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Carotenoids and Related Compounds

Part XIII.[1] Synthesis of 4-Keto-γ-Carotene and its 1′-Hydroxy-1′,2′-dihydro Derivative

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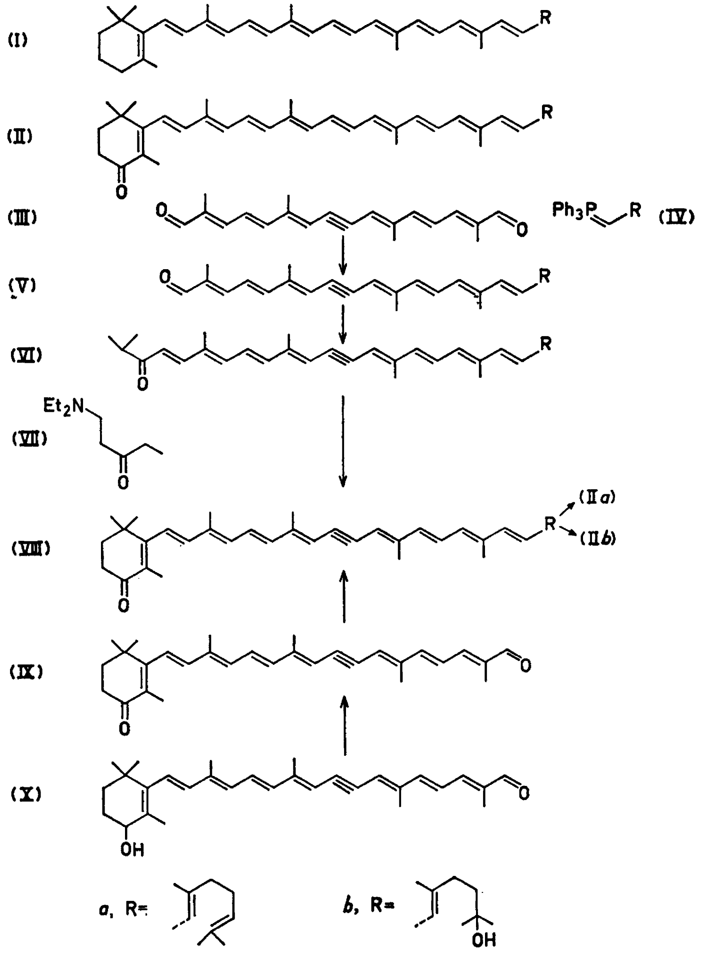
The two natural carotenoids named in the title have been synthesised.

A recent examination of the minor carotenoids of *Mycobacterium phlei* strain Vera by Hertzberg and Jensen[2] revealed three pigments which had not previously been encountered in Nature and which were formulated as (I *b*), (II *a*), and (II *b*). The first of these had already been synthesised in our laboratory in connection with studies[3] on "HO-chlorobactene"; we now report syntheses of the others.

Reaction of the geranyl Wittig reagent[4] (IV *a*) with dehydrocrocetindial (III)[4] gave the dehydro-apo-3-lycopenal (V *a*). This condensed with methyl isopropyl ketone in the presence of ethanolic potassium hydroxide to give the expected product (VI *a*) (under similar conditions apo-3-lycopenal[3] yielded a mixture of conjugated and unconjugated ketones). Condensation of (VI *a*) with the methiodide of the Mannich base (VII) yielded the required ketone (VIII *a*) (*cf.* analogous syntheses in the echinenone and canthaxanthin series[5]). The 1′-hydroxy-1′,2′-dihydro-derivative (VIII *b*) was prepared similarly starting with the Wittig reagent (IV *b*).[3,6] In both cases the overall yield was poor, and therefore an alternative approach was examined.

Oxidation of 4-hydroxy-15,15′-dehydro-β-apo-2-carotenal (X)[7] with 2,3-dichloro-5,6-dicyano-benzoquinone gave the keto-aldehyde (IX) in *ca.* 60 % yield. This reacted with the Wittig reagents (IV *a*) and (IV *b*) to give the 15,15′-dehydro-carotenoids (VIII *a*) and (VIII *b*), respectively, in *ca.* 40 % yields. Partial reduction over a Lindlar catalyst,[8] and stereomutation of the *cis*-15 isomers first formed, furnished the required all-*trans* polyenes (II *a*) and (II *b*).

