Carotenoids and Related Compounds. Part XXXIII.[1] Synthesis of Dehydroflexixanthin and Deoxyflexixanthin †

By **Ruth E. Coman** (née **Holzel**) and **Basil C. L. Weedon,*** Department of Chemistry, Queen Mary College, Mile End Road, London E1 4NS

The structures assigned to the two *Flexibacter* pigments flexixanthin (3,1'-dihydroxy-3',4'-didehydro-1',2'-dihydro-β,ψ-caroten-4-one) and deoxyflexixanthin (1'-hydroxy-3',4'-didehydro-1',2'-dihydro-β,ψ-caroten-4-one) have been confirmed by synthesis of the latter, and of dehydroflexixanthin (3,1'-dihydroxy-2,3,3',4'-tetradehydro-1',2'-dihydro-β,ψ-caroten-4-one), the autoxidation product of the former.

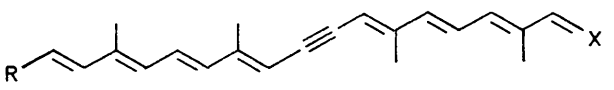
FLEXIXANTHIN (11) and deoxyflexixanthin (9) constitute *ca.* 80 and 20%, respectively, of the carotenoids present in a species of *Flexibacter* examined by Aasen and Jensen.[2] The structure of the former was assigned mainly from studies on a crystalline product obtained from an isolation procedure developed before the α-ketol constitution of the main pigment was recognised, and which involved alkaline hydrolysis. This product was subsequently shown to contain 88% of dehydroflexixanthin (10) (the diosphenol formed by autoxidation of flexixanthin under the isolation conditions used), 10% of flexixanthin (11), and 2% of deoxyflexixanthin (9). The structure of deoxyflexixanthin was deduced from the mass spectrum of this mixture of three pigments, and from various transformations which were carried out on a spectroscopic scale with the pure carotenoid. In this paper we report syntheses of both structures (9) and (10) which confirm those of the two natural carotenoids.

† The trivial names of carotenoids are defined in the Experimental section according to the I.U.P.A.C.–I.U.B. Recommendations for the Nomenclature of Carotenoids (*Pure Appl. Chem.*, 1975, **41**, 405).

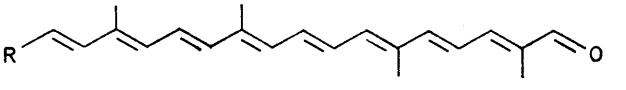
[1] Part XXXII, R. D. G. Cooper, J. B. Davis, A. P. Leftwick, C. Price and B. C. L. Weedon, *J.C.S. Perkin I*, 1975, 2195.

[2] A. J. Aasen and S. L. Jensen, *Acta Chem. Scand.*, 1966, **20**, 1970.

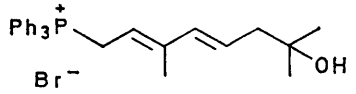
Partial hydrogenation of the (C_{30}) acetylenic keto-aldehyde (1) [3] over palladium, and stereomutation of the 15-*cis*-isomer thus formed, gave the polyene (5). After model studies with β-apo-8′-carotenal (4),[4] a Wittig condensation of (5) with the phosphonium salt (7) [5] (for which an improved synthesis is described in the Experimental section) gave the required hydroxy-ketone (9). Its n.m.r. properties (see Table)were consistent with those of the two related symmetrical carotenoids, canthaxanthin (12) and the glycol (13), and its visible and i.r. absorption spectra were in good agreement with those reported for deoxyflexixanthin.[2]



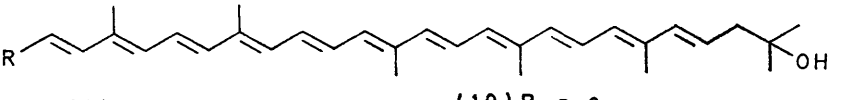
(1) R = b, X = O (3) R = c, X = O
(2) R = b, X = $(OEt)_2$



