360. *Carotenoids and Related Compounds. Part XI.*[1] *Syntheses of δ-Carotene and ε-Carotene*

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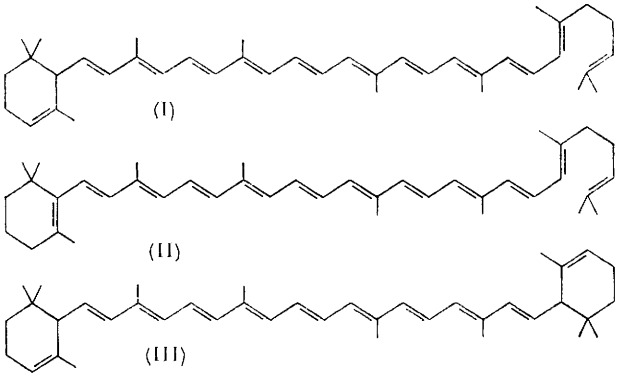
The structure of δ-carotene is confirmed by three syntheses. New routes to γ-carotene, ε-carotene, and lycopene are reported.

Preparations are described of analogues of vitamin A and retinal in which end groups of the β-carotene type are replaced by those associated with α- or γ-carotene.

δ-CAROTENE was first detected in *Gonocaryum pyriforme* by Winterstein.[2] From a consideration of its chromatographic behaviour and spectral properties, Winterstein suggested that it was related to γ-carotene (II) in the same way as α-carotene to β-carotene, and therefore proposed the structure (I). It has since been found in carrots, tomatoes, and elsewhere,[3] and was isolated as an optically active crystalline solid from tomato mutants by Porter and Murphey.[4] These workers showed it to be a C_{40}-hydrocarbon, but considered the molecule to contain 11 (rather than 12) double bonds. A more recent investigation by Kargl and Quackenbush [5] lent support to the structure (I), even though these authors were unable to detect isogeronic acid after ozonolysis. Winterstein's formulation (I) has now been confirmed by syntheses of the racemic modification of the pigment.

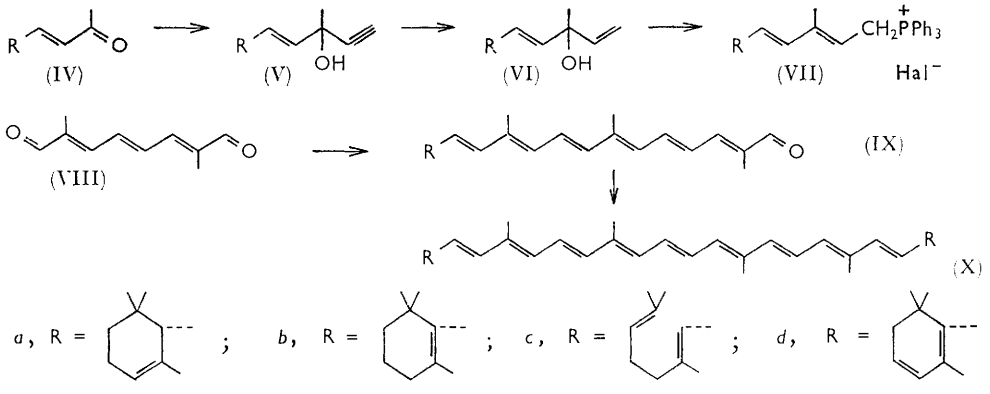


δ-Carotene is the last of the naturally occurring structural isomers of β-carotene (X*b*) to be prepared (for syntheses of other members of the family, see a review by Isler and Schudel [6]). Two main routes have been used: that based on the $C_{15} + C_{10} + C_{15} = C_{40}$ approach was carried out in London, and that using the $C_{20} + C_{20} = C_{40}$ principle in Basle.

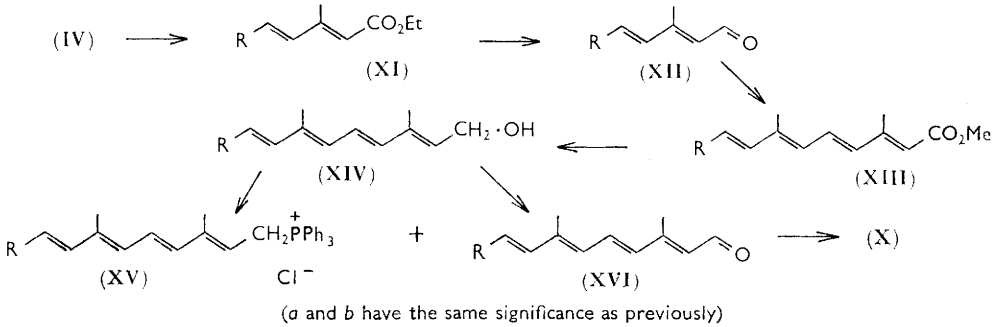
The δ-carotene intermediates have also been used to provide convenient new syntheses of ε-carotene (III). This compound was first prepared by Karrer *et al.*,[7] using the $C_{16} + C_8 + C_{16} = C_{40}$ building principle. It was termed "ε_1-carotene," but has recently been identified with natural ε-carotene (apart from the possibility of optical activity) by Chapman and Haxo.[8] We also report new syntheses of γ-carotene (II) and lycopene (X*c*).

[1] Part X, Cooper, Davis, and Weedon, *J.*, 1963, 5637.
[2] Winterstein, *Z. Physiol. Chem.*, 1933, **219**, 249.
[3] Cf. Goodwin, "Comparative Biochemistry of the Carotenoids," Chapman and Hall, London, 1952.
[4] Porter and Murphey, *Arch. Biochem. Biophys.*, 1951, **32**, 21.
[5] Kargl and Quackenbush, *Arch. Biochem. Biophys.*, 1960, **88**, 59.
[6] Isler and Schudel, *Adv. Org. Chem.*, 1963, **4**, 115.
[7] Karrer and Eugster, *Helv. Chim. Acta*, 1950, **33**, 1433; cf. Tscharner, Eugster, and Karrer, *Helv. Chim. Acta*, 1958, **41**, 32.
[8] Chapman and Haxo, *Plant and Cell Physiol.*, 1963, **4**, 57.

