323. *Studies in the Polyene Series. Part XXVIII. The Structure of the* C_{14} *Aldehyde derived from* β*-Ionone and its Use for the Synthesis of Norvitamin A and* iso*Vitamin A Derivatives.*

By G. W. H. Cheeseman, Sir Ian Heilbron, E. R. H. Jones, F. Sondheimer, and B. C. L. Weedon.

Evidence for the structure of the C_{14} aldehyde, formed by application of the Darzens reaction to β-ionone, is reviewed. The conclusion is drawn that (I) is the only formulation compatible with the reactions of the aldehyde.

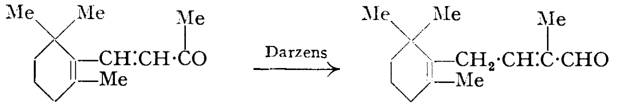
Condensation of (I) with 1-methoxypent-2-en-4-yne (X; $R_1 = H$, $R_2 = Me$) yields the methoxy-carbinol (XI; $R_1 = H$, $R_2 = Me$), which on partial hydrogenation gives the tetraene (XII; $R_1 = H$, $R_2 = Me$). The latter, on treatment with iodine, is converted into the norvitamin A methyl ether (XIII; $R_1 = H$, $R_2 = Me$). The *iso*vitamin A methyl ether (XIII; $R_1 = R_2 = Me$) is similarly prepared from the methoxy-carbinol (XI; $R_1 = R_2 = Me$).

By condensation of pent-2-en-4-yn-1-ol and hex-3-en-5-yn-2-ol with (I), the glycols (XI; $R_1 = R_2 = H$) and (XI; $R_1 = Me, R_2 = H$) are obtained. Partial hydrogenation of the former product yields the tetraene glycol (XII; $R_1 = R_2 = H$), the monoacetate of which, on treatment with iodine, gives the norvitamin A acetate (XIII; $R_1 = H, R_2 = Ac$). The product formed on partial hydrogenation of the diacetate of the glycol (XI; $R_1 = Me, R_2 = H$) yields, on treatment with iodine, the *iso*vitamin A acetate (XIII; $R_1 = Me, R_2 = Ac$) and a hydrocarbon, $C_{20}H_{28}$, exhibiting light absorption similar to that of anhydrovitamin A. [The nor- and *iso*-vitamin A derivatives described are obtained as concentrates containing 15—45% of the required polyenes.]

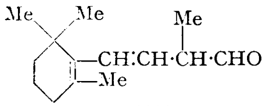
The norvitamin A methyl ether (XIII; $R_1 = H, R_2 = Me$) possesses definite growth promoting properties (not less than one-thirtieth of that of vitamin A) when fed orally to vitamin-A-deficient rats.

THE decarboxylation, in the presence of copper powder, of the glycide acid derived from β-ionone was described by Heilbron, Johnson, Jones, and Spinks (*J.*, 1942, 727) and shown to give the C_{14} aldehyde (I), which was purified by regeneration from the thiosemicarbazone or semicarbazone (Cymerman, Heilbron, Jones, and Lacey, *J.*, 1946, 500). Subsequently Isler, Huber, Ronco, and Kofler (*Helv. Chim. Acta*, 1947, **30**, 1911) found that, when the Darzens condensation of β-ionone with ethyl chloroacetate was carried out at −10° and the product hydrolysed at *ca.* +5° without isolation of the glycide ester, the pure C_{14} aldehyde (I) was obtained directly in 80% yield. We have confirmed this important observation and by comparison of their derivatives and reactions, established that the aldehydes prepared by the two routes are identical.

Recently, Milas *et al.* (*J. Amer. Chem. Soc.*, 1948, **70**, 1584; Milas, "Vitamins and Hormones," New York, 1947, **5**, 1) reported the decarboxylation of the pyridine salt of the glycide acid and concluded that the main product had the structure (II). In view of the fact that the C_{14} aldehyde is a key intermediate for the synthesis of vitamin A and related compounds (Isler *et al., loc. cit.*; *Experientia*, 1946, **2**, 31; Emil Barell Jubilee Volume, Hoffmann–La Roche and Co., Ltd., Basel, 1946, p. 31; Heilbron, *J.*, 1948, 386; Milas *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 1591, 1597), it is highly desirable that any remaining doubts as to its structure should be dispelled. Accordingly we summarise the existing evidence, which we regard as clearly indicating the structure (I), and at the same time advance new evidence as confirmation. It should be noted at the outset that in all our experiments we have employed only the pure aldehyde, either prepared directly by the method of the Swiss workers, or regenerated under mild conditions from a crystalline derivative. On the other hand, Milas *et al.* (*loc. cit.*) have used material, the homogeneity of which, on the evidence provided, is in our opinion extremely doubtful. Their crude decarboxylation product was twice fractionated through a 6-inch Vigreux column and the main fraction was used in all synthetic and structural studies since " it was felt that this, being the largest portion, represented the main product of the reaction."



(I.)



(II.)

(*a*) The light absorptions (see Table I) of the 2 : 4-dinitrophenylhydrazone, semicarbazone, thiosemicarbazone, and phenylsemicarbazone (Heilbron *et al., loc. cit.*) are typical of those of αβ-unsaturated aldehydes. The formation of crystalline derivatives from the main fraction of Milas *et al.* " was slow and the yields were low." Whereas the 2 : 4-dinitrophenylhydrazone and semicarbazone described by these authors agree reasonably in melting point and light-absorption data with those prepared by us (in yields of *ca.* 80% from the pure aldehyde), the thiosemicarbazone, like that obtained previously by Ishikawa and Matsuura (*Sci. Rep. Tokyo Bunrika Daigaku, A*, 1937, **3**, 173; *Chem. Zentr.*, 1937, II, 3452), melts considerably lower (*ca.* 30—40°) than those prepared by us and by Isler *et al.* (Emil Barell Jubilee Volume). It is to be regretted that Milas *et al.* have not reported the light-absorption properties of their thiosemicarbazone.