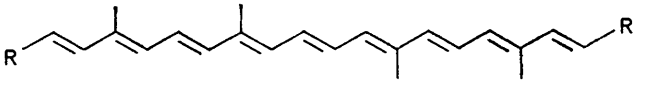
(4) R = a
(5) R = b
(6) R = c



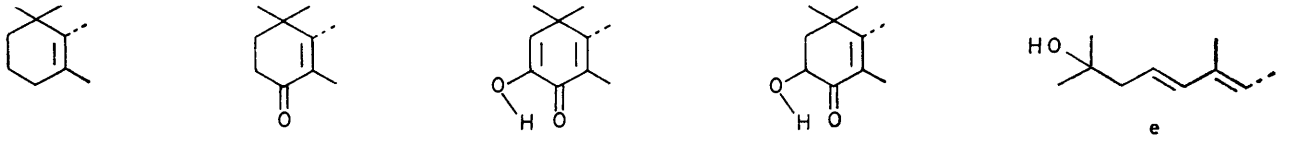
(7)



(8) R = a
(9) R = b
(10) R = c
(11) R = d



(12) R = b
(13) R = e
(14) R = c



a b c d e

Reaction of the acetylenic keto-aldehyde (1) with triethyl orthoformate in the presence of toluene-*p*-sulphonic acid gave the keto-acetal (2). Autoxidation of the latter in the presence of potassium t-butoxide [1] yielded a mixture from which, after acidic hydrolysis, the acetylenic diosphenol (3) was isolated in good yield. Partial hydrogenation, and stereomutation of the product formed initially, furnished the polyene diosphenol (6). This on Wittig condensation with the phosphonium salt (7) yielded the hydroxy-diosphenol (10). Its n.m.r. properties (see Table) were consistent with those of the two related symmetrical carotenoids, astacene (14) and the glycol (13). Its visible, i.r., and n.m.r. spectra were all in good agreement with those reported for dehydroflexixanthin.[2]

The mass spectra of the compounds discussed above exhibited the expected fragmentations.[6,7]

[3] A. P. Leftwick and B. C. L. Weedon, *Acta Chem. Scand.*, 1966, **20**, 1195.
[4] R. Rüegg, M. Montavon, G. Ryser, G. Saucy, U. Schwieter, and O. Isler, *Helv. Chim. Acta*, 1959, **42**, 854.

EXPERIMENTAL

N.m.r. spectra were determined at 60 MHz for dilute solutions in deuteriochloroform, and i.r. spectra for solutions in chloroform. Selected bands only are quoted for n.m.r., i.r., and mass spectra. Where appropriate, polyenes were handled in an atmosphere of nitrogen, and without exposure to bright light. Solutions were evaporated under reduced pressure. M.p.s were determined for samples in evacuated capillary tubes and are corrected. Light petroleum refers to the fraction of b.p. 60—80°, unless the contrary is indicated.

2,6-Dimethyloct-7-en-4-yne-2,6-diol.—Lithium (1.0 g) was dissolved in liquid ammonia (1 l). A few crystals of iron(III) nitrate were added to the blue solution to promote the conversion of lithium into lithamide. When the solution had turned grey, 2-methylpent-4-yn-2-ol [5] (3.92 g) in ether (20 ml) was added dropwise. A solution of methylvinyl ketone (1.4 g) in ether (15 ml) was added slowly, and the mixture was then diluted with ether (200 ml) and stirred until the liquid ammonia had boiled off (18 h). An excess of saturated aqueous ammonium chloride was added, and the product isolated with ether in the usual way. Chromatography on alumina (grade IV) (elution first with light petroleum, then with 5% ether in light petroleum, and finally with ether, and evaporation of the ethereal eluate) gave the glycol as a viscous oil (1.38 g, 20%). Its i.r. and n.m.r. properties were in good agreement with those reported for the product prepared in 4% yield by using the lithium acetylide in benzene.[5]

7-Hydroxy-3,7-dimethylocta-2,4-dienyltriphenylphosphonium Bromide (7).—Reduction of the preceding glycol with lithium aluminium hydride [5] gave 2,6-dimethylocta-4,7

[5] D. F. Schneider and B. C. L. Weedon, *J. Chem. Soc.* (*C*), 1967, 1686.
[6] J. Baldas, Q. N. Porter, A. P. Leftwick, R. Holzel, B. C. L. Weedon, and J. Szabolcs, *Chem. Comm.*, 1969, 415.
[7] B. C. L. Weedon, *Progr. Chem. Nat. Prod.*, 1969, **27**, 81.

diene-2,6-diol in 75% yield. Reaction of the latter with triphenylphosphonium bromide as described by Schneider and Weedon [5] gave the required salt (82%) which crystallised from dichloromethane–ethyl acetate and had m.p. 184°; δ 1.19 (6 H), 1.42 (3 H, d, *J* 3.5 Hz), 2.25br (2 H), and 4.70 (2 H, dd, *J* 15 and 8 Hz) (lit.,[5] m.p. 186°).