Partial hydrogenation over a Lindlar catalyst [9] of the acetylene alcohols (V*a* and V*c*) derived from α- and ψ-ionone (IV*a* and IV*c*) gave the vinyl alcohols (VI*a* and VI*c*) which, as expected by analogy [10] with their analogue (VI*b*) from β-ionone (IV*b*), reacted with triphenylphosphine hydrogen halides to give the phosphonium halides (VII*a* and VII*c*) (*ca.* 45% overall yields from the ionones). Reaction of 2,7-dimethylocta-2,4,6-trienedial [11] (VIII) with an excess of the Wittig reagents from these halides then gave ε-carotene (III) (presumably as a mixture of racemic and meso-forms) and lycopene (X*c*) in 90 and 55% yields, respectively. When the same Wittig reagents were generated in the presence of the dial (*ca.* 1 mol.), the C_{25}-α-apo-12′-carotenal (IX*a*) and the C_{25}-apo-12′-lycopenal (IX*c*) were obtained in 45% yield. These were made to react severally with the Wittig reagents from (VII*c* and VII*a*) to give (±)-δ-carotene in *ca.* 60 and 80% yields, respectively. A similar Wittig reaction of (VII*b*) [10] with the lycopenal (IX*c*) gave γ-carotene (II).



The C_{20}-intermediates of the α-series were also prepared from α-ionone (IV*a*). A Horner condensation with ethyl diethylphosphonoacetate in the presence of sodium methoxide gave ethyl α-ionylideneacetate (XI*a*), which was reduced with lithium aluminium hydride to the corresponding alcohol. The latter was oxidised with manganese dioxide to the C_{15}-aldehyde (XII*a*) in *ca.* 45% overall yield from α-ionone. The C_{15}-aldehyde (XII*a*), like its analogue (XII*b*) from β-ionone (IV*b*),[12] condensed with ethyl senecioate in the



(*a* and *b* have the same significance as previously)

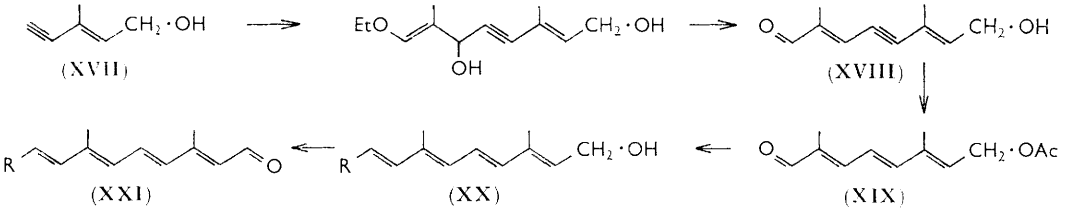
presence of potassamide. The " α-vitamin A acid " thus formed was isolated as the methyl ester (XIII*a*) which was reduced with lithium aluminium hydride to give " α-vitamin A " (XIV*a*), in *ca.* 45% overall yield from the C_{15}-aldehyde. Treatment of α-vitamin A with triphenylphosphine hydrochloride gave (20%) the crystalline phosphonium salt (XV*a*),

[9] Lindlar, *Helv. Chim. Acta*, 1952, **35**, 446.
[10] Pommer, *Angew. Chem.*, 1960, **72**, 811, 911.
[11] Mildner and Weedon, *J.*, 1953, 3294; Inhoffen and von der Bey, *Annalen*, 1953, **583**, 100.
[12] Matsui, Okano, Yamashita, Miyano, Kitamura, Kobayashi, Sato, and Mikami, *J. Vitaminol.* (*Osaka*), 1958, **4**, 178.

and oxidation with manganese dioxide gave (90%) " α-retinal " (XVI*a*). A Wittig reaction between these two C_{20}-components then furnished ε-carotene (III) in 35% yield.

The C_{20}-intermediates of the γ-series were constructed by a new $C_{10} + C_{10}$ approach. A Grignard reaction of *trans*-3-methylpent-2-en-4-yn-1-ol (XVII) [13] with the ethyl enol ether of methylmalondialdehyde,[14] and acidic hydrolysis of the product, gave the acetylenic hydroxy-aldehyde (XVIII) which was partly reduced over a Lindlar catalyst giving, after stereomutation and acetylation, the acetoxy-aldehyde (XIX) in *ca.* 20% overall yield from methylpentenynol. A Wittig reaction with geranyltriphenylphosphonium bromide,[15] followed by hydrolysis, then afforded (25%) " γ-vitamin A " (XX*c*) which was oxidised (30%) with manganese dioxide to " γ-retinal " (XXI*c*). Treatment of the latter with the Wittig reagent from (XV*a*) then gave (45%) (±)-δ-carotene, identical with the specimen described above. The visible light absorption spectrum and chromatographic behaviour of the synthetic material were the same as those of a sample of natural δ-carotene, for which the authors are greatly indebted to Professor F. W. Quackenbush of the University of Purdue.

α-Vitamin A (XIV*a*) has previously been synthesised by Robeson *et al.*,[16] and an alternative route to γ-vitamin A (XX*c*) and γ-retinal (XXI*c*) was recently outlined by Davis *et al.*[17] Both the γ-compounds crystallise readily, and it is of interest to note that the structure (XX*c*) was at one time proposed [18] for vitamin A_2 (XX*d*). As expected the



(*c* and *d* have the same significance as previously)

light absorption properties of γ-vitamin A and γ-retinal differ markedly from those of the corresponding compounds in the natural A_1 and A_2 series where steric interference between the ring methyl groups and the polyene side chain results in a shift of the light absorption maxima to shorter wavelengths, and in loss of both fine structure and intensity of absorption.

