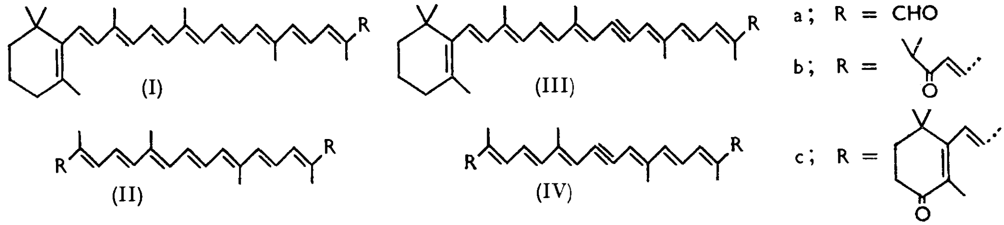
814. *Carotenoids and Related Compounds. Part VIII.* Novel Syntheses of Echinenone and Canthaxanthin.*

By M. Akhtar and B. C. L. Weedon.

Syntheses of echinenone and canthaxanthin, by use of Robinson's Mannich base reaction, are described.

In Part VII unambiguous total syntheses of echinenone and canthaxanthin were reported. Recently details of an alternative route to the latter were given by Isler *et al.*[1] The present paper describes convenient new syntheses of both carotenoids, and records the first applications in this field of Robinson's Mannich base method for the formation of cyclohexenone rings.



Condensation of apo-2-carotenal (Ia)[2] and crocetindial (IIa)[3] with isopropyl methyl ketone in the presence of alcoholic potassium hydroxide gave the decaenone (Ib) and nonaenedione (IIb)[4] in 80—85% yields. Reaction of these ketones with a large excess of 1-diethylaminopentan-3-one methiodide and alcoholic potassium ethoxide then gave echinenone (Ic) and canthaxanthin (IIc) directly in 27 and 12% yields, respectively.

It seemed of interest to examine the substitution of the polyene aldehydes by their acetylenic analogues (IIIa)[2] and (IVa)[3] in the above syntheses. Condensation with isopropyl methyl ketone gave the ketones (IIIb) and (IVb) in 90 and 70% yields, respectively. When treated with the Mannich base these ketones gave 15,15'-dehydroechinenone (IIIc) and 15,15'-dehydrocanthaxanthin (IVc) in *ca.* 60 and 40% yield,

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* Part VII, *J.*, 1958, 3986.

[1] Zeller, Bader, Lindlar, Montavon, Müller, Rüegg, Ryser, Saucy, Schaeren, Schwieter, Stricker, Tamm, Zürcher, and Isler, *Helv. Chim. Acta*, 1959, **42**, 841.

[2] Rüegg, Montavon, Ryser, Saucy, Schwieter, and Isler, *Helv. Chim. Acta*, 1959, **42**, 854.

[3] Isler, Gutman, Lindlar, Montavon, Rüegg, Ryser, and Zeller, *Helv. Chim. Acta*, 1956, **39**, 463.

[4] Warren and Weedon, *J.*, 1958, 3972.

respectively. The marked superiority of the acetylenic, compared with the polyenic, intermediates in the Robinson reaction is surprising. Condensation of the ketone (IIIb) with ethyl vinyl ketone also gave dehydroechinenone (45%).

Reduction of dehydroechinenone over a Lindlar catalyst gave (85%) "central-*cis*" echinenone which yielded "all-*trans*" echinenone (Ic) on irradiation in the presence of a trace of iodine. The similar conversion of 15,15′-dehydrocanthaxanthin into canthaxanthin (IIc) has already been described by Isler *et al.*[1] The dehydrocanthaxanthin prepared in the present studies was identical in all respects with a sample kindly supplied by Dr. O. Isler.