3′,4′-Didehydro-1′,2′-dihydro-β,ψ-caroten-1′-ol (8).—Sodium methoxide (10 mg) was added to a stirred solution of the phosphonium salt (7) (70 mg) in methanol (10 ml). A solution of β-apo-8′-carotenal (4) [4] (20 mg) in benzene (15 ml) was added slowly. The mixture was heated gently under reflux and the reaction was monitored by t.l.c. After 3.5 h the mixture was cooled and poured into water. Isolation of the product with chloroform, chromatography on a column of alumina (grade IV) (gradient elution with light petroleum–benzene), collection of the main band, and evaporation gave the *carotenol* (25 mg), which crystallised from chloroform–hexane and had m.p. 172—173°; $\lambda_{max.}$ (hexane) 503, 471, and 445 nm; $\lambda_{max.}$ (C_6H_6) 521, 486, and 460 nm (10^{-3} ε 104.9, 122.4, and 87.4); $\lambda_{max.}$ ($CHCl_3$) 519, 486, and 460 nm; $\lambda_{max.}$ (EtOH) 505, 473, and 449 nm; $\lambda_{max.}$ (CS_2) 452, 508, and 469 nm; $\nu_{max.}$ (KBr) 970 cm^{-1}; δ see Table; *m/e* 552 ($M^{+\cdot}$ 6.2%), 534 (*M* − 18, 0.9%), 460 (*M* − 92, 0.6%), 446 (*M* − 106, 14%), 428 (*M* − 18 − 106, 3.2%), 106 (100%), and 91 (100%) (Found: $M^{+\cdot}$, 552.434. $C_{40}H_{56}O$ requires *M*, 552.433).

4-Oxo-8′-apo-β-carotenal (5).—A solution of 4-oxo-15,15′-didehydro-8′-apo-β-carotenal (1) [3] (40 mg) in ethyl acetate (10 ml) was shaken in the dark, in an atmosphere of hydrogen, and in the presence of Lindlar catalyst (30 mg). The reaction was monitored spectroscopically. After 4.5 h it was interrupted and the catalyst filtered off. Evaporation gave the 15-*cis*-isomer as a crystalline solid; $\lambda_{max.}$ (C_6H_6) 462 and 347 nm; δ see Table.

A solution of the 15-*cis*-isomer and a trace of iodine in benzene (300 ml) was kept in sunlight and the reaction was monitored spectroscopically. After 3 h the solution was washed with aqueous sodium thiosulphate and then with water, and evaporated; the residue was crystallised from chloroform–hexane to give *4-oxo-8′-apo-β-carotenal* (35 mg, 87%), m.p. 164—165°; $\lambda_{max.}$ (C_6H_6) 467 (10^{-3} ε 86) and 484infl nm; $\lambda_{max.}$ ($CHCl_3$) 472 nm; $\lambda_{max.}$ (EtOH) 468 nm; $\lambda_{max.}$ (CS_2) 483 and 505infl nm; $\nu_{max.}$ (KBr) 1 660, 1 610, 1 560, 985, and 970 cm^{-1}; δ see Table; *m/e* 430 ($M^{+\cdot}$, 78%), 361 (*M* − 69, 0.8%), 281 (*M* − 149, 0.6%), and 57 (100%) (Found: $M^{+\cdot}$, 430.287. $C_{30}H_{38}O_2$ requires *M*, 430.287).

Deoxyflexixanthin (*1′-Hydroxy-3′,4′-didehydro-1′,2′-dihydro-β,ψ-caroten-4-one*) (9).—Sodium methoxide (100 mg) in methanol (10 ml) was added to a stirred solution of the phosphonium salt (7) (400 mg) in methanol (20 ml). A solution of the keto-aldehyde (5) (80 mg) in benzene (20 ml) was added dropwise, and the reaction was monitored by t.l.c. After 18 h the mixture was poured into water and the product isolated with chloroform. Chromatography on alumina (grade IV) (gradient elution with 5—10% chloroform in benzene), collection of the main band, evaporation, and crystallisation of the residue from chloroform–hexane, gave deoxyflexixanthin (24 mg), m.p. 135—136° (unchanged on recrystallisation); $\lambda_{max.}$ (light petroleum) 504 and 474 nm, $\lambda_{max.}$ (C_6H_6) 520 and 490 nm; $\lambda_{max.}$ (acetone) 508 and 479 nm; $\lambda_{max.}$ ($CHCl_3$) 519 and 490 nm (10^{-3} ε 106); $\nu_{max.}$ (KBr) 1 650 and 960 cm^{-1}; δ see Table; *m/e* 566 ($M^{+\cdot}$, 1.6%), 548 (*M* − 18, 2%), 508 (*M* − 58, 0.5%), 474 (*M* − 92, 0.17%), 460 (*M* − 106, 6%), 442 (*M* − 18 − 106, 6%) and 91 (100%) (Found: $M^{+\cdot}$ 566.412. Calc. for $C_{40}H_{54}O_2$: *M*, 566.412).