In the nuclear magnetic resonance spectrum of ε-carotene at 60 Mc./sec. the bands due to the different types of methyl group were clearly resolved. Two bands at high fields (9·17 and 9·09) must be ascribed to the geminal methyls at $C_{(1)}$ and $C_{(1')}$, and another at 8·40 to the methyls at $C_{(5)}$ and $C_{(5')}$ situated on isolated double bonds. The " in-chain " methyl groups give rise to two bands of which that at 8·03 is very similar to the " in-chain " methyl band of β-carotene and lycopene [19] and is therefore attributed to the $C_{(13)}$- and $C_{(13')}$-methyls. The band at slightly higher fields (8·10) is assigned to the $C_{(9)}$ and $C_{(9')}$ methyls which are nearer the end of the polyene chain and are therefore, presumably, less deshielded. The other carotenoids, and the C_{25}-aldehydes (IX*a* and IX*c*), all exhibited the methyl bands to be expected from previous studies on related compounds.[19] The slight differentiation of the $C_{(9)}$ and $C_{(13)}$ " in-chain " methyls was again apparent in the C_{25}-aldehydes, and with (±)-δ-carotene the band due to the $C_{(9)}$-methyl at the cyclic end of the molecule was just resolvable.

[13] Oroshnik, *J. Amer. Chem. Soc.*, 1956, **78**, 2651.
[14] Rüegg, Lindlar, Montavon, Saucy, Schaeren, Schwieter, and Isler, *Helv. Chim. Acta*, 1959, **42**, 847.
[15] Isler, Gutmann, Lindlar, Montavon, Rüegg, Ryser, and Zeller, *Helv. Chim. Acta*, 1956, **39**, 463.
[16] Robeson, Cawley, Weisler, Stern, Eddinger, and Chechak, *J. Amer. Chem. Soc.*, 1955, **77**, 4111, 4117.
[17] Davis, Jackman, Siddons, and Weedon, *Proc. Chem. Soc.*, 1961, 261.
[18] Karrer, Geiger, and Bretscher, *Helv. Chim. Acta*, 1941, **24**, 161E.
[19] Barber, Davis, Jackman, and Weedon, *J.*, 1960, 2870.

Experimental

When possible all operations were carried out in nitrogen, and solutions were evaporated under reduced pressure.

Alumina for chromatography was graded according to Brockmann and Schodder.[20] Manganese dioxide for the oxidation of allylic alcohols was prepared by the method of Attenburrow *et al.*[21]

Visible light absorption spectra were determined on solutions in light petroleum or hexane, unless stated otherwise. Infrared absorption spectra were determined on liquid films, unless a solvent is indicated. Nuclear magnetic resonance spectra were determined on a Varian A60 instrument with deuterochloroform as solvent and tetramethylsilane as an internal standard.

M. p.s were determined in evacuated capillary tubes, and are corrected, unless otherwise stated.

Preparation of C_{15}*-Intermediates.*—*Vinyl-α-ionol* (VI*a*). Ethynyl-α-ionol was prepared (68%) from α-ionone and lithium acetylide by the method of Oroshnik and Mebane,[22] and had b. p. 92—93°/0·7 mm., n_D^{16} 1·4950; $\nu_{max.}$ 3400 (O–H), 3280 (C:C–H), and 2100 cm.$^{-1}$ (C≡C) (Oroshnik and Mebane,[22] give b. p. 89°/0·55 mm., n_D^{20} 1·4937).

A solution of the ethynyl alcohol (10·9 g.) in ethyl acetate (100 ml.) containing quinoline (2 drops) was shaken with Lindlar catalyst [9] (2·0 g.) in hydrogen until absorption ceased (1300 ml. at 20°/760 mm., equivalent to 1·1 mol. of hydrogen). Removal of catalyst and solvent, and distillation of the residue gave *vinyl-α-ionol* (9·6 g.) as a colourless oil, b. p. 91—92°/1 mm., n_D^{16} 1·4970; $\lambda_{max.}$ (EtOH) 220 mμ, $10^{-3}\varepsilon = 21$; $\nu_{max.}$ 3380 (O–H), and 916 cm.$^{-1}$ (–CH:CH_2) (Found: C, 81·8; H, 11·0. $C_{15}H_{24}O$ requires C, 81·75; H, 10·95%). (This alcohol was prepared by Rüegg *et al.*,[23] but not fully characterised.)

α-Ionylidene-ethyltriphenylphosphonium bromide (VII*a*). A solution of the preceding alcohol (2·0 g.) and triphenylphosphine hydrobromide [24] (2·3 g.) in dry methanol (30 ml.) was stirred at 20° for 56 hr. The solvent was evaporated *in vacuo*, and the residue was washed thoroughly with ether. This left the salt (3·9 g.) as a colourless semisolid which was used without further purification.

Vinyl-ψ-ionol (VI*c*). Ethynyl-ψ-ionol was prepared (51%) from ψ-ionone and lithium acetylide by the method of Oroshnik and Mebane,[22] and had b. p. 107—108°/0·7 mm., n_D^{14} 1·5140; $\nu_{max.}$ 3367 (O–H), 3300 (C:C–H), and 2100 cm.$^{-1}$ (C≡C) (Oroshnik and Mebane [22] give b. p. 107°/0·7 mm., n_D^{20} 1·5110).