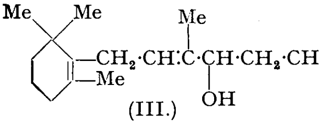
(*b*) Condensation of the C_{14} aldehyde with ethylmagnesium bromide furnishes a secondary *carbinol* (in 90% yield) which exhibits no light absorption of appreciable intensity in the region 2200—4000 A., in agreement with the formulation (III). On the other hand, Milas *et al.*, from their main fraction possessing $\varepsilon_{max.} = 20,500$ (2320 A.), obtained a product which had $\varepsilon_{max.} = 6000$ (2260 A.). A carbinol derived from an aldehyde of structure (II) must show light-absorption properties very similar (in both $\lambda_{max.}$ and $\varepsilon_{max.}$) to those of the original aldehyde.

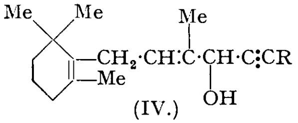
TABLE I.

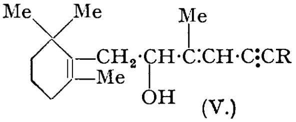
2 : 4-*Dinitrophenylhydrazone* (CHCl$_3$)	$\lambda_{max.}$ A	$\varepsilon_{max.}$
Of $CH_3\cdot CH_2\cdot CHO$[1]	3610	21,000
Of citral[1] ($>C{=}CH\cdot CHO$)	3850	31,000
Of C$_{14}$ aldehyde[1] ($-CH{=}\overset{|}{C}\cdot CHO$)	3830	29,500
Semicarbazone.		
Of *iso*pulegone[2] ($CH_2{=}\overset{|}{C}\cdot\overset{|}{C}H\cdot\overset{|}{C}O$)	<2400	—
Of citral[3] ($>C{=}CH\cdot CHO$)	2720	31,500
Of C$_{14}$ aldehyde ($-CH{=}\overset{|}{C}\cdot CHO$)	2650	29,500
	2690	29,000
Thiosemicarbazone.		
Of $CH_3\cdot CH_2\cdot CHO$[4]	2700	20,500
Of α-ionone[4] ($-CH{=}CH\cdot\overset{|}{C}O$)	3025	36,500
Of C$_{14}$ aldehyde[5] ($-CH{=}\overset{|}{C}\cdot CHO$)	2990	39,000
Phenylsemicarbazone.		
Of β-*cyclo*citral[3] ($>C{=}\overset{|}{C}\cdot CHO$)	2805	26,500
Of C$_{14}$ aldehyde[5] ($-CH{=}\overset{|}{C}\cdot CHO$)	2780	37,000

[1] Braude and Jones, *J.*, 1945, 498.
[2] Menschick, Page, and Bossert, *Annalen*, 1932, **495**, 225.
[3] Burawoy, *J.*, 1941, 20.
[4] Evans and Gillam, *J.*, 1943, 565.
[5] Heilbron, Johnson, Jones, and Spinks, *loc. cit.*

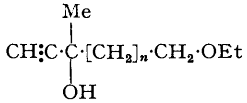
(*c*) Condensation of the C$_{14}$ aldehyde with sodium acetylide in liquid ammonia gives the acetylenic carbinol (IV; R = H) in 33% yield (Heilbron, Johnson, Jones, and Spinks, *J.*, 1942, 727), and by the use of lithium acetylide the yield of this substance has now been increased to 75%. Condensation with hexynylmagnesium bromide furnishes the carbinol (IV; R = Bu^n) (Cymerman, Heilbron, Jones, and Lacey, *loc. cit.*); neither of these carbinols shows light absorption of appreciable intensity in the ultra-violet. When the carbinol (IV; R = Bu^n) is shaken with dilute sulphuric acid, the rearranged carbinol (V; R = Bu^n) is obtained in nearly quantitative yield. The latter shows the typical light-absorption properties ($\lambda_{max.}$ = 2290 A.) of a conjugated enyne. Again, the carbinol (IV; R = CH:CH·CHMe·OMe) on shaking with dilute acid gives (V; R = CH:CH·CHMe·OMe) which shows the characteristic light-absorption properties of a conjugated dienyne (*idem, loc. cit.*). The very occurrence of these anionotropic rearrangements, and the light-absorption properties of the products, can only be interpreted if the parent C$_{14}$ aldehyde is αβ-unsaturated.


(III.)

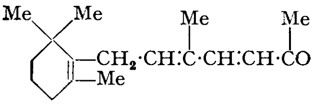

(IV.)

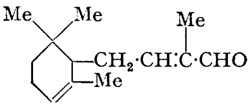

(V.)

Milas *et al.* condensed their main fraction with acetylene (*loc. cit.*, p. 1584) and also with the ethynylcarbinols (VI; *n* = 1 and 2) (*loc. cit.*, p. 1591, 1597). None of the products exhibited absorption at 2200—2260 A. of intensity ($\varepsilon_{max.}$ = 9500, 4470, and 9800, respectively) comparable with that of the starting material ($\varepsilon_{max.}$ = 20,500), as would have been the case had the latter consisted of an aldehyde of structure (II).


$CH{\vdots}C\cdot\underset{OH}{\overset{Me}{C}}\cdot[CH_2]_n\cdot CH_2\cdot OEt$

(VI.)


(VII.)


(VIII.)

(*d*) Condensation of the C$_{14}$ aldehyde with acetone under Oppenauer conditions (*cf.* Heilbron, Johnson, Jones, and Spinks, *loc. cit.*) has now provided the ketone (VII) as a crystalline solid. Its light-absorption properties are typical of those of a doubly unsaturated ketone. In this instance, however, the possibility of migration of a double bond under the experimental conditions cannot be definitely excluded.

(*e*) That no migration of the cyclic double bond occurs during the formation of the C_{14} aldehyde (I) from β-ionone is shown by the fact that an entirely different, isomeric, αβ-unsaturated aldehyde (VIII) is obtained by decarboxylation of the glycide acid from α-ionone (*idem, loc. cit.*). Further, the successful application of (I) in the preparation of vitamin A (Isler *et al., loc. cit.*) and related polyenes (see below) provides additional confirmation that the position of the cyclic double bond has been correctly assigned.