The spectral properties of most of the compounds mentioned above are summarised in the Tables. The acetylenic compounds exhibited maximal light absorption in the visible region at wavelengths *ca.* 25—30 mμ shorter than their polyene counterparts, and "central-*cis*" echinenone displayed a pronounced "*cis*-peak." The carbonyl bands were only poorly resolved in the infrared spectra of the isopropyl ketones. As expected (cf. ref. 4) the cyclohexenones exhibited well-defined carbonyl bands at lower frequencies and of greater intensity. The acetylenic compounds were characterised by weak C≡C stretching frequencies at *ca.* 2155 cm.$^{-1}$, and by an absorption at *ca.* 960 cm.$^{-1}$ which occurred either as a separate maximum or as a shoulder on the main band in the CH out-of-plane deformation region of conjugated *trans*-CH=CH-bonds. Differences between the spectra of the polyenes and their monoacetylenic analogues were also apparent in the C=C stretching region.

TABLE 1. *Light absorption of polyene aldehydes and ketones in benzene.*

(Max in mμ; $\epsilon \times 10^{-3}$ in parentheses.)

Polyenes		*Monoacetylenes*	
Ia	469 (85)	IIIa	440 (71)
Ib	480 (118)	IIIb	454 (99)
Ic[a]	472 (115)	IIIc	445 (90)
IIa	470 (85) 443 (92) 422 (62)	IVa	445 (62) 417 (73)
IIb[b]	518 (103) 483 (115) 458 (78)	IVb	485 (85) 454 (98)
IIc	480 (118)	IVc	448 (80)

[a] Cf. Warren and Weedon, *J.*, 1958, 3986. [b] Warren and Weedon, *J.*, 1958, 3972.

TABLE 2. *Infrared light absorption of polyene aldehydes and ketones.*

(Chloroform solutions or, where indicated, potassium bromide disc. Frequencies in cm.$^{-1}$ with an indication of relative intensity; ε for carbonyl bands in parentheses.)

Compd.	Conj. C≡C stretch.	Conj. C=O stretch.			Conj. C=C stretching region			CH out-of-plane deformation region of conj. *trans*-CH=CH		
Ia†		1639 vs			1600 s	1563 m		1000 m	967 ms	
IIIa	2141 m	1658 vs			1597 s	1570 m		1000 m	990 * 957 m	961 m
Ib		1678 *	1658 s	1645 s		1577 vs 1504 s	1550 vs	996 *	971 vs	
IIIb	2151 m	1672 ms (~100)	1650 s	1639 s		1587 * 1550 vs	1575 s 1515 *	981 *	975 s	963 *
Ic		1655 s (440)			1613 w	1577 w	1558 w		971 vs	
IIIc	2151 w	1653 s (470)			1613 w		1563 w		972 s	957 *
IIa		1667 vs			1605 s	1570 s		998 s	966 s	
IVa	2151 w	1667 vs			1605 s	1587 s		1000 s	988 *	959 s
IIb[a]		1675 s (~250)	1656 m	1645 m		1585 † s	1545 vs †	980 s †	970 s †	
IVb	2155 w	1672 s (~200)	1656 s	1645 s		1587 s	1555 vs	981 s	987 m	962 s
IIc[b]		1651 vs (940)			1608 w †	1581 m †	1555 s †		966 s †	
IVc	2155 w	1653 vs (920)			1613 w	1587 *	1563 m		972 s	958 *

* Shoulder. † KBr disc. w, weak; m, medium; s, strong; vs, very strong.

[a] Warren and Weedon, *J.*, 1958, 3972. [b] Warren and Weedon, *J.*, 1958, 3986.

EXPERIMENTAL

As far as possible all operations were carried out in an inert atmosphere, usually of nitrogen. Alumina for chromatography was pretreated as described by Cheeseman *et al.*[5] and was Grade IV on the Brockmann and Schodder [6] activity scale.

Those m. p.s determined on a Kofler block are corrected.

1-*Diethylaminopentan*-3-*one*.—Reaction of propionyl chloride (300 g.) in chloroform (1 l.) with ethylene in the presence of aluminium chloride (453 g.) gave 1-chloropentan-3-one (160 g.), b. p. 40°/1 mm., n_D^{23} 1·4360 (McMahon *et al.*[7] give b. p. 33°/2·5 mm., n_D^{20} 1·4361).