A solution of the ethynyl alcohol (8·4 g.) in ethyl acetate (80 ml.) containing quinoline (2 drops) was shaken with Lindlar catalyst [9] (1·5 g.) in hydrogen until absorption ceased. Removal of catalyst and solvent, and distillation of the residue gave *vinyl-ψ-ionol* (7·4 g.), as a colourless oil, b. p. 88—90°/0·05 mm., n_D^{16} 1·5120; $\lambda_{max.}$ (EtOH) 243 mμ, $10^{-3}\varepsilon = 24$; $\nu_{max.}$ 3367 (O–H), 1653 (C=C) and 980 cm.$^{-1}$ (–CH=CH_2) (Found: C, 81·95; H, 11·05. $C_{15}H_{24}O$ requires C, 81·75; H, 10·95%). (This alcohol was prepared by Rüegg *et al.*,[23] but not fully characterised.)

ψ-Ionylidene-ethyltriphenylphosphonium halides (VII*c*). A solution of the preceding alcohol (2·2 g.) and triphenylphosphine hydrobromide (3·4 g.) in dry methanol (50 ml.) was stirred at 20° for 56 hr. Isolation of the product as described for the α-ionylidene isomer gave the bromide as a viscous oil (4·50 g.) which was used without further purification.

Vinyl-ψ-ionol (1·0 g.) was added in portions to a suspension of triphenylphosphine (1·2 g.) in methanol (4 ml.) containing hydrogen chloride (0·165 g.). The mixture was shaken occasionally until a clear solution was obtained and then set aside for 24 hr. The methanol was evaporated, and the viscous residue was dried at 40° under high vacuum. The chloride was used without further purification.

Preparation of C_{25}*-Intermediates.*—(C_{25})-α-*apo*-12′-*Carotenal* (IX*a*). To a stirred solution of α-ionylidene-ethyltriphenylphosphonium bromide (500 mg.) and 2,7-dimethylocta-2,4,6-triene-dial [11] (200 mg.) in dimethylformamide (50 ml.), 1·1N-methanolic sodium methoxide was slowly added until (after 1 hr.) the concentration of the required product in the reaction mixture reached a maximum (ascertained by visible light absorption spectroscopy, and thin-layer chromatography). The mixture was stirred for a further hour, diluted with water, and extracted with benzene. The extract was washed with water, dried (Na_2SO_4), and evaporated.

[20] Brockmann and Schodder, *Ber.*, 1941, **74**, 73.
[21] Attenburrow, Cameron, Chapman, Evans, Hems, Jansen, and Walker, *J.*, 1952, 1094.
[22] Oroshnik and Mebane, *J. Amer. Chem. Soc.*, 1949, **71**, 2062.
[23] Rüegg, Schwieter, Ryser, Schudel, and Isler, *Helv. Chim. Acta*, 1961, **44**, 985.
[24] Schwieter, v. Planta, Rüegg, and Isler, *Helv. Chim. Acta*, 1962, **45**, 541.

Chromatography of the residue on alumina (Peter Spence, Grade II) first from benzene, and then from a mixture (1 : 1) of light petroleum (b. p. 60—80°) and benzene, collection of the main band, evaporation, and crystallisation of the residue from light petroleum (b. p. 60—80°) at 0°, gave α-*apo*-12′-*carotenal* (193 mg., 45%) as yellow needles, m. p. 123—124°; $\lambda_{max.}$ 431, 409, and 390 mμ, $10^{-3}\varepsilon$ = 59, 64, and 30, respectively; $\nu_{max.}$ ($CHCl_3$) 1664 (CHO), 1608 (C:C), 1552, and 963 cm.$^{-1}$ (*trans*-CH:CH); τ 9·16, 9·07, 8·39, 8·08, 8·03, and 7·94, bands of comparable intensity (Found: C, 86·25; H, 9·35. $C_{25}H_{34}O$ requires C, 85·7; H, 9·7%).

(C_{25})-*apo*-12′-*Lycopenal* (IX*c*). Sodium methoxide (1·1N) was added dropwise, during 1 hr., to a stirred solution of the ψ-ionylidene-ethyltriphenylphosphonium bromide (250 mg.) and 2,7-dimethylocta-2,4,6-trienedial [11] (100 mg.) in dimethylformamide (30 ml.). The reaction was followed spectroscopically and by thin-layer chromatography. Stirring was continued for a further 1½ hr., the mixture was diluted with water and extracted with benzene; the extract was washed with water, dried (Na_2SO_4), and evaporated. Chromatography of the residue on alumina (Peter Spence, Grade II) first from benzene and then from a mixture (4 : 1) of benzene and light petroleum (b. p. 60—80°), collection of the main band, evaporation and crystallisation of the residue from light petroleum (b. p. 60—80°) gave the *apo*-12′-*lycopenal* (110 mg., 52%) as red needles, m. p. 105—106°; $\lambda_{max.}$ 454, 429, and 406 mμ; $\lambda_{max.}$ ($CHCl_3$) 468, 443, and 418; $10^{-3}\varepsilon$ = 65, 81, and 62, respectively; $\nu_{max.}$ ($CHCl_3$) 1665 (CHO), 1609 (C:C), 1554 and 964 cm.$^{-1}$ (*trans*-CH:CH) (Found: C, 85·0; H, 9·5. $C_{25}H_{34}O$ requires C, 85·7; H, 9·7%).

The same product was obtained in *ca.* 40% yield from the phosphonium chloride.

Preparation of C_{20}-*Intermediates.*—*Ethyl* α-*ionylideneacetate* (XI*a*). A solution of sodium methoxide (from sodium, 26 g.) in methanol (300 ml.) was slowly added to a mixture of ethyl diethylphosphonoacetate (224 g.) and α-ionone (192 g.) in benzene (500 ml.). After it had been stirred for 4 hr. at 40° the mixture was poured on ice–water, diluted with ether, washed repeatedly with water, dried (Na_2SO_4), and evaporated. Chromatography of the residue (239 g.) on alumina (4 kg. Camag, Grade II deactivated by addition of 2% water) from light petroleum gave the ester (199·8 g., 76%); $\lambda_{max.}$ (EtOH) 268 mμ, $E^{1\%}_{1cm.}$ = 1060 [Robeson *et al.*[16] report $\lambda_{max.}$ (EtOH) 270 mμ, $E^{1\%}_{1cm.}$ = 978].