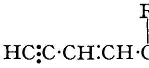
(*f*) Milas *et al.* (*loc. cit.*, p. 1584), in support of formula (II) for their main fraction, stated that ozonolysis by the method of Strain (*J. Biol. Chem.*, 1933, **102**, 137) gave geronic acid in 40% yield. We have ozonised the pure aldehyde (I), also following the method of Strain, and failed to detect any geronic acid. Working under identical conditions we obtained geronic acid in 45% yield from β-ionone.

We have always realised that the crude product from the copper-bronze decarboxylation of the glycide acid is a mixture, quite probably of oxide and aldehydes, and for this reason we have used either the regenerated C_{14} aldehyde or, latterly, the aldehyde made according to Isler *et al.* (*Helv. Chim. Acta*, 1947, **30**, 1911). On the basis of the evidence obtained by us and submitted above, we are convinced that only the structure (I) is compatible with the reactions of the pure C_{14} aldehyde prepared by either of the two routes described.†

As part of an extensive study of the relations between chemical constitution and biological activity in the vitamin A field (*vide* Heilbron, *J.*, 1948, 386; Heilbron, Jones, and Richardson, this vol., p. 287), we have synthesised the acetate and methyl ether of both the norvitamin A (XIII; $R_1 = R_2 = H$) and the *iso*vitamin A (XIII; $R_1 = Me$, $R_2 = H$). The procedures employed were essentially those envisaged by Heilbron *et al.* (*J.*, 1942, 727; 1944, 141) and used later by Isler *et al.* (*loc. cit.*) for the preparation of vitamin A (XIV) and its methyl ether.

$HC\vdots C{\cdot}CH(OH){\cdot}CH{:}CH_2$

(IX.)

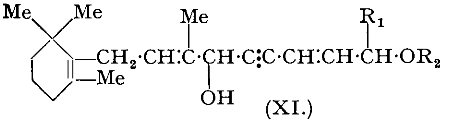


$HC\vdots C{\cdot}CH{:}CH{\cdot}\overset{R_1}{CH}{\cdot}OR_2$

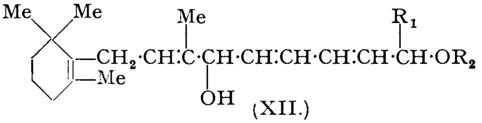
(X.)

Bromination, with phosphorus tribromide, of vinylethynylcarbinol (IX) (Jones and McCombie, *J.*, 1942, 733) or the isomeric pent-2-en-4-yn-1-ol (X; $R_1 = R_2 = H$) (Haynes, Heilbron, Jones, and Sondheimer, *J.*, 1947, 1583), and treatment of the resulting crude bromide with sodium methoxide yielded (55 and 65%, respectively) 1-*methoxypent*-2-*en*-4-*yne* (X; $R_1 = H, R_2 = Me$). Condensation of the Grignard complex of this ether with the C_{14} aldehyde (I) gave the *methoxycarbinol* (XI; $R_1 = H$, $R_2 = Me$) in 75% yield. This compound, containing a conjugated vinylacetylene chromophore, was partly hydrogenated in the presence of a quinoline-poisoned palladium–charcoal catalyst (for a gift of which the authors are indebted to Messrs. Hoffmann-La Roche and Co., Ltd., Basel). The resulting crude tetraene (XII; $R_1 = H$, $R_2 = Me$), on being heated with a trace of iodine in toluene solution, underwent simultaneous rearrangement and dehydration yielding the norvitamin A methyl ether (XIII; $R_1 = H$, $R_2 = Me$). Similarly, the methoxy-carbinol (XI; $R_1 = R_2 = Me$) (Cymerman, Heilbron, Jones, and Lacey, *loc. cit.*) gave the *iso*vitamin A methyl ether (XIII; $R_1 = R_2 = Me$). The intensity of maximal light absorption in the region 3230—3280 A. indicated that the reaction products contained *ca.* 45 and 40%, respectively, of the ethers.

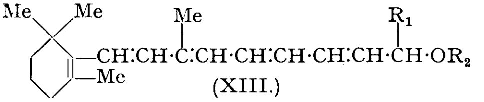
Condensation of the di-Grignard complex of both pent-2-en-4-yn-1-ol (X; $R_1 = R_2 = H$) and hex-3-en-5-yn-2-ol (X; $R_1 = Me$, $R_2 = H$) (Heilbron, Jones, Smith, and Weedon, *J.*, 1946, 54) with the C_{14} aldehyde (I) gave (60 and 55%) the *glycols* (XI; $R_1 = R_2 = H$) and (XI; $R_1 = Me$, $R_2 = H$), respectively. Partial hydrogenation of (XI; $R_1 = R_2 = H$) yielded a



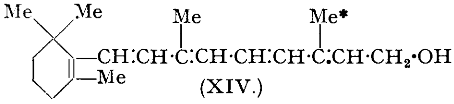
(XI.)



(XII.)



(XIII.)



(XIV.)

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† *Added in Proof*.—Since this paper was written, Inhoffen *et al.* (*Annalen*, 1948, **561**, 26) have reported that the Raman spectrum of the C_{14} aldehyde both supports the structure (I) and disproves the formula (II) favoured by Milas.

mixture consisting essentially of the polyene *glycol* (XII; $R_1 = R_2 = H$). The primary hydroxyl group was protected by selective acetylation with acetyl chloride and pyridine, and the *monoacetate* (XII; $R_1 = H$, $R_2 = Ac$) thus formed was heated with a trace of iodine in light petroleum; from the intensity of the light-absorption maximum at 3240 A., the product was estimated to contain *ca.* 25% of the norvitamin A acetate (XIII; $R_1 = H$, $R_2 = Ac$).

Acetylation of the glycol (XI; $R_1 = Me$, $R_2 = H$) with acetic anhydride and pyridine gave the corresponding *diacetate*; this was partly hydrogenated, and the resulting crude tetraene heated with a trace of iodine in toluene. The product, exhibiting a light-absorption maximum at 3260 A., was estimated to contain *ca.* 15% of the *iso*vitamin A acetate (XIII; $R_1 = Me$, $R_2 = Ac$).

Iodine treatment of the diacetate of (XII; $R_1 = Me$, $R_2 = H$) was found frequently to give rise, not only to the required polyene acetate (XIII; $R_1 = Me$, $R_2 = Ac$), but also, by loss of two molecules of acetic acid, to an unstable *hydrocarbon* which was readily isolated by chromatography and exhibited light absorption similar to that of anhydrovitamin A (Table II).