The three synthetic carotenoids (I *b*), (II *a*), and (II *b*), were identical with the natural pigments.[2]



EXPERIMENTAL

Whenever possible reactions were carried out in an atmosphere of nitrogen, and solvents were evaporated under reduced pressure.

Melting points were determined in evacuated capillary tubes, and are corrected.

Unless stated to the contrary visible and ultra-violet light absorption spectra were determined on solutions in light petroleum, infra-red light absorption spectra on chloroform solutions (main bands only are given), and nuclear magnetic resonance spectra on deuterochloroform solutions (only bands due to methyl and aldehydic protons are cited).

Light petroleum refers to the fraction b.p. 60—80°. Alumina (Peter Spence, type H) was treated as described by Cheeseman *et al.*,[9] and graded.[10] Micro-cel refers to graded micro-cel C from Johns-Manville and Co. Ltd.

15,15′-Dehydro-apo-3-lycopenal (V *a*) (with P.S. Manchand). Sodium methoxide (from 50 mg of sodium) in methanol (10 ml) was added slowly to a stirred mixture of geranyl triphenylphosphonium bromide[4] (500 mg) in methanol (15 ml) and 8,8′-dehydrocrocetindial[4] (294 mg) in benzene (30 ml). The course of the reaction was followed by thin layer chromatography of small samples taken at intervals. After the mixture had been stirred for 1.5 h, water was added, and the product was extracted with benzene. The extract was washed, dried (Na_2SO_4) and evaporated. Chromatography of the residue in benzene on alumina (Grade II), collection of the second band, evaporation, and crystallisation from benzene-light petroleum, gave the *aldehyde* (118 mg), m.p. 151—153°; λ_{max} 475 and 449 mμ; λ_{max} (C_6H_6) 493 and 464 mμ, 10^{-3} ε = 74 and 91.2, respectively; ν_{max} 2210, 1665, 1610, and 925 cm^{-1}; τ 8.39, 8.32, 8.20, 8.13, 8.04, 7.92, and 0.62, relative intensities *ca.* 3:3:3:3:3:6:1. (Found: C 86.85; H 9.3. $C_{30}H_{38}O$ requires: C 86.9; H 9.25).

2,6,10,15,19,23,27-*Heptamethyloctacosa*-4,6,8,10,14,16,18,20,22,26-*decaen*-12-*yn*-3-*one* (VI *a*). 5 % Ethanolic potassium hydroxide (4.8 ml) was added slowly to a stirred solution of 15,15′-dehydro-β-apo-3-lycopenal (80 mg) in methyl isopropyl ketone (1.6 ml). The mixture was diluted with methyl isopropyl ketone until homogeneous, and then kept at 20° overnight. Preparative thin layer chromatography on Kieselgel H using a mixture (1:4) of acetone-light petroleum as eluant, collection of the main product, and crystallisation from ethanol, gave the required ketone (32 mg), m.p. 138—139°; λ_{max} 450 mμ; λ_{max} ($CHCl_3$) 463 mμ, 10^{-3} ε = 80; ν_{max} 2150, 1655, 1602, 990 (shoulder), and 965 cm^{-1}; τ 8.88 (doublet, J = 7.5 cps), 8.38, 8.31, 8.18, 8.03, and 7.90, relative intensities *ca.* 2:1:1:1:2:2.

1′-*Hydroxy*-1′,2′-*dihydro*-15,15′-*dehydro*-*apo*-3-*lycopenal* (V *b*). Sodium methoxide (from 100 mg of sodium) in methanol (2 ml) was added slowly to a stirred mixture of triphenyl-(7-hydroxy-3,7-dimethyloct-2-enyl) phosphonium bromide[3,6] (650 mg) in methanol (10 ml) and 8,8′-dehydro-crocetindial (400 mg) in benzene (7 ml). The mixture was kept at 20° overnight. Benzene was added, and the solution was washed with water until neutral, and then evaporated. Chromatography of the residue in benzene on alumina (Grade II), elution of the main band with 1 % methanol in benzene, evaporation, and crystallisation of the residue from acetone-hexane, gave the hydroxy-aldehyde (497 mg), m.p. 135°; λ_{max} (EtOH) 446 mμ; λ_{max} ($CHCl_3$) 457 mμ; λ_{max} (C_6H_6) 454 mμ, 10^{-3} ε = 73.4; ν_{max} (Nujol) 3350, 2140, 1672, 1605, and 970 cm^{-1}; τ (CCl_4) 8.85, 8.20, 8.13, 8.05, 7.90, and 0.65, relative intensities *ca.* 6:3:3:3:6:1.