α-*Ionylidene-ethanol.* A solution of the preceding ester (199·8 g.) in anhydrous ether (250 ml.) was treated at 0° with lithium aluminium hydride (26·5 g.) in anhydrous ether (550 ml.). After 1 hr. the excess of lithium aluminium hydride was destroyed by careful addition of ethyl acetate. The reaction mixture was poured on ice and 1N-sulphuric acid, and diluted with ether. The ethereal layer was separated, washed with water, saturated sodium hydrogen carbonate solution and water, dried (Na_2SO_4), and evaporated. The crude α-ionylidene-ethanol (168 g., 100%) had n_D^{20} 1·5315; $\lambda_{max.}$ (EtOH) 238, 272, 281 mμ, $E^{1\%}_{1cm.}$ = 1205, 194, and 194, respectively [Robeson *et al.*[16] report, $\lambda_{max.}$ (EtOH) 240 mμ, $E^{1\%}_{1cm.}$ = 985].

α-*Ionylideneacetaldehyde* (XII*a*). A solution of crude α-ionylidene-ethanol (7·7 g.) in light petroleum (b. p. 60—90°, 150 ml.) was shaken with manganese dioxide (40 g.) for 16 hr. at 20°. The suspension was then filtered and the filter cake was thoroughly washed with ether. Evaporation of the filtrate and washings gave the crude aldehyde (6·0 g.), n_D^{24} 1·5543; $\lambda_{max.}$ (EtOH) 286 mμ, $E^{1\%}_{1cm.}$ = 1165. This was purified by chromatography on alumina (Camag, Grade II). The material eluted with light petroleum was discarded; further elution with a mixture (9 : 1) of light petroleum and ether yielded α-ionylideneacetaldehyde (4·5 g., 59%); n_D^{19} 1·5610; $\lambda_{max.}$ (EtOH) 286 mμ, $E^{1\%}_{1cm.}$ = 1230 [Robeson *et al.*[16] found $\lambda_{max.}$ (EtOH) 285 mμ, $E^{1\%}_{1cm.}$ = 860]. The n.m.r. spectrum indicated that the aldehyde was a *cis–trans* mixture (the *trans* isomer predominating), and contaminated with *ca.* 2% of β-ionylideneacetaldehyde.

Methyl ester of α-*vitamin A acid* (XIII*a*). Potassamide was prepared from potassium (18 g.) in liquid ammonia (1000 ml.). The ammonia was replaced by anhydrous ether. A solution of α-ionylideneacetaldehyde (40 g.) and ethyl senecioate (30 g.) in anhydrous ether (200 ml.) was slowly added. The mixture was stirred at 20° for 16 hr., poured on ice, acidified with 1N-sulphuric acid, and extracted with ether. The ethereal solution was washed with water, dried (Na_2SO_4), filtered, and evaporated. The residual α-vitamin A acid [34·5 g., $\lambda_{max.}$ (EtOH) 342 mμ, $E^{1\%}_{1cm.}$ = 975] was dissolved in ethyl methyl ketone (300 ml.). Potassium carbonate (20 g.) and methyl iodide (20 ml.) were added. The mixture was refluxed for 6 hr., cooled, poured on ice, and diluted with ether. The ethereal layer was separated, washed successively with saturated sodium hydrogen carbonate solution and water, dried (Na_2SO_4), filtered, and evaporated. On chromatography of the residue on alumina (1 kg., Camag, Grade II, deactivated by addition of 4% water) α-vitamin A acid methyl ester (24·9 g., 43%) was eluted from the

column with a mixture (95 : 5) of light petroleum (b. p. 40—45°) and ether; $\lambda_{max.}$ 347 mμ, $E^{1\%}_{1\,cm.}$ = 1360.

α-*Vitamin A* (XIV*a*). Lithium aluminium hydride (2·5 g.) in ether (100 ml.) was added slowly to α-vitamin A methyl ester (24·9 g.) in ether (150 ml.) at 0°. The mixture was stirred for 2 hr. at 0°, then poured on ice, acidified with 1N-sulphuric acid, and diluted with ether. The ethereal layer was separated, washed with water, saturated sodium hydrogen carbonate solution and water, dried (Na_2SO_4), filtered, and evaporated, giving α-vitamin A (22·9 g.); $\lambda_{max.}$ (EtOH) 324, 310, and 298 mμ, $E^{1\%}_{1\,cm.}$ = 1335, 1590, and 1150, respectively [Robeson *et al.*[16] give $\lambda_{max.}$ (EtOH) 325, 311, and 298 mμ, $E^{1\%}_{1\,cm.}$ = 1500, 1650, and 1220, respectively].

α-*Retinyltriphenylphosphonium chloride* (XV*a*). Triphenylphosphine (23 g.) was added to a solution of α-vitamin A (22·9 g.) in anhydrous ethanol (150 ml.). To the stirred suspension ethanolic hydrogen chloride (4 g. in 50 ml.) was added dropwise at 0°. After the mixture had been kept for 24 hr. at 20° the ethanol was evaporated. The residue was purified by partition between light petroleum (b. p. 40—45°) and aqueous methanol (80%) in three separatory funnels. The methanol extracts were diluted with water and extracted with ethyl acetate. The ethyl acetate extracts were washed several times with water, dried (Na_2SO_4), filtered, and evaporated. Crystallisation of the residue [37 g., $\lambda_{max.}$ (EtOH) 327 mμ, $E^{1\%}_{1\,cm.}$ = 650] from ethyl acetate gave α-*retinyltriphenylphosphonium chloride* (8·4 g., 18%) as yellow needles, m. p. 180—182° uncorr.; $\lambda_{max.}$ (EtOH) 325, 276 (shoulder), and 269 (shoulder), $E^{1\%}_{1\,cm.}$ = 1035, 261, and 207, respectively (Found: C, 77·8; H, 7·8; Cl, 6·2; H_2O, 2·97. $C_{38}H_{44}PCl,H_2O$ requires C, 78·0; H, 7·9; Cl, 6·05; H_2O, 3·1%).