TABLE II.

	$\lambda_{max.}$ A.	$\varepsilon_{max.}$
HC⋮C·CH:CH·CH$_2$·OMe	2220	12,500
	2290 *	11,500
HC⋮C·CH:CH·CHMe·OMe [1]	2235	12,500
	2320 *	11,000
HO·CH$_2$·C⋮C·CH:CH·CH$_2$·OH [2]	2270	15,000
	2370 *	12,000
(XI; $R_1 = H$, $R_2 = Me$)	2290	17,500
	2370 *	15,000
(XI; $R_1 = R_2 = H$)	2280	16,000
	2380 *	13,000
(XI; $R_1 = R_2 = Me$) [3]	2235	16,000
	2270	16,000
	2350 *	13,500
(XI; $R_1 = Me$, $R_2 = H$)	2280	13,500
	2410 *	10,500
Diacetate of (XI; $R_1 = Me$, $R_2 = H$)	2280	15,000
Hydrocarbon, $C_{20}H_{28}$	3510	46,500
	3660	55,000
	3840	40,000
Anhydrovitamin A [4]	3520	51,000
	3700	78,000
	3910	70,000

* Inflexion.

[1] Heilbron, Jones, and Weedon, *J.*, 1945, 81. [2] Heilbron, Jones, and Sondheimer, *J.*, 1947, 1586.

[3] Cymerman, Heilbron, Jones, and Lacey, *loc. cit.*

[4] Isler, Huber, Ronco, and Kofler, *Helv. Chim. Acta*, **1947, 30,** 1911.

This hydrocarbon was also obtained on iodine treatment of the glycol (XII; $R_1 = Me$, $R_2 = H$), prepared by partial hydrogenation of (XI; $R_1 = Me$, $R_2 = H$).

The various intermediates in the polyene syntheses described above exhibited the expected light-absorption properties. The glycols (XI; $R_1 = H$ and Me, $R_2 = H$) and the methoxy-carbinols (XI; $R_1 = H$ and Me, $R_2 = Me$) all showed the characteristic maximum and inflexion observed with a conjugated vinylacetylene.

The norvitamin A derivatives were found to be very unstable and as a result no accurate biological assays were possible. Owing to the instability of these compounds, purification could not be achieved by chromatography. However, when the crude methyl ether (XIII; $R_1 = H$, $R_2 = Me$) was fed orally to vitamin-A-deficient rats in daily doses of 40 γ, definite growth responses were produced at doses which indicated that the ether possessed activity not less than one-thirtieth that of vitamin A itself. The *iso*vitamin A acetate (XIII; $R_1 = Me$, $R_2 = Ac$) and methyl ether (XIII; $R_1 = R_2 = Me$), although considerably more stable than the corresponding norvitamin A derivatives, exhibited no biological activity. (The tests were carried out at doses which would have revealed activity of the order of one-hundredth and one-thousandth, respectively, of that of vitamin A.) It may be concluded that the presence of the $C_{(3)}$-methyl group (Me*) in the polyene chain of vitamin A (XIV), although contributing very appreciably to the stability of the molecule, is not essential for biological activity.

EXPERIMENTAL.

Light-absorption data were determined in ethanol, except where stated otherwise. The purities of the polyene concentrates were estimated on the assumptions that absorption in the region 3230—3280 A. was due entirely to the nor- and *iso*-vitamin A derivatives, and that the latter, when pure, would exhibit absorption of the same intensity as vitamin A. All the operations were carried out in an atmosphere of nitrogen.

γ-(2 : 6 : 6-*Trimethyl*cyclo*hex*-1-*enyl*)-α-*methylcrotonaldehyde* (C_{14} *Aldehyde*) (I).—Sodium methoxide (38 g.; commercial) was added in portions, during 30 minutes, to a well-stirred mixture of ethyl chloroacetate (80 g.) and β-ionone (100 g.; light absorption: maxima, 2230, 2960 A.; ε, 6,500 and 10,000 respectively), the temperature being maintained at −15° by means of an alcohol–carbon dioxide bath. Stirring was continued for 4 hours at −10°, and then a cold solution of sodium hydroxide (45 g.) in water (50 c.c.) and methanol (250 c.c.) was added during 30 minutes, the temperature being kept at 0°. After the mixture had been stirred for a further 2 hours at 5°, water was added and the product was isolated by means of ether and distilled. The fraction (87 g.), b. p. 110—125°/0·3 mm., was carefully redistilled to give the aldehyde (71 g.), b. p. 91—92°/0·015 mm., $n_D^{19°}$ 1·5113 (light absorption: maximum, 2290 A.; ε, 16,000). The semicarbazone had m. p. 156—157° (Cymerman, Heilbron, Jones, and Lacey, *J.*, 1946, 500, give m. p. 148—150°; Milas *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 1584, give m. p. 149·5—150·5°); the 2 : 4-dinitrophenylhydrazone (obtained in 80% yield) had m. p. 173° (Heilbron, Johnson, Jones, and Spinks, *J.*, 1942, 727 give m. p. 164·5°; Milas *et al.*, *loc. cit.*, give m. p. 169—170°); the thiosemicarbazone (obtained in 80% yield) had m. p. 200°, undepressed on admixture with a specimen (m. p. 200°) prepared by the method of Heilbron *et al.* (*loc. cit.*) [Isler *et al.*, Emil Barell Jubilee Volume, Hoffmann–La Roche and Co., Ltd., Basel, 1946, p. 31, give m. p. 193—194° (corr.); Ishikawa and Matsuura, *loc. cit.*, give m. p. 160° (corr.); Milas *et al.*, *loc. cit.*, give m. p. 156—159°]. A sample of C_{14} aldehyde, regenerated from the thiosemicarbazone by steam-distillation in the presence of oxalic acid, had $n_D^{16°}$ 1·5120. Light-absorption maximum: 2300 A.; ε, 17,500.