For natural deoxyflexixanthin crystallised from ether–light petroleum Aasen and Kensen [2] give ' indistinct m.p. 150—160° '; $\lambda_{max.}$ (light petroleum) 503 and 476.5 nm; $\lambda_{max.}$ (acetone) 508 and 480.5 nm; $\nu_{max.}$ (KBr) 1 650 and 960 cm^{-1}.

4-Oxo-15,15′-didehydro-8′-apo-β-carotenal Diethyl Acetal (2).—A crystal of toluene-*p*-sulphonic acid was added to a solution of 4-oxo-15,15′-didehydro-8′-apo-β-carotenal [3] (100 mg) and triethyl orthoformate (10 ml) in ethanol (50 ml). After 8 h the mixture was poured into cold (0°) aqueous sodium hydrogen carbonate, and the product was extracted with benzene. The extracts were washed thoroughly with water and then evaporated. Preparative t.l.c. of the residue on alumina (15% acetone in light petroleum as eluant), extraction of the required product with ethanol, and crystallisation from acetone–light petroleum, gave the acetal (40 mg, 40%), m.p. 96—98°; $\lambda_{max.}$ (C_6H_6) 419 (10^{-3} ε 75.7) and 430infl nm; $\nu_{max.}$ ($CHCl_3$) 1 650 and 970 cm^{-1}; δ see Table.

3-Hydroxy-4-oxo-2,3,15,15′-tetradehydro-8′-apo-β-carotenal (3).—Potassium t-butoxide (200 mg) in t-butyl alcohol (10 ml) was added to a solution of the preceding acetal (20 mg)

Principal n.m.r. bands (δ values; 60 MHz; *J* in Hz; dilute solutions in $CDCl_3$)

Compound	C-1 Me_2	C-5 Me	C-9 Me	C-13 Me	C-13′ Me	C-9′ Me	C-5′ Me	C-1′ Me_2	Other
(1)	1.20	1.88	2.02	2.15	2.15	1.90			2.52 (2 H, t, *J* 6.5, C-3 H_2), 9.46 (1 H, CHO)
(2)	1.18	1.84	1.99	2.08	2.08	1.80			1.20 (6 H, t, *J* 7, CH_2CH_3), 2.50 (2 H, t, *J* 7), 3.52 (4 H, m, CH_2CH_3), 4.71 1 H, C-10′ H)
(3)	1.30	2.10	2.05	2.15	2.15	1.91			9.48 (1 H, CHO)
(5)	1.18	1.87	2.00	2.00	2.00	1.90			2.50 (2 H, t, *J* 7, C-4 H_2)
(5) (15-*cis*)	1.20	1.86	2.00	2.00	2.00	1.90			2.51 (2 H, t, *J* 7, C-4 H_2), 9.50 (1 H, CHO)
(6)	1.31	2.11	2.02	2.02	2.02	1.91			9.53 (1 H, CHO)
(8)	1.03	1.73	1.99	1.99	1.99	1.99	1.93	1.23	2.30 (2 H, d, *J* 7, C-2′ H_2)
(9)	1.20	1.87	1.98	1.98	1.98	1.98	1.95	1.23	*ca.* 2.4 (4 H, m, C-4 and C-2′ H_2)
(10) *	1.28	2.09	2.02	1.97	1.97	1.97	1.93	1.24	2.30 (2 H, d, *J* 6, C-2′ H_2)
(10)[2,*]	1.28	2.05	2.00	1.97	1.97	1.97	1.92	1.24	2.29 (2 H, d, *J* 7, C-2′ H_2)
(12) [7]	1.19	1.86	1.96	1.96	1.96	1.96	1.86	1.19	
(13) [5]	1.23	1.98	1.98	1.98	1.98	1.98	1.98	1.23	2.31 (4 H, d, *J* 6, C-2 and C-2′ H_2)
(14) [1]	1.30	2.10	2.02	2.02	2.02	2.02	2.10	1.30	