α-*Retinal* (XVI*a*). To a suspension of manganese dioxide (50 g.) in light petroleum (b. p. 60—90°, 300 ml.) a solution of α-vitamin A (10 g., $\lambda_{max.}$ 324, 309, and 296, $E^{1\%}_{1\,cm.}$ = 1415, 1655, and 1240, respectively) in ether (100 ml.) was added; the mixture was shaken for 16 hr. at 20° and then filtered. The manganese dioxide was washed thoroughly with ether, and the filtrate and washings were combined and evaporated giving α-retinal (8·7 g.) which was used without further purification in the next step; $\lambda_{max.}$ (EtOH) 369 mμ, $E^{1\%}_{1\,cm.}$ = 1270.

8-*Hydroxy*-2,6-*dimethylocta*-2,6-*dien*-4-*yn*-1-*al* (XVIII). A solution of *trans*-3-methylpent-2-en-4-yn-1-ol [13] (127 g.) in dichloromethane (1400 ml.) was added dropwise at 0° to ethylmagnesium bromide (from magnesium, 70 g., and ethyl bromide, 315 g.) in ether (600 ml.). The reaction mixture was refluxed for 1 hr. and cooled. A solution of methylmalondialdehyde ethyl enol ether [14] (136 g.) in dichloromethane (800 ml.) was added slowly at 20° and the mixture was refluxed for 2 hr., cooled, poured on ice-cold 1N-sulphuric acid, and diluted with dichloromethane. The organic layer was separated, washed repeatedly with water, dried (Na_2SO_4), filtered, and evaporated. The residue (240 g.) was dissolved in acetone (1800 ml.) and 1N-sulphuric acid (300 ml.) was added at 20°. After 1 hr. the solution was diluted with water (4 l.) and extracted with ether. The ether extract was washed with saturated sodium hydrogen carbonate solution and water, dried (Na_2SO_4), and evaporated, giving the crude hydroxy-aldehyde (170 g.). Part (80 g.) of the product was chromatographed on alumina (2 kg., Camag, Grade II, deactivated by addition of 7% water). The chromatogram was developed with light petroleum (b. p. 40—45°) to which ether was subsequently added. With 20% of ether a by-product was eluted. With a 3 : 2 mixture of the solvents a fraction was eluted which, on evaporation, gave the required hydroxy-aldehyde (33·5 g.), $\lambda_{max.}$ (EtOH) 312 mμ, $E^{1\%}_{1\,cm.}$ = 1200.

8-*Acetoxy*-2,6-*dimethylocta*-2,4,6-*trien*-1-*al* (XIX). The preceding hydroxy-aldehyde (33·5 g.) in toluene (600 ml.) and quinoline (2 ml.) was shaken with Lindlar catalyst [9] (15 g.) in hydrogen until absorption ceased. Removal of catalyst and solvent gave crude 8-hydroxy-2,6-dimethylocta-2,4,6-trien-1-al which, in dichloromethane (40 ml.) and pyridine (20 ml.), was treated at 0° with acetyl chloride (20 g.) in dichloromethane (20 ml.). The mixture was stirred for 2 hr. at 0°, poured on ice, and diluted with ether. The ethereal layer was separated, washed with 1N-sulphuric acid, saturated sodium hydrogen carbonate solution, and water, dried (Na_2SO_4), and evaporated. The residual stereoisomeric mixture (which was partly crystalline) was dissolved in ether (100 ml.), and iodine (150 mg.) in ether (20 ml.) was added. The solution was kept in the dark at 20° for 16 hr., then diluted with ether, washed with 0·1N-sodium thiosulphate, and water, dried (Na_2SO_4), filtered, and evaporated. Crystallisation of the residue first from light petroleum (b. p. 40—45°) and ether, and then from methanol gave 8-*acetoxy*-2,6-*dimethylocta*-2,4,6-*trien*-1-*al* (10·4 g.) as yellow needles, m. p. 73—74° (uncorr.), $\lambda_{max.}$ (EtOH) 314 mμ, $10^{-3}\varepsilon$ = 45·5 (Found: C, 69·5; H, 7·8. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·75%).

γ-*Vitamin A* (XX*c*). Sodium ethoxide (from 2·5 g. sodium) in ethanol (100 ml.) was added

dropwise at 0° to a stirred suspension of geranyltriphenylphosphonium bromide [15] (51·5 g.) and 8-acetoxy-2,6-dimethylocta-2,4,6-trien-1-al (21 g.) in benzene (200 ml.). The mixture was heated at 50° for 3 hr., and cooled. A solution of potassium hydroxide (10 g.) in 90% aqueous ethanol (200 ml.) was added. The mixture was kept at 20° for 1 hr. and then poured on ice–water, and diluted with ether. The ethereal layer was separated, washed repeatedly with water, dried (Na_2SO_4), and evaporated. Chromatography of the residue on alumina (600 g. Camag, Grade II, deactivated by addition of 7% water and 0·5% pyridine), elution of the main product with a mixture (7 : 3) of light petroleum (b. p. 40—45°) and ether, evaporation, and crystallisation of the residue from light petroleum (b. p. 60—90°) and methanol gave *γ-vitamin A* (6·9 g.) as yellow needles, m. p. 107—108° (uncorr.), $\lambda_{max.}$ (EtOH) 359, 341, and 324 mμ, $10^{-3}\varepsilon$ = 78·5, 86, and 56, respectively (Found: C, 83·95; H, 10·55. $C_{20}H_{30}O$ requires C, 83·85; H, 10·55%).