6-(2′ : 6′ : 6′-*Trimethyl*cyclo*hex*-1′-*enyl*)-4-*methylhex*-4-*en*-3-*ol* (III).—The C_{14} aldehyde (10·3 g.) in ether (100 c.c.) was added gradually, with stirring, to a solution of ethylmagnesium bromide (prepared from 1·8 g. of magnesium) in ether (100 c.c.), and the mixture was boiled under reflux for 3 hours. Decomposition of the Grignard complex with aqueous ammonium chloride, and isolation of the product with ether, yielded the *carbinol* (10·5 g.) as a viscous liquid, b. p. 101°/0·05 mm., $n_D^{19°}$ 1·5012 (Found: C, 81·1; H, 11·85. $C_{16}H_{28}O$ requires C, 81·3; H, 11·95%). The carbinol showed no light absorption of appreciable intensity at >2200 A.

6-(2′ : 6′ : 6′-*Trimethyl*cyclo*hex*-1′-*enyl*)-4-*methylhex*-4-*en*-1-*yn*-3-*ol* (IV; R = H).—A rapid stream of dry acetylene was passed through a stirred suspension of lithium (0·7 g.), in small pieces, in liquid ammonia (400 c.c.), cooled in a carbon dioxide–alcohol bath. When all the lithium had reacted, C_{14} aldehyde (12 g.) in ether (50 c.c.) was added dropwise and the mixture was stirred overnight, a slow stream of acetylene being passed in throughout. Ammonium chloride (10 g.) was added, the ammonia was evaporated on the steam-bath, and the residue was extracted thoroughly with ether. The ethereal extract was washed with water, dried, and evaporated. Distillation of the residue then gave the acetylenic carbinol (10·1 g.) as a pale yellow oil, b. p. 120—122°/0·2 mm., $n_D^{20°}$ 1·5130 (Found: C, 82·6; H, 10·5. Calc. for $C_{16}H_{24}O$: C, 82·8; H, 10·35%). The carbinol showed no light absorption of appreciable intensity at >2200 A. It formed a white silver derivative with ammoniacal silver nitrate.

7-(2′ : 6′ : 6′-*Trimethyl*cyclo*hex*-1′-*enyl*)-5-*methylhepta*-3 : 5-*dien*-2-*one* (VII).—A solution of C_{14} aldehyde (10 g.) and freshly prepared aluminium *tert.*-butoxide (12 g.) in benzene (300 c.c.) and acetone (200 c.c.) was heated under reflux for 48 hours. After cooling it, 10% (w/v) sulphuric acid was added and the organic layer was separated, washed well with water, dried, and evaporated. Distillation of the residue gave the ketone (3·6 g.), b. p. 118—122°/10^{-3} mm., which rapidly solidified. Crystallisation from pentane and then from aqueous methanol gave colourless prisms, m. p. 67—68° (Found: C, 82·5; H, 10·5. Calc. for $C_{17}H_{26}O$: C, 82·9; H, 10·6%) (light absorption: maxima, 2810 and 2900 A.; ε, 30,500 and 25,500, respectively). [ψ-Ionone, having the same chromophoric system, has light absorption: maximum, 2910 A.; ε, 22,000 (Burawoy, *J.*, 1941, 20).] The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol in dark red plates, m. p. 174—175° (Found: N, 13·2. $C_{23}H_{30}O_4N_4$ requires N, 13·15%) [light absorption in chloroform (main band only): maximum, 3990 A.; ε, 33,000].

1-*Methoxypent*-2-*en*-4-*yne* (X; R_1 = H, R_2 = Me).—(*a*) Phosphorus tribromide (45 g.) in dry ether (30 c.c.) was added to a stirred and cooled solution of vinylethynylcarbinol (24·6 g.; Jones and McCombie, *J.*, 1942, 733) in dry ether (100 c.c.) during 15 minutes, the temperature being kept at −10°. The reaction mixture was stirred for a further 2 hours at −10° and then poured on ice. The ethereal layer was washed with sodium hydrogen carbonate solution and water. Ether was removed from the dried extract, the residue was added to a solution of sodium (14 g.) in methanol (200 c.c.), and the mixture was heated to 50° and then kept at 20° overnight. Water and ether were added, and the ethereal layer was washed with water, dried, and evaporated. Distillation of the residue yielded 1-*methoxypent*-2-*en*-4-*yne* (15·8 g.) as a pungent liquid, b. p. 80—82°/160 mm., $n_D^{18°}$ 1·4637 (Found: C, 74·75; H, 8·6. C_6H_8O requires C, 74·95; H, 8·4%) (light absorption: see Table II).

(*b*) The foregoing experiment was repeated using pent-2-en-4-yn-1-ol (24·6 g.; Haynes, Heilbron, Jones, and Sondheimer, *J.*, 1947, 1583) instead of vinylethynylcarbinol. This gave 1-methoxypent-2-en-4-yne (19·2 g.), b. p. 58—60°/70 mm., $n_D^{22°}$ 1·4603.

9-*Methoxy*-1-(2′ : 6′ : 6′-*trimethyl*cyclo*hex*-1′-*enyl*)-3-*methylnona*-2 : 7-*dien*-5-*yn*-4-*ol* (XI; R_1 = H, R_2 = Me).—1-Methoxypent-2-en-4-yne (11 g.) in ether (50 c.c.) was slowly added to an ice-cooled solution of ethylmagnesium bromide (from 2·6 g. magnesium) in ether (150 c.c.), and the mixture was heated under reflux for 2 hours. After cooling to 0°, C_{14} aldehyde (11·7 g.) in ether (50 c.c.) was added dropwise. Stirring was continued overnight (15 hours), and the reaction was completed by boiling under reflux for a further 2 hours. The cold mixture was decomposed with ammonium chloride solution, and the ethereal layer was washed with water, dried, and evaporated. Distillation of the residue yielded the *methoxy-carbinol* (13 g.) as a rather viscous yellow liquid, b. p. (bath temp.)

120—130°/10^{-4} mm., $n_{\mathrm{D}}^{20^\circ}$ 1·5290 (Found : C, 78·95; H, 10·1. $C_{20}H_{30}O$ requires C, 79·4; H, 10·0%) (light absorption : see Table II).

