemicarbazide gave the same derivative, m. p. 191—192° (mixed m. p.), as was obtained immediately from the decarboxylation.

3-(2′ : 6′ : 6′-*Trimethyl*-Δ²′-cyclo*hexenyl*)-1-*methylcrotonaldehyde* (X).—The α-ionone glycide acid (18 g.) on decarboxylation by the method described above yielded an aldehyde (8·7 g.), b. p. 135—145°/0·3 mm., $n_{\mathrm{D}}^{24^\circ}$ 1·5016. *Thiosemicarbazone :* plates from aqueous methyl alcohol, m. p. 158—159° (Found : N, 14·9. $C_{15}H_{25}N_3S$ requires N, 15·05%). *Phenylsemicarbazone :* needles from aqueous methyl alcohol, m. p. 123—124° (Found : N, 12·3. $C_{21}H_{29}ON_3$ requires N, 12·4%). 2 : 4-*Dinitrophenylhydrazone :* red needles from methyl alcohol, m. p. 148·5—149·5° (Found : N, 14·35. $C_{20}H_{26}O_4N_4$ requires N, 14·5%). Regeneration of the aldehyde from the thiosemicarbazone yielded pure 3-(2′ : 6′ : 6′-*trimethyl*-Δ²′-cyclo*hexenyl*)-1-*methylcrotonaldehyde*, b. p. 45° (bath temp.)/10^{-4} mm., $n_{\mathrm{D}}^{24^\circ}$ 1·5024 (Found : C, 81·6; H, 10·6. $C_{14}H_{22}O$ requires C, 81·6; H, 10·7%).

2 : 4-*Dimethylpentenals* (XII and XIII).—The glycide acid from mesityl oxide (crude, 40 g.) was heated with copper powder at 145°/760 mm. for ½ hour. The mixture of 2 : 4-dimethylpentenals (9·5 g.) obtained had b. p. 125—135°, $n_{\mathrm{D}}^{24^\circ}$ 1·4310, and no appreciable separation was observed on attempted fractionation. *Light absorption :* see Table III. Treatment of the aldehyde (1 g.) with semicarbazide acetate, followed by repeated crystallisation of the product from aqueous methyl alcohol, gave needles of the *semicarbazone* of 2 : 4-*dimethylpent-2-enal* (50 mg.), m. p. 184° (Found : C, 56·6; H, 8·95. $C_8H_{15}ON_3$ requires C, 56·8; H, 8·8%). *Light absorption :* Maximum, 2634 A.; log $\epsilon = 4{\cdot}42$. Regeneration of the aldehyde from the twice crystallised semicarbazone gave a product, containing a high proportion of the αβ-isomer, b. p. 130—135°, $n_{\mathrm{D}}^{27^\circ}$ 1·4355 (Found : C, 74·8; H, 10·65. $C_7H_{12}O$ requires C, 75·0; H, 10·7%). *Light absorption :* Maximum, 2270 A.; log $\epsilon = 3{\cdot}94$. The corresponding *phenylsemicarbazone* after repeated crystallisation from aqueous alcohol had m. p. about 125°, but after ten crystallisations from light petroleum (b. p. 40—60°) a small fraction was obtained in needles with the constant m. p. 178° (Found : C, 68·7; H, 7·9. $C_{14}H_{19}ON_3$ requires C, 68·6; H, 7·8%). The 2 : 4-*dinitrophenylhydrazone* was obtained in orange needles from alcohol, m. p. 164—165° (Found : N, 19·6. $C_{13}H_{16}O_4N_4$ requires N, 19·2%).

7-(2′ : 6′ : *6′-Trimethyl*cyclo*hexenyl)-5-methylhepta*-3 : *5-dien-2-one* (XIV).—A solution of the β-ionone C_{14} aldehyde (10 g., log ε at 2300 A. = 4·12) in a mixture of dry A.R. benzene (300 c.c.) and dry acetone (200 c.c.) was refluxed in an atmosphere of nitrogen for 48 hours together with freshly prepared aluminium *tert.*-butoxide (12 g.). The deep red suspension was treated with water and filtered, the benzene solution washed with water and dried, and the solvent removed under diminished pressure. Distillation of the residue from an electrically heated retort gave two fractions. (1) B. p. 60°/10^{-4} mm. (1·9 g.), $n_{\mathrm{D}}^{20^\circ}$ 1·5190. Unchanged aldehyde (phenylsemicarbazone, m. p. 182°). (2) B. p. 70—80°/10^{-4} mm. (4·2 g.), $n_{\mathrm{D}}^{20^\circ}$ 1·5420. *Light absorption:* Maximum, 2850 A.; log ε = 4·27. The *semicarbazone*, obtained in poor yield (2·0 g.), formed needles from methyl alcohol, m. p. 189—190° (decomp.), which varied with the rate of heating (Found: C, 71·2; H, 9·7; N, 14·1. $C_{18}H_{29}ON_3$ requires C, 71·25; H, 9·65; N, 13·9%). *Light absorption:* Maximum, 2930 A.; log ε = 4·67. Inflexion, 3040 A.; log ε = 4·62.