γ-Retinal (XXI*c*). A solution of γ-vitamin A (5·0 g.) in anhydrous ether (100 ml.) was shaken with manganese dioxide (35 g.) for 16 hr. at 20°. The mixture was filtered, the filter cake was thoroughly washed with ether, and the combined filtrate and washings were evaporated. Crystallisation of the residue from light petroleum (b. p. 60—90°) gave γ-retinal (1·5 g.) as orange plates, m. p. 67—68°, $\lambda_{max.}$ (EtOH) 408 mμ, $10^{-3}\varepsilon$ = 57 (Found: C, 84·45; H, 9·7. $C_{20}H_{28}O$ requires C, 84·45; H, 9·9%).

Preparation of Carotenoids.—(±)-δ-*Carotene* (I). (*a*) Ethereal n-butyl-lithium (1·1N) was added slowly (30 min.) to a stirred suspension of ψ-ionylidene-ethyltriphenylphosphonium bromide (300 mg.) in dry ether (50 ml.) until all the Wittig salt had been converted into the deep red phosphoran. The mixture was stirred for a further 15 min. and then dichloromethane (3·0 ml.) was added to decompose any excess of butyl-lithium. A solution of α-apo-12′-carotenal (120 mg.) in dichloromethane (5 ml.) was added dropwise (10 min.), and the mixture was stirred for a further 4 hr. at 20°. The solvents were evaporated and 90% aqueous methanol was added to the residue. The crude product was extracted with light petroleum (b. p. 40—60°), and the extract was washed with water, dried (Na_2SO_4), and evaporated. Chromatography of the residue on alumina (Peter Spence, Grade II) from 15% benzene in light petroleum (b. p. 60—80°), collection and evaporation of the main band, and crystallisation of the residue from methanol–light petroleum (b. p. 40—60°) gave (±)-δ-carotene (147 mg., 80%) as red needles, m. p. 150—151°; $\lambda_{max.}$ 488, 456, 431, and 280 mμ, $10^{-3}\varepsilon$ = 165, 174, 110, and 40, respectively; $\nu_{max.}$ ($CHCl_3$) 963 cm.$^{-1}$ (*trans*-C=C); τ ($CDCl_3$) 9·17, 9·1, 8·40, 8·33, 8·20, 8·10, and 8·04, relative intensities *ca.* 1 : 1 : 2 : 1 : 1 : 1 : 3 (Found: C, 89·45; H, 10·3. $C_{40}H_{56}$ requires C, 89·5; H, 10·5%).

(*b*) Vinyl α-ionol (0·30 g.) was added in portions to a suspension of triphenylphosphine (0·35 g.) in methanol (3 ml.) containing hydrogen chloride (0·05 g.). The mixture was warmed, left for two days at 20°, and then evaporated. The residual oil was dissolved in dimethylformamide (20 ml.) and apo-12′-lycopenal (110 mg.) was added, followed by an equivalent of methanolic sodium methoxide. The mixture was stirred overnight, then diluted with water, and extracted with light petroleum. The extracts were washed, dried, and concentrated. Chromatography on alumina (Grade III) from light petroleum (b. p. 60—80°) gave (±)-δ-carotene (98 mg., 59%) as a mixture of stereoisomers. Further chromatography on alumina (Grade II) from light petroleum (b. p. 40—60°) and benzene, isolation of the main fraction, and crystallisation from benzene–methanol gave the *trans*-isomer as red needles, m. p. 150—151°; $\lambda_{max.}$ 487, 456, and 431 mμ, $10^{-3}\varepsilon$ = 151, 171, and 110, respectively; $\nu_{max.}$ (CCl_4) 961 cm.$^{-1}$; τ 9·17, 9·10, 8·39, 8·31, 8·19, 8·10, and 8·06, relative intensities *ca.* 1 : 1 : 2 : 1 : 1 : 1 : 3 (Found: C, 89·25; H, 10·2. Calc. for $C_{40}H_{56}$: C, 89·5; H, 10·5%). A thin-layer chromatogram with a sample from (*a*) showed no separation.

(*c*) Sodium ethoxide (from 200 mg. of sodium) in ethanol (20 ml.) was added dropwise to a solution of α-retinyltriphenylphosphonium chloride (3·5 g.) and γ-retinene (1·4 g.) in ethanol (40 ml.) at 0°. δ-Carotene precipitated immediately. The mixture was heated for 3 hr. at 50°, cooled, poured on ice, and diluted with ether. The ethereal layer was separated, washed successively with 1N-sulphuric acid, saturated sodium hydrogen carbonate solution, and water, dried (Na_2SO_4), and evaporated. Crystallisation of the residue repeatedly from benzene–ethanol, and finally from ethyl acetate, gave (±)-δ-carotene (1·2 g.) as red needles, m. p. 151—152° (uncorr.); $\lambda_{max.}$ 489, 456, 431, and 281 mμ, $10^{-3}\varepsilon$ = 159, 174, 111, and 44, respectively (Found: C, 89·8; H, 10·45. Calc. for $C_{40}H_{56}$: C, 89·5; H, 10·5%). The visible light absorption was identical with that of δ-carotene from tomatoes. Mixed thin-layer chromatograms with the natural product, and with a sample from (*a*), revealed no separation.