27-*Hydroxy*-2,6,10,15,19,23,27-*heptamethyloctacosa*-4,6,8,10,14,16,18,20,22-*nonaen*-12-*yn*-3-*one* (VI *b*). 5 % Ethanolic potassium hydroxide (12 ml) was added dropwise to a stirred solution of the preceding hydroxyaldehyde (200 mg) in methyl isopropyl ketone (3.4 ml). The mixture was diluted with methyl isopropyl ketone until homogeneous, and then kept at 20° overnight. Benzene was added, and the solution was washed with water until neutral. Evaporation, chromatography of the residue in benzene on alumina (Grade II), elution of the main band with 1 % methanol in benzene, evaporation, and crystallisation of the residue from acetone-light petroleum gave the *hydroxy-ketone* (137 mg), m.p. 163—164°; λ_{max} (EtOH) 452 mμ; λ_{max} (C_6H_6) 465 mμ, 10^{-3} ε = 93.8; ν_{max} (Nujol) 3320, 2150, 1673, 1628, 1603, and 970 cm^{-1}; τ (CCl_4) 8.88 (doublet, J = 7.0 cps), 8.83, 8.20, 8.03, and 7.91, relative intensities *ca.* 2:2:1:2:2. (Found: C 83.45; H 9.55. $C_{35}H_{48}O_2$ requires: C 83.95: H 9.65).

4-*Hydroxy*-15,15′-*dehydro*-β-*apo*-2-*carotenal* (X). This compound was prepared from 15,15′-dehydro-β-apo-2-carotenal by the method of Entschel and Karrer.[7] It crystallised from light petroleum — dichloromethane in yellow needles, m.p. 160—161°; λ_{max} 428 mμ; λ_{max} (C_6H_6) 438 mμ, 10^{-3} ε = 75.6; ν_{max} (Nujol) 3400, 2140, 1650, 1635 (shoulder), 1603, and 965 cm^{-1}; τ 8.98, 8.96, 8.16, 8.10, 8.02, 7.87, and 0.51, relative intensities *ca.* 3:3:3:3:3:6:1. (Entschel and Karrer[7] give m.p. 161—163°, λ_{max} (hexane) 430 mμ, 10^{-3} ε = 82.5).

4-*Keto*-15,15′-*dehydro*-β-*apo*-2-*carotenal* (IX). A solution of 2,3-dichloro-5,6-dicyano-benzoquinone (300 mg) in dry dioxan (15 ml) was added to one of 4-hydroxy-15,15′-dehydro-β-apo-2-carotenal (300 mg) in the same solvent (15 ml). After the mixture had been kept at 20° for 3 h it was poured into a short column of alumina (Grade IV), and the product was eluted with chloroform. Removal of solvent, and crystallisation of the residue from light petroleum gave red needles (200 mg), m.p. 157—159°. Recrystallisation from acetone-hexane gave the *keto-aldehyde*, m.p. 167—168°; λ_{max} 426 mμ; λ_{max} ($CHCl_3$) 444 mμ; λ_{max} (EtOH) 436 mμ; λ_{max} (C_6H_6) 440 mμ, 10^{-3} ε = 86.6; ν_{max} 2150, 1655, 1605, and 975 cm^{-1}; τ 8.81, 8.13, 8.08, 7.99, 7.87, and 0.49, relative intensities *ca.* 6:3:3:3:6:1. (Found: C 84.3; H 8.7. $C_{30}H_{36}O_2$ requires: C 84.05; H 8.45).