Treatment of the chloro-ketone (160 g.) in ether (400 c.c.) with diethylamine (192 g.) in ether (500 c.c.) yielded 1-diethylaminopentan-3-one (160 g.), b. p. 98—99°/50 mm., n_D^{22} 1·4345 (Adamson *et al.*[8] give b. p. 84°/13 mm., n_D^{15} 1·4368). Reaction of the amino-ketone with an equal amount of methyl iodide [9] afforded a methiodide as a hygroscopic solid which was used without purification.

2,6,10,15,19-*Pentamethyl*-21-(2,6,6-*trimethylcyclohex*-1-*enyl*)*heneicosa*-4,6,8,10,12,14,16,18,20-*nonaen*-3-*one* (Ib).—A solution of β-apo-2-carotenal (60 mg.) and 3-methylbutan-2-one (1 c.c.) in 5% ethanolic potassium hydroxide (4 c.c.) was kept at 20° for 12 hr. The product (59 mg.) which had crystallised from the reaction medium had m. p. 156—158°. Crystallisation from benzene–methanol gave the *ketone*, m. p. 158—159° (Kofler block), 159—161·5° (evacuated sealed capillary tube) (Found: C, 86·6; H, 9·85. $C_{35}H_{48}O$ requires C, 86·7; H, 10·0%).

Echinenone (Ic).—A solution of the preceding ketone (40 mg.) in benzene (5 c.c.) was added to one of potassium ethoxide (from 250 mg. of potassium) in ethanol (5 c.c.). 1-Diethylaminopentan-3-one methiodide (2·0 g.) in alcohol (10 c.c.) was added and the mixture ($\lambda_{max.}$ 480 mμ) was stirred and boiled under reflux for 2½ hr. Potassium ethoxide (from 250 mg. of potassium) in ethanol (10 c.c.) was added and the mixture boiled overnight. The mixture ($\lambda_{max.}$ 470 mμ) was cooled and poured into dilute hydrochloric acid. Extraction of the product with light petroleum (b. p. 60—80°), chromatography from benzene–light petroleum (b. p. 60—80°) on alumina, collection of the main band, evaporation, and crystallisation of the residue from pentane–chloroform, gave echinenone (11 mg.), m. p. and mixed m. p. 178—179° (evacuated capillary tube) (Petracek and Zechmeister [10] give m. p. 175—178°). A chromatogram of a mixture with an authentic specimen showed no separation.

2,6,10,15,19,23-*Hexamethyltetracosa*-4,6,8,10,12,14,16,18,20-*nonaene*-3,22-*dione* (IIb).—A mixture of crocetindial (1·0 g.), 3-methylbutan-2-one (60 c.c.), and 5% ethanolic potassium hydroxide (80 c.c.) was shaken occasionally and kept at 20° for 24 hr. The product (1·2 g.) which had crystallised had m. p. 180—182°. Recrystallisation from benzene-light petroleum (b. p. 60—80°) gave the nonaenedione (1·0 g.) as purple plates, m. p. 184—186° (Warren and Weedon [4] give m. p. 187°).

Canthaxanthin (IIc).—A solution of the preceding nonaenedione (86 mg.) in benzene (7 c.c.) was added to one of potassium ethoxide (from 315 mg. of potassium) in ethanol (7 c.c.), and the mixture was stirred at 20° for 1 hr. 1-Diethylaminopentan-3-one methiodide (2·5 g.) in alcohol (12 c.c.) was added, and the mixture was boiled and diluted with ethanol (35 c.c.). The resulting homogeneous solution was boiled under reflux for 6·5 hr. Potassium ethoxide (from 270 mg. of potassium) in ethanol (6 c.c.) was added and boiling was continued for another hour. The mixture, which no longer showed an ultraviolet light absorption maximum with $\lambda > 500$ mμ, was cooled and poured into dilute hydrochloric acid. Extraction of the product with benzene, and chromatography from benzene–light petroleum (b. p. 60—80°) on alumina gave three red bands. Collection of the middle band, evaporation, and crystallisation of the residue from pentane–chloroform gave canthaxanthin (12 mg.), m. p. and mixed m. p. 211—212° (evacuated capillary tube) (Petracek and Zechmeister [10] give m. p. 213—214°). A chromatogram of a mixture with an authentic specimen revealed no separation.