1-*Methoxy*-9-(2′ : 6′ : 6′-*trimethyl*cyclo*hex*-1′-*enyl*)-7-*methylnona*-2 : 4 : 6 : 8-*tetraene* (XIII; $R_1 = H$, $R_2 = Me$).—The above methoxy-carbinol (6·25 g.) in methanol (50 c.c.) was shaken in hydrogen in the presence of a palladium–charcoal catalyst (1 g., containing 0·5 g. of quinoline and 4% Pd) until 513 c.c. of gas had been absorbed at 19°/752 mm. (equivalent to 1 double bond). The catalyst was filtered off, the solvent was removed under diminished pressure, and the residue (6·3 g.; $n_{\mathrm{D}}^{20^\circ}$ 1·5216) was dissolved in toluene (120 c.c.). This solution was heated to 95°, and iodine (90 mg.) in toluene (30 c.c.) was added during 5 minutes with stirring. Heating at 95° was continued for a further 20 minutes. After cooling, the solution was washed with, successively, sodium thiosulphate solution, dilute sulphuric acid, sodium hydrogen carbonate solution, and water. The toluene was removed under reduced pressure, the residue was dissolved in light petroleum (240 c.c.; b. p. 40—60°), and the solution was washed 6 times with 95% aqueous methanol (6 × 60 c.c.). The combined methanol extracts were shaken twice with light petroleum, and the combined petroleum solutions were washed with water, dried, and evaporated. The residue (2·6 g.) was a yellow viscous liquid, $n_{\mathrm{D}}^{20^\circ}$ 1·577. The light absorption (maximum, 3230 A.; $E_{1\,\mathrm{cm.}}^{1\%}$, 720) corresponds to *ca.* 45% content of the ether (XIII; $R_1 = H$, $R_2 = Me$). The product, which gave a dark-blue colour with chloroformic antimony trichloride, was unstable, and decomposed on attempted purification by chromatography on alumina.

9-(2′ : 6′ : 6′-*Trimethyl*cyclo*hex*-1′-*enyl*)-7-*methylnona*-2 : 7-*dien*-4-*yne*-1 : 6-*diol* (XI; $R_1 = R_2 = H$).—A solution of ethylmagnesium bromide was prepared from magnesium (11·2 g.; 0·46 mole) in ether (200 c.c.). Benzene (300 c.c.) was added slowly, and at the same time the ether was distilled off. When the temperature of the escaping vapours had reached 70°, the mixture was cooled in ice, pent-2-en-4-yn-1-ol (18 g.; 0·22 mole) in benzene (50 c.c.) was added slowly, and the mixture was stirred for another hour, during which time a fine grey powder separated. The C_{14} aldehyde (I) (30 g.; 0·15 mole) in benzene (50 c.c.) was added dropwise to the ice-cooled suspension, which was then stirred for another 14 hours at room temperature and for 1 hour under reflux. After cooling, the reaction mixture was decomposed with aqueous ammonium chloride, and the organic layer was washed thoroughly with water and dried. The solvent was evaporated under reduced pressure; unchanged starting materials were removed by heating at 10^{-3} mm. The residue (34·6 g.) was suspended in light petroleum (b. p. 40—60°; 380 c.c.) and extracted four times with aqueous methanol, (75%; 4 × 120 c.c.) whereupon most of the dark red colour remained in the petroleum layer. The light-yellow methanol extracts were diluted with water, and the glycol was extracted with ether. The dried ethereal extract was evaporated and the residue was heated at 100°/10^{-4} mm., to give the *diol* (25·2 g.) as a light orange, very viscous oil, $n_{\mathrm{D}}^{18^\circ}$ 1·5437 (light absorption : maximum, 2290 A.; ε, 14,500; inflexion, 2370 A.; ε, 12,500). A small sample was distilled for analysis at 120—130° (bath temp.)/10^{-5} mm., whereafter the product had $n_{\mathrm{D}}^{19^\circ}$ 1·5460 (Found : C, 78·9; H, 9·7. $C_{19}H_{28}O_2$ requires C, 79·1; H, 9·8%) (light absorption; see Table II).

When the Grignard condensation was carried out in ethereal solution the yield of glycol was only 35%.

9-(2′ : 6′ : 6′-*Trimethyl*cyclo*hex*-1′-*enyl*)-7-*methylnona*-2 : 4 : 7-*triene*-1 : 6-*diol* (XII; $R_1 = R_2 = H$).—The above diol (13·0 g.) in methanol (70 c.c.) was shaken in hydrogen in the presence of a partly-poisoned palladium–charcoal catalyst (1·4 g.; containing 0·7 g. of quinoline and 4% of Pd). The absorption of hydrogen was rather slow, and more catalyst (0·7 g.) was added during the hydrogenation, which was interrupted when 1130 c.c. of gas had been absorbed at 19°/768 mm. (equivalent to 1·03 double bonds). After removal of catalyst and solvent, water and ether were added and the ethereal layer was shaken with, successively, dilute acetic acid (until free from quinoline), sodium hydrogen carbonate solution, and water. The extract was dried and evaporated, giving the *diol* (12·6 g.), $n_{\mathrm{D}}^{18^\circ}$ 1·5348 [light absorption : maxima, 2310, 2710; ε, 13,500 and 4,500, respectively (the second maximum, probably due to a small amount of rearranged material, was observed in every case in which this experiment was carried out]. A small amount was distilled for analysis at 130—140° (bath temp.)/10^{-5} mm., $n_{\mathrm{D}}^{19^\circ}$ 1·5340 (Found : C, 78·35; H, 10·1. $C_{19}H_{30}O_2$ requires C, 78·55; H, 10·4%).

9-*Acetoxy*-1-(2′ : 6′ : 6′-*trimethyl*cyclo*hex*-1′-*enyl*)-3-*methylnona*-2 : 5 : 7-*trien*-4-*ol* (XII; $R_1 = H$, $R_2 = Ac$).—The preceding diol (11·7 g.) was dissolved in dry benzene (60 c.c.) and pyridine (60 c.c.), and a solution of acetyl chloride (3·5 g.) in benzene (60 c.c.) was added during 10 minutes with stirring and cooling. The reaction mixture was stirred for a further 14 hours at room temperature and then decomposed with ice. Ether was added and the organic layer was freed from pyridine by shaking with dilute acetic acid. After being washed with sodium hydrogen carbonate solution and water the ethereal solution was dried and evaporated, finally at 100°/10^{-4} mm., giving the *monoacetate* (12·9 g.) as a viscous liquid, $n_{\mathrm{D}}^{15^\circ}$ 1·5210; distillation was not attempted (Found : C, 75·0; H, 9·65. $C_{21}H_{32}O_3$ requires C, 75·85; H, 9·7%) (light-absorption: maximum, 2340 A.; ε, 11,500: inflexion, 2680 A.; ε, 5500). With chloroformic antimony trichloride it gave a deep violet colour.