4-*Keto*-15,15′-*dehydro*-γ-*carotene* (VIII *a*). (i) A solution of geranyl triphenylphosphonium bromide[4] (320 mg) in methanol (10 ml) was added to one of 4-keto-15,15′-

dehydro-β-apo-2-carotenal (200 mg) in benzene (10 ml). Sodium methoxide (from 10 mg of sodium) in methanol (2 ml) was slowly added to the stirred mixture at 20°. The mixture was boiled under reflux for 7 h, and then kept at 20° overnight. Benzene was added, the solution was washed with water until neutral, and then evaporated. Chromatography of the residue in benzene on alumina (Grade II), elution of the main band with benzene, evaporation, and crystallisation of the residue from ethanol-light petroleum gave 4-*keto-15,15′-dehydro-γ-carotene* (80 mg) as needles, m.p. 144—145°; $\lambda_{\max}$ (C_6H_6) 456 mμ, 10^{-3} $\varepsilon = 96.8$; $\nu_{\max}$ 2170, 1655, 1570, and 970 cm^{-1}; τ 8.81, 8.36, 8.31, 8.13, 8.01, and 7.89, relative intensities *ca.* 2:1:1:2:2:2. (Found: C 87.3; H 9.75. $C_{40}H_{25}O$ requires: C 87.55; H 9.55).

(ii) Diethylaminopentan-3-one methiodide [5] (4.0 g) in ethanol (20 ml) was added to a stirred mixture of potassium ethoxide (from 500 mg of potassium) in ethanol (10 ml) and the isopropyl ketone (VI *a*) (80 mg) in benzene (10 ml), and the mixture was boiled under reflux for 2.5 h. Further potassium ethoxide (from 500 mg of potassium) in ethanol (20 ml) was added, and the mixture was boiled under reflux overnight and then cooled. Chloroform was added, and the solution was washed with dilute hydrochloric acid, saturated sodium hydrogen carbonate, and finally with water. Evaporation of the solvents, preparative thin layer chromatography of the residue on Kieselgel H using a mixture (1:4) of acetone and light petroleum as eluant, and collection of the main band, yielded the crude ketone (*ca.* 10 mg); $\lambda_{\max}$ (C_6H_6) 456 mμ; $\lambda_{\max}$ ($CHCl_3$) 453 mμ; τ (main bands only) 8.81, 8.36, 8.31, 8.13, 8.01, and 7.89. A mixed thin layer chromatogram with a sample from (i) revealed no separation.

4-*Keto-γ-carotene* (II *a*). A solution of the preceding ketone (50 mg) and a trace of quinoline in ethyl acetate (10 ml) was shaken with Lindlar's catalyst [8] (60 mg) in an atmosphere of hydrogen in the dark for 3 h. Removal of catalyst and solvent, and chromatography of the residue on alumina (Grade II) using 0.1 % methanol in benzene as eluant, and collection of the main band gave the *cis*-15 polyene, $\lambda_{\max}$ 461 and 350 mμ.

A solution of the *cis*-isomer and a trace of iodine in benzene (150 ml) was irradiated with a 100 watt tungsten filament lamp for 4 h. The solution was washed with dilute aqueous sodium thiosulphate, then with water, and evaporated. Chromatography of the residue in benzene on micro-cel then yielded 4-keto-γ-carotene as a red gum; $\lambda_{\max}$ 462 mμ; $\nu_{\max}$ (CCl_4) 1665, 1635, 1620, and 975 cm^{-1}; τ 8.81, 8.37, 8.31, 8.16, 8.12, and 8.02, relative intensities *ca.* 2:1:1:1:1:4.