The finely powdered semicarbazone (2·3 g., m. p. 189—190°) was suspended in a mixture of light petroleum (100 c.c.; b. p. 40—60°) and 2N-sulphuric acid (40 c.c.) and heated under reflux for 48 hours with vigorous stirring. Working up in the usual manner gave 7-(2′ : 6′ : *6′-trimethyl*cyclo*hexenyl)-5-methylhepta*-3 : *5-dien-2-one* (0·8 g.) (0·9 g. of semicarbazone was recovered), as a pale yellow oil, b. p. 75—80° (bath temp.)/10^{-4} mm., $n_{\mathrm{D}}^{19^\circ}$ 1·5412 (Found: C, 82·8; H, 10·2. $C_{17}H_{26}O$ requires C, 82·9; H, 10·6%). This regenerated ketone gave the same semicarbazone, m. p. 189—190°, as did the crude material, indicating that the regeneration process has no adverse effect on the ketone.

8-(2′ : 6′ : *6′-Trimethyl*cyclo*hexenyl)-3* : *6-dimethylocta-4* : *6-dien-3-ol* (XVII).—The C_{17} ketone described above (450 mg., $n_{\mathrm{D}}^{25^\circ}$ 1·5399, regenerated from the semicarbazone) was treated with ethylmagnesium bromide (from 100 mg. of magnesium) in ethereal solution. Decomposition of the Grignard complex with ammonium chloride and isolation of the product by means of ether yielded 8-(2′ : 6′ : *6′-trimethyl*cyclo*hexenyl)-3* : *6-dimethylocta-4* : *6-dien-3-ol* (400 mg.) as a viscous oil, b. p. 70—80° (bath temp.)/10^{-4} mm., $n_{\mathrm{D}}^{21^\circ}$ 1·5003 (Found: C, 82·7; H, 11·8. $C_{19}H_{32}O$ requires C, 82·5; H, 11·7%). The carbinol (143 mg.) gave 12 c.c. of methane at 19°/758 mm. equivalent to 1·0 active hydrogen atom per molecule.

1-*Ethinylgeraniol* (XVIII).—Purified dry acetylene was rapidly passed into a stirred solution of sodium (18 g.) in liquid ammonia (1000 c.c.) until the solution became colourless. A solution of citral (100 g.) in dry ether (400 c.c.) was then added during ½ hour and stirring and cooling were continued for a further 3 hours. After standing overnight the residue was decomposed with dilute hydrochloric acid (ice), and the ethereal layer washed, dried, and evaporated. Distillation of the product through a Widmer column gave 1-*ethinylgeraniol* (80 g.) as a colourless oil, b. p. 88°/0·02 mm., $n_{\mathrm{D}}^{20^\circ}$ 1·4875 (Found: C, 80·9; H, 10·9. $C_{12}H_{18}O$ requires C, 80·85; H, 10·2%). The carbinol (140 mg.) evolved 34·7 c.c. of methane at 767 mm./19° (after heating to 90°), equivalent to 1·9 active hydrogen atoms per molecule. The carbinol yielded insoluble silver and mercury salts and its ultra-violet absorption spectrum showed only end absorption (at 2150 A.; $E^{1\%}_{1\,\mathrm{cm.}}$ = 250). A mixture of the carbinol (27·5 g.), acetic anhydride (34 g.), and pyridine (27·5 g.) was heated at 100° for an hour in nitrogen. After removal of the reagents the *acetyl* derivative (26·5 g.) was obtained, b. p. 92—95°/0·5 mm., $n_{\mathrm{D}}^{22^\circ}$ 1·4728 (Found: C, 76·5; H, 9·0; OAc, 19·4. $C_{14}H_{20}O_2$ requires C, 76·4; H, 9·1; OAc, 19·5%). The acetate (4·00 mg.) evolved 0·376 c.c. of methane at 24°/771 mm. (after heating to 90°), equivalent to 0·9 active hydrogen atom per molecule. The ultra-violet absorption spectrum was similar to that of the carbinol.

6-(2′ : 6′ : *6′-Trimethyl*cyclo*hexenyl)-4-methylhex-4-en-1-yn-2-ol* (XX).—Prepared by a similar method as for 1-ethinylgeraniol from the β-ionone C_{14} aldehyde (16 g.), the *carbinol* (6 g.) had b. p. 115—120°/10^{-3} mm., $n_{\mathrm{D}}^{22^\circ}$ 1·5165 (Found: C, 83·1; H, 10·2. $C_{16}H_{24}O$ requires C, 82·8; H, 10·35%). It (7·70 mg.) evolved 0·14 c.c. of methane at 25°/771 mm. (after heating to 90°), equivalent to 1·8 active hydrogen atoms per molecule. The *acetyl* derivative, prepared by the method used with 1-ethinylgeraniol, had b. p. 130—135°/0·1 mm., $n_{\mathrm{D}}^{21\cdot5^\circ}$ 1·5135 (Found: C, 78·6; H, 9·8. $C_{18}H_{26}O_2$ requires C, 78·8; H, 9·5%). It (6·65 mg.) evolved 0·52 c.c. of methane at 22°/761 mm. (after heating to 90°), equivalent to 0·9 active hydrogen atom per molecule.

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