1-*Acetoxy*-9-(2′: 6′: 6′-*trimethyl*cyclo*hex*-1′-*enyl*)-7-*methyl*-2 : 4 : 6 : 8-*tetraene* (XIII; $R_1 = H$, $R_2 = Ac$).—A solution of the above monoacetate (12 g.) and a trace of quinol in light petroleum (b. p. 80—100°; 210 c.c.) was boiled under reflux. Iodine (120 mg.) in light petroleum (b. p. 80—100°; 30 c.c.) was added to the stirred solution during 5 minutes, and the reaction mixture was heated under reflux for a further 40 minutes. The cooled solution was washed once with sodium thiosulphate solution and five times with aqueous methanol (95%; 5 × 100 c.c.). The combined methanol extracts were once more washed with light petroleum, and the combined petroleum extracts were washed with water, dried, and evaporated under reduced pressure. The residue (7·6 g.) was an orange, rather viscous liquid, $n_{\mathrm{D}}^{12^\circ}$ 1·5527. The light absorption (maxima, 2290, 2430, 2810, and 3240 A.; $E_{1\,\mathrm{cm.}}^{1\%}$, 270, 270, 420, and 400, respectively; inflexion, 3150 A.; $E_{1\,\mathrm{cm.}}^{1\%}$, 350) corresponds to a *ca.* 25% content of the norvitamin A acetate (XIII; $R_1 = H$, $R_2 = Ac$). With chloroformic antimony trichloride it gave a bluish-violet colour. The acetate was unstable and decomposed on attempted purification by chromatography on alumina. When the iodine treatment was carried out for only 15 minutes, the product had light-absorption maxima (2410, 2790, 3240 A.; $E_{1\,\mathrm{cm.}}^{1\%}$, 290, 370, and 240, respectively), corresponding to a *ca.* 15% content of the norvitamin acetate.

9-*Methoxy*-1-(2′ : 6′ : 6′-*trimethyl*cyclo*hex*-1′-*enyl*)-3-*methyldeca*-2 : 7-*dien*-5-*yn*-4-*ol* (XI; $R_1 = R_2 =$ Me).—This was prepared by the method of Cymerman, Heilbron, Jones, and Lacey (*J.*, 1946, 500) and had b. p. 90—100° (bath temp.)/10^{-4} mm., $n_{\text{D}}^{18^\circ}$ 1·5332 (light-absorption: maxima, 2280 and 3080 A.; ε, 19,500 and 3,000, respectively) [*idem, loc. cit.*, give b. p. 94—98° (bath temp.)/10^{-4} mm., $n_{\text{D}}^{17^\circ}$ 1·5300, and maxima at 2235 and 2270 A.; ε, 16,000 in each case, and an inflexion at 2350 A.; ε, 13,500].

2-*Methoxy*-10-(2′ : 6′ : 6′-*trimethyl*cyclo*hex*-1′-*enyl*)-8-*methyldeca*-3 : 5 : 7 : 9-*tetraene* (XIII; $R_1 = R_2 =$ Me).—The preceding methoxy-carbinol (4·8 g.) in methanol (40 c.c.) was shaken in hydrogen in the presence of a partly-poisoned palladium–charcoal catalyst (0·4 g.; containing 0·2 g. of quinoline and 4% Pd) until 359 c.c. of gas had been absorbed at 18°/769 mm. (equivalent to 1 double bond). Removal of the catalyst and evaporation of the solvent under diminished pressure gave crude 2-methoxy-10-(2′ : 6′ : 6′-trimethyl*cyclo*hex-1′-enyl)-8-methyldeca-3 : 5 : 8-trien-7-ol (4·8 g.) as an oil (light absorption: maxima, 2270 and 2910 A.; $E^{1\%}_{1\,\text{cm.}}$, 500 and 100, respectively).

A solution of the hydrogenation product (2 g.) and a trace of quinol in toluene (40 c.c.) was heated to 95°. Iodine (30 mg.) in toluene (10 c.c.) was added to the stirred solution during 5 minutes, and the reaction mixture was maintained at 95° for a further 20 minutes. After cooling, the toluene solution was washed with a solution of sodium thiosulphate and water, dried, and evaporated under reduced pressure. The residue was dissolved in light petroleum (b. p. 40—60°; 80 c.c.), and the solution was washed five times with aqueous methanol (95%; 5 × 20 c.c.). The combined methanol extracts were washed once more with light petroleum, and the combined petroleum solutions were washed with water, dried, and evaporated under reduced pressure, giving a dark-yellow viscous liquid (1·3 g.), $n_{\text{D}}^{21^\circ}$ 1·5903. The light absorption (maxima, 3280 and 3830 A.; $E^{1\%}_{1\,\text{cm.}}$, 630 and 290, respectively) corresponds to a *ca.* 40% content of the methyl ether (XIII; $R_1 = R_2 =$ Me). In view of the biological inactivity of this material, further purification was not attempted.