Substitution of potassium hydroxide for potassium ethoxide in the above reaction had no ill-effect.

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[5] Cheeseman, Heilbron, Jones, and Weedon, *J.*, 1949, 3120.
[6] Brockmann and Schodder, *Ber.*, 1941, **74**, 73.
[7] McMahon, Roper, Utermohlen, Hasek, Harris, and Brant, *J. Amer. Chem. Soc.*, 1948, **70**, 2971.
[8] Adamson, McQuillin, Robinson, and Simonsen, *J.*, 1937, 1576.
[9] Wilds and Shunk, *J. Amer. Chem. Soc.*, 1943, **65**, 469.
[10] Petracek and Zechmeister, *J. Amer. Chem. Soc.*, 1956, **78**, 1427.

2,6,10,15,19-*Pentamethyl*-21-(2,6,6-*trimethylcyclohex*-1-*enyl*)*heneicosa*-4,6,8,10,14,16,18,20-*octaen*-12-*yn*-3-*one* (IIIb).—A solution of 8,9-dehydro-β-apo-2-carotenal (300 mg.) and 3-methylbutan-2-one (3 c.c.) in 5% ethanolic potassium hydroxide (12 c.c.) was kept at 20° for 14 hr. The product (315 mg.) which had crystallised had m. p. 151—153°; crystallisation from benzene-methanol gave the *ketone* as deep-orange plates, m. p. 153—154·5° (Kofler block) (Found: C, 87·45; H, 9·6. $C_{35}H_{46}O$ requires C, 87·1; H, 9·6%).

15,15′-*Dehydroechinenone* (IIIc).—(i) A solution of the preceding ketone (43 mg.) in benzene (3 c.c.) was added to one of potassium ethoxide (from 150 mg. of potassium) in ethanol (3 c.c.). 1-Diethylaminopentan-3-one methiodide (1·2 g.) in ethanol (6 c.c.) was added and the mixture ($\lambda_{max.}$ 454 mμ) was stirred and boiled under reflux for 1½ hr. Potassium ethoxide (from 100 mg. of potassium) in ethanol (5 c.c.) was added, and the mixture was boiled for 18 hr. The reaction mixture ($\lambda_{max.}$ 442—445 mμ) was cooled and poured into dilute hydrochloric acid. Extraction of the product with benzene-light petroleum (b. p. 60—80°), chromatography from benzene-light petroleum (b. p. 60—80°) on alumina, collection of the main band, evaporation, and crystallisation from light petroleum (b. p. 40—60°) gave a solid (27·5 mg.), m. p. 164—166°. Recrystallisation from the same solvent yielded *dehydroechinenone*, as deep-orange plates, m. p. 168—171° (Kofler block) (Found: C, 87·65; H, 9·4. $C_{40}H_{52}O$ requires C, 87·55; H, 9·55%).

(ii) A solution of the isopropyl ketone (IIIb) (50 mg.) in benzene (3 c.c.) was added to one of potassium ethoxide (from 135 mg. of potassium) in ethanol (2·5 c.c.). The solution was stirred and boiled whilst ethyl vinyl ketone[11] (1 c.c.) in ethanol (5 c.c.) was added slowly during 7 hr. Potassium ethoxide (from 23 mg. of potassium) in ethanol (5·5 c.c.) and benzene (1 c.c.) was added, and the mixture was boiled under reflux overnight. The mixture ($\lambda_{max.}$ 445 mμ) was cooled and poured into dilute hydrochloric acid. Isolation of the product as in the previous experiment gave dehydroechinenone (25 mg.), m. p. 170—172° undepressed on admixture with the preceding specimen.