ε-*Carotene* (III). (*a*) Ethereal butyl-lithium (1·1N) was added slowly (20 min.) to a stirred suspension of α-ionylidene-ethyltriphenylphosphonium bromide (612 mg.) in dry ether (50 ml.) until all the Wittig salt was seen to have been converted into the deep red phosphoran. The mixture was stirred for a further 10 min. and then dichloromethane (3·0 ml.) was added to decompose any excess of butyl-lithium. A solution of 2,7-dimethylocta-2,4,6-trienedial [11] (82 mg.) in dichloromethane (5 ml.) was added slowly, and the resulting mixture was stirred under reflux for 3 hr. and then cooled. The solvents were evaporated and 90% aqueous methanol was added to the residue. The crude product was extracted with light petroleum (b. p. 40—60°), and the extract was washed with water, dried (Na_2SO_4), and evaporated. Chromatography of the residue on alumina (Peter Spence, Grade II) from a mixture (1 : 1) of benzene and light petroleum (b. p. 60—80°), re-chromatography of the main band from 15% benzene in light petroleum (b. p. 60—80°), collection and evaporation of the main band, and crystallisation of the residue from methanol–light petroleum (b. p. 60—80°) gave ε-carotene (238 mg., 89%) as orange-red needles, m. p. 196—197°, raised by one further crystallisation to m. p. 198—199°; $\lambda_{max.}$ 471, 441, 417, and 267 mμ, $10^{-3}\varepsilon$ = 161, 161, 100, and 35, respectively; $\lambda_{max.}$ (C_6H_6) 488·5, 458, 434, and 414 (inflexion) mμ; $\nu_{max.}$ ($CHCl_3$) 964 cm.$^{-1}$ (*trans*-CH:CH); τ 9·17, 9·09, 8·40, 8·10, and 8·03, all bands of comparable intensity.

(*b*) Sodium methoxide (from 250 mg. of sodium) in ethanol (20 ml.) was added dropwise at 0° to a stirred solution of α-retinyltriphenylphosphonium chloride (3·5 g.) and α-retinene (1·9 g.) in anhydrous ethanol (20 ml.). The mixture was stirred at 50° for 3 hr., then cooled and diluted with light petroleum (b. p. 40—45°). The hydrocarbon layer was separated, washed successively with 85% aqueous methanol (1 l.) and water, dried (Na_2SO_4), and evaporated. Crystallisation of the residue from benzene–ethanol gave ε-carotene (1·3 g.) as red needles, m. p. 199—201° (uncorr.); $\lambda_{max.}$ 470, 440, 416, and 266 mμ, $10^{-3}\varepsilon$ = 168, 167, 104, and 36, respectively (Found: C, 89·65; H, 10·55. Calc. for $C_{40}H_{56}$: C, 89·5; H, 10·5%). From the mother-liquors a stereoisomer was isolated which, after repeated crystallisation from benzene–ethanol, formed red plates, m. p. 187° (uncorr.), partly resolidified and remelted at 199—200°; $\lambda_{max.}$ 470, 440, 416, and 266 mμ, $10^{-3}\varepsilon$ = 162, 160, 104, and 36, respectively (Karrer *et al.*[7] give m. p. 190°; $\lambda_{max.}$ 470, 440, 418, and 265 mμ).

Lycopene (X*c*). 1 Equiv. of 2N-methanolic sodium methoxide was added to a solution of 2,7-dimethylocta-2,4,6-triene-1,8-dial [11] (50 mg.) and ψ-ionylidene-ethyltriphenylphosphonium chloride (prepared from 0·3 g. of vinyl-ψ-ionol) in dimethylformamide (50 ml.). The mixture was stirred overnight at 20° and then water was added. The mixture was extracted with light petroleum (b. p. 40—60°) and the extracts were washed, dried ($MgSO_4$), and concentrated Chromatography of the residue on alumina (Grade II) from light petroleum (b. p. 60—80°) and benzene gave lycopene (89 mg., 55%). The all-*trans* isomer was isolated by further chromatography and crystallisation from benzene–methanol. It had m. p. 176°, undepressed on admixture with an authentic specimen; $\lambda_{max.}$ (hexane) 507, 476, 448, 425, 295, and 286 mμ; $\nu_{max.}$ (CCl_4) 956 cm.$^{-1}$. A mixed chromatogram with an authentic specimen showed no separation.

γ-*Carotene* (II). Vinyl-β-ionol (0·30 g.) was added slowly to a suspension of triphenylphosphine (0·36 g.) in methanol (3 ml.) containing hydrogen chloride (0·05 g.). The mixture was shaken until a clear solution as obtained and was then kept at 20° for 1 day. The methanol was removed under vacuum, the residue was dissolved in dimethylformamide (20 ml.), and apo-12′-lycopenal (93 mg.) was added, followed by 1 equiv. of methanolic sodium methoxide. The mixture was stirred overnight, and then diluted with water. The mixture was extracted with light petroleum (b. p. 40—60°) and the extracts were washed, dried ($MgSO_4$), and evaporated. Chromatography of the residue on alumina (Grade II) using light petroleum (b. p. 60—80°)-benzene as eluant, and evaporation of the main band gave γ-carotene as a mixture of stereoisomers (119 mg., 83%). Further chromatography under similar conditions, and crystallisation from benzene–methanol, gave the all-*trans* isomer, m. p. 154° (corr.); $\lambda_{max.}$ 490, 459, and 433 mμ, $10^{-3}\varepsilon$ = 150, 171, and 119, respectively; $\nu_{max.}$ (CCl_4) 1627, 960 cm.$^{-1}$; τ 8·97, 8·40, 8·33, 8·30, 8·19, and 8·04; relative intensities *ca.* 2 : 1 : 1 : 1 : 1 : 4. The product did not separate from an authentic specimen during thin-layer chromatography on 80% calcium hydroxide and 20% Kieselgel using light petroleum (b. p. 60—80°) as eluant.

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