10-(2′ : 6′ : 6′-*Trimethyl*cyclo*hex*-1′-*enyl*)-8-*methyldeca*-3 : 8-*dien*-5-*yne*-2 : 7-*diol* (XI; $R_1 =$ Me, $R_2 =$ H).—A solution of ethylmagnesium bromide was prepared from magnesium (9·5 g.; 0·39 mole) in ether (300 c.c.). Benzene (200 c.c.) was added slowly and at the same time the ether was distilled off. When the temperature of the escaping vapours had reached 70°, the solution was cooled to 0° and hex-3-en-5-yn-2-ol (17·5 g.; 0·18 mole; Heilbron, Jones, Smith, and Weedon, *J.*, 1946, 54) in benzene (100 c.c.) was added during 30 minutes. After the mixture had been stirred for a further 5 hours at 20° and the resulting suspension had been cooled to 0°, a solution of C_{14} aldehyde (I) (25 g.; 0·12 mole) in benzene (75 c.c.) was added during 30 minutes, and the mixture was then stirred at 20° for 24 hours. The complex was decomposed by adding aqueous ammonium chloride, and the organic layer was separated, washed with water, dried, and evaporated. Hex-3-en-5-yn-2-ol (5·9 g.) was recovered by distillation at 25 mm., and the residue (31 g.) was suspended in light petroleum (b. p. 40—60°; 250 c.c.). The solution was extracted four times with aqueous methanol (80%; 4 × 100 c.c.), and the combined extracts were washed once with light petroleum (b. p. 40—60°) and then diluted with water. Isolation with ether in the usual manner gave the *diol* (20·7 g.) as a yellow viscous oil, $n_{\text{D}}^{20^\circ}$ 1·5342 (light absorption: see Table II). A small portion was distilled for analysis; b. p. 105—120° (bath temp.)/10^{-4} mm., $n_{\text{D}}^{16^\circ}$ 1·5380 (Found: C, 79·0; H, 10·0. $C_{20}H_{30}O_2$ requires C, 79·4; H, 10·0%).

2 : 7-*Diacetoxy*-10-(2′ : 6′ : 6′-*trimethyl*cyclo*hex*-1′-*enyl*)-8-*methyldeca*-3 : 8-*dien*-5-*yne*.—Acetic anhydride (13·6 g.) was slowly added to a solution of the foregoing diol (16·7 g.) in pyridine (75 c.c.), and the mixture was set aside at 20° for 24 hours. Water was then added and the product (17 g.) was isolated in the usual way. Distillation gave the *diacetate* (14 g.) as a pale yellow viscous oil, b. p. 120—140° (bath temp.)/10^{-3} mm., $n_{\text{D}}^{20^\circ}$ 1·5070 (Found: C, 74·25; H, 8·9. $C_{22}H_{34}O_2$ requires C, 74·6; H, 8·8%) (light absorption: see Table II).

2-*Acetoxy*-10-(2′ : 6′ : 6′-*trimethyl*cyclo*hex*-1′-*enyl*)-8-*methyldeca*-3 : 5 : 7 : 9-*tetraene* (XIII; $R_1 =$ Me, $R_2 =$ Ac).—The preceding diacetate (13·7 g.) in methanol (30 c.c.) was shaken in hydrogen in the presence of a partly-poisoned palladium–charcoal catalyst (2 g.; containing 1 g. of quinoline and 4% of Pd) until 890 c.c. of gas had been absorbed at 21°/754 mm. (equivalent to 1 double bond). Removal of catalyst and solvent gave the crude product (13 g.), $n_{\text{D}}^{22^\circ}$ 1·5090 (light absorption: maxima, 2280 and 2790 A.; $E^{1\%}_{1\,\text{cm.}}$, 400 and 190, respectively).

The partly hydrogenated diacetate (0·55 g.) and a trace of quinol were dissolved in toluene (10 c.c.), and the solution was heated to 95°. Iodine (10 mg.) in toluene (10 c.c.) was added with stirring during 5 minutes, and the solution was maintained at 95—100° for a further 90 minutes. After cooling, the toluene solution was washed with, successively, sodium thiosulphate solution, 10% (w/v) sulphuric acid, sodium hydrogen carbonate solution, and water. The solution was dried and then evaporated under reduced pressure, giving a yellow viscous oil (0·5 g.) which gave a dark blue colour with chloroformic antimony trichloride. It had light absorption: maxima at 2230 and 3260 A.; $E^{1\%}_{1\,\text{cm.}}$, 350 and 270, respectively: inflexion at 2820 A.; $E^{1\%}_{1\,\text{cm.}}$, 230, which corresponds to a *ca.* 15% content of the acetate (XIII; $R_1 =$ Me, $R_2 =$ Ac).

The Hydrocarbon, $C_{20}H_{28}$.—The partly hydrogenated diacetate (11·8 g.) was subjected to iodine treatment, in the manner described above, and the crude product (11·5 g.) (light absorption: maxima, 2270, 2790, 3230, 3450, 3620, and 3840 A.; $E^{1\%}_{1\,\text{cm.}}$, 300, 250, 220, 270, 270, and 175, respectively) was dissolved in light petroleum (b. p. 40—60°; 100 c.c.); the solution was filtered through a column of partly deactivated alumina (800 g.; grade III—IV; cf. Brockmann and Schodder, *Ber.*, 1941, **74**, 73). The chromatogram was developed with light petroleum (b. p. 40—60°; 900 c.c.), and the bright-yellow, clearly defined, and least-strongly adsorbed zone was removed and eluted with acetone. Evaporation of the solvent under reduced pressure gave an oil (1·1 g.) (light absorption: maxima, 3500, 3640, and 3840 A.; $E^{1\%}_{1\,\text{cm.}}$, 1150, 1250, and 1000, respectively) which was distilled; b. p. 80—100° (bath temp.)/10^{-4} mm. (light absorption: maxima, 3470, 3650, and 3840 A.; $E^{1\%}_{1\,\text{cm.}}$, 1300, 1560, 1250, respectively). The product was again adsorbed on a column of alumina, and the main band eluted, giving the *hydrocarbon* which polymerised rapidly on standing at 0°. Redistillation resulted in no further increase in intensity of light absorption (maxima, 3510, 3660, and 3840 A.; $E^{1\%}_{1\,\text{cm.}}$, 1740, 2050, and 1500; ε, 46,500, 55,000, and 40,000, respectively) (Isler *et al.*, *Helv. Chim. Acta*, 1947, **30**, 1911, give light absorption of anhydrovitamin A: maxima, 3520, 3700, and 3910 A., $E^{1\%}_{1\,\text{cm.}}$, 1900, 2910, and 2620, respectively) (Found: C, 88·8; H, 10·75. $C_{20}H_{28}$ requires C, 89·5; H, 10·5%).

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IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
LONDON, S.W.7.

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