4-*Keto*-1′-*hydroxy*-1′,2′-*dihydro*-15,15′-*dehydro-γ-carotene* (VIII *b*). (i) A solution of triphenyl-(7-hydroxy-3,7-dimethyloct-2-enyl) phosphonium bromide [3,6] (240 mg) in methanol (10 ml) was added to one of 4-keto-15,15′-dehydro-β-apo-2-carotenal (150 mg) in benzene (6 ml). Sodium methoxide (from 2.5 mg of sodium) in methanol (0.5 ml) was added slowly to the stirred mixture at 20°. The mixture was stirred for 4 h, then diluted with benzene, washed with water, and evaporated. Chromatography of the residue on micro-cel, using 0.1 % methanol in benzene as eluant, collection of the main band, evaporation, and crystallisation of the residue from acetone-light petroleum gave the *hydroxy-ketone* (77 mg) as needles, m.p. 128—130°; $\lambda_{\max}$ (C_6H_6) 455 mμ, 10^{-3} $\varepsilon = 98.7$; $\nu_{\max}$ 3540, 2150, 1648, 1613, and 970 cm^{-1}; τ 8.81, 8.78, 8.17, 8.13, 8.00, and 7.89, relative intensities *ca.* 2:2:1:1:2:2. (Found: C 84.1; H 9.85. $C_{40}H_{54}O_2$ requires: C 84.75; H 9.6).

(ii) Diethylaminopentan-3-one methiodide [5] (6.0 g) in ethanol (30 ml) was added to a stirred mixture of potassium ethoxide (from 750 mg of potassium) in ethanol (30 ml) and the hydroxy-ketone (VI *b*) (120 mg) in benzene (15 ml), and the mixture was boiled under reflux for 2.5 h. Further potassium ethoxide (from 750 mg of potassium) in ethanol (60 ml) was added, and the mixture was boiled under reflux overnight and then cooled. Benzene was added, and the solution was washed with dilute hydrochloric acid, saturated sodium hydrogen carbonate, and finally with water. Evaporation of the solvent, and chromatography of the residue on micro-cel using 0.1 % methanol in benzene as eluant, led to the required hydroxy-ketone (8 mg), m.p. 128—129°, undepressed on admixture with a sample from (i); $\lambda_{\max}$ (C_6H_6) 455 mμ. A mixed thin layer chromatogram with a sample from (i) revealed no separation.

4-*Keto*-1′-*hydroxy*-1′,2′-*dihydro-γ-carotene* (II *b*). A solution of the preceding hydroxy-ketone (30 mg) and a trace of quinoline in ethyl acetate (10 ml) was shaken with Lindlar's catalyst [8] (35 mg) in an atmosphere of hydrogen in the dark for 3 h. Removal of catalyst and solvent gave the *cis*-15 polyene, $\lambda_{\max}$ (C_6H_6) 474 and 365 mμ.

A solution of the *cis*-isomer and a trace of iodine in benzene (150 ml) was irradiated with a 100 watt tungsten filament lamp for 4 h. The solution was washed with dilute aqueous sodium thiosulphate, then with water, and evaporated. Preparative thin layer chromatography of the residue on Kieselgel H, using 1 % methanol in benzene as eluant, then yielded 4-keto-1′-hydroxy-1′,2′-dihydro-γ-carotene as a red gum; $\lambda_{\max}$ 462 mμ; $\nu_{\max}$ (CCl_4) 3660, 1670, 1635, 1620, and 980 cm^{-1}; τ 8.81, 8.74, 8.19, 8.12, and 8.03.

4,1′-*Dihydroxy*-1′,2′-*dihydro*-15,15′-*dehydro*-γ-*carotene*. Reaction of 4-hydroxy-15,15′-dehydro-β-apo-2-carotenal (100 mg) with triphenyl-(7-hydroxy-3,7-dimethyloct-2-enyl) phosphonium bromide [3,6] (170 mg) following the general procedure described above for the preparation of (VIII *b*), furnished the *glycol* (52 mg) which crystallised from dichloromethane-light petroleum and had m.p. 163 – 164°; $\lambda_{\max}$ (C_6H_6) 481 and 453 mμ, $10^{-3}\,\varepsilon = 85.9$ and 104.4, respectively; $\nu_{\max}$ 3560, 2150, 1630, and 970 cm^{-1}; τ 8.96, 8.79, 8.18, 8.03, and 7.90, relative intensities *ca.* 1:1:1:1:1. (Found: C 84.15; H 10.05. $C_{40}H_{56}O_2$ requires: C 84.45; H 9.9).

An attempt to oxidise the glycol in dioxan with 2,3-dichloro-5,6-dicyanobenzoquinone gave a mixture of products; none of the required carotenoid (II *b*) could be detected by thin layer chromatography at any stage.

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