2,6,10,15,19,23-*Hexamethyltetracosa*-4,6,8,10,14,16,18,20-*octaen*-12-*yne*-3,22-*dione* (IVb).—A mixture of 8,8′-dehydrocrocetindial (350 mg.), 3-methylbutan-2-one (6 c.c.), and 5% ethanolic potassium hydroxide (8 c.c.) was shaken occasionally and kept at 20° for 18 hr. The product (330 mg.) which had crystallised had m. p. 192—195°. Recrystallisation from benzene-methanol gave the *diketone* (310 mg.) as deep-orange plates, m. p. 193·5—195° (Kofler block) (Found: C, 83·2; H, 8·75. $C_{30}H_{38}O_2$ requires C, 83·65; H, 8·9%).

15,15′-*Dehydrocanthaxanthin* (IVc).—A solution of the preceding diketone (43 mg.) in benzene (3 c.c.) was added to one of potassium ethoxide (from 154 mg. of potassium), in ethanol (3 c.c.). 1-Diethylaminopentan-3-one methiodide (1·2 g.) in alcohol (6·0 c.c.) was added, and the mixture ($\lambda_{max.}$ 454 and 485 mμ) was stirred and boiled under reflux for 2½ hr. Potassium ethoxide (from 100 mg. of potassium) in ethanol (6 c.c.) was added, and the mixture was boiled for another 18 hr. The mixture ($\lambda_{max.}$ 440 mμ) was cooled and poured into dilute hydrochloric acid. Extraction of the product with benzene-light petroleum (b. p. 60—80°), chromatography from benzene-light petroleum (b. p. 60—80°) on alumina, collection of the main band, evaporation, and crystallisation of the residue from benzene-light petroleum (b. p. 60—80°) gave pale-red needles (23 mg.), m. p. 187—190°. Recrystallisation from chloroform-light petroleum (b. p. 60—80°) gave dehydrocanthaxanthin, m. p. 192—193° (Kofler block) (Found: C, 85·7; H, 8·7. Calc. for $C_{40}H_{50}O_2$: C, 85·35; H, 8·95%). It was identical with the product described by Isler *et al.*[1] (mixed m. p. and chromatogram, comparison of visible, infrared, and nuclear magnetic resonance spectra), who report m. p. 187—188° (uncorr.), $\lambda_{max.}$ (light petroleum) 438 mμ.

15,15′-cis-*Echinenone*.—A solution of 15,15′-dehydroechinenone (27·5 mg.) in ethyl acetate (4 c.c.) was shaken with Lindlar's[12] catalyst (32 mg.) in the dark in an atmosphere of hydrogen until 1·15 mol. of the latter had been absorbed (30 min.). Removal of catalyst and solvent in the dark at 20°, and crystallisation of the residue from light petroleum (b. p. 60—80°) gave 15,15′-*cis*-echinenone (24 mg.), m. p. 156—158° (Kofler block); $\lambda_{max.}$ 454 and 349 mμ, ε = 84,000 and 43,000, respectively, [light petroleum (b. p. 60—80°)].

A solution of the *cis*-isomer (7 mg.) in light petroleum (b. p. 60—80°) containing a trace of iodine was kept in sunlight for 2½ hr. and then evaporated. Crystallisation of the residue from benzene-methanol gave a solid (4·5 mg.), m. p. 170—176°. Recrystallisation from the same

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[11] Woodward, Sondheimer, Taub, Heusler, and Mclamore, *J. Amer. Chem. Soc.*, 1952, **74**, 4223.
[12] Lindlar, *Helv. Chim. Acta*, 1952, **35**, 446.

solvent gave " all-*trans* "-echinenone, m. p. and mixed m. p. 176—178°; $\lambda_{max.}$ 456 mμ. ε = 118,000 [light petroleum (b. p. 60—80°)].

Analyses were carried out in the microanalytical (Miss J. Cuckney) laboratory of this Department, and the infrared (Mr. R. L. Erskine), and some of the ultraviolet and visible (Mrs. A. I. Boston) light-absorption measurements in the spectrographic laboratory. The authors thank Messrs Hoffmann-La Roche and Co. Ltd. for generous gifts of chemicals. One of them (M. A.) is indebted to the Pakistan Government for a research grant.

DEPARTMENT OF CHEMISTRY, IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
SOUTH KENSINGTON, LONDON, S.W.7.
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