*At 100 MHz.

in benzene (5 ml), and the mixture was shaken in oxygen for 24 h. It was then poured into chloroform and the solution was washed thrice with dilute hydrochloric acid, and then with water until neutral. Evaporation, preparative t.l.c. of the residue on Kieselgel (20% acetone in light petroleum as eluant), extraction of the required product with chloroform–methanol, and crystallisation from chloroform–benzene, gave the *diosphenol* (10 mg), m.p. 177—179°; $\lambda_{max.}$ (C_6H_6) 442 nm (10^{-3} ε 70.2); $\nu_{max.}$ (KBr) 1 670, 1 615, 1 610, and 960 cm^{-1}; δ see Table; *m/e* 442 ($M^{+\cdot}$, 21%), 427 (M — 15, 3.7%), 413 (M — 29, 1.2%), 203 (14%), and 83 (100%) (Found: $M^{+\cdot}$, 442.250. $C_{30}H_{34}O_3$ requires M, 442.251).

4-Oxo-15,15′-didehydro-8′-apo-β-carotenal (6 mg) was also obtained.

3-Hydroxy-4-oxo-2,3-didehydro-8′-apo-β-carotenal (6).—A solution of the preceding acetylene (50 mg) in ethyl acetate (15 ml) was shaken in the dark, in an atmosphere of hydrogen, and in the presence of Lindlar catalyst (60 mg). The reaction was monitored spectroscopically. After 7 h the reaction was interrupted and the catalyst and solvent were removed. The residue was dissolved in benzene, and a small crystal of iodine was added. The solution was kept in sunlight for 2 h, then washed with aqueous sodium thiosulphate, and finally with water. Evaporation, and crystallisation of the residue from chloroform–hexane gave the *diosphenol* (46 mg), m.p. 196—197°; $\lambda_{max.}$ (C_6H_6) 471 nm; $\lambda_{max.}$ (acetone) 465 nm; $\lambda_{max.}$ ($CHCl_3$) 477 nm; $\lambda_{max.}$ (EtOH) 461 nm; $\lambda_{max.}$ (CS_2) 484 nm; $\nu_{max.}$ (KBr) 1 670, 1 620, 1 610, 1 560, and 970 cm^{-1}; δ see Table; *m/e* 444 ($M^{+\cdot}$, 100%), 442 (M — 2, 4%), 428 (M — 16, 6%), 352 (M — 92, 2.2%), 338 (M — 106, 1.2%), and 203 (60%) (Found: *m/e* 444.266 and 203.107. $C_{30}H_{36}O_3$ requires 444.266. $C_{13}H_{15}O_2$ requires 203.107).

Dehydroflexixanthin (*3,1′-Dihydroxy-2,3,3′,4′-tetradehydro-1′,2′-dihydro-β,ψ-caroten-4-one*) (10).—Sodium methoxide (60 mg) in methanol (20 ml) was added to a stirred solution of the phosphonium salt (7) (250 mg) in methanol (12 ml). A solution of the aldehyde (6) (30 mg) in methanol (20 ml) and benzene (20 ml) was added slowly and the reaction was monitored by t.l.c. After 5 h the mixture was poured into water and the product was extracted with chloroform. The extract was washed thoroughly with water and then evaporated. Chromatography of the residue on a column of silica gel (18% water) [gradient elution with 0—15% acetone in light petroleum (b.p. 40—60°)], collection of the most polar band, and evaporation gave the crude product (15 mg). Crystallisation from chloroform–hexane gave dehydroflexixanthin, m.p. 161—162°; $\lambda_{max.}$ (C_6H_6) 495 and 512infl nm; $\lambda_{max.}$ ($CHCl_3$) 495 nm (10^{-3} ε 91.2); $\lambda_{max.}$ (acetone) 480 and 500infl nm; $\lambda_{max.}$ (EtOH) 483 nm; $\nu_{max.}$ (KBr) 1 680w, 1 620, 1 570, 1 550, and 960 cm^{-1}; δ see Table; *m/e* 580 ($M^{+\cdot}$, 3.5%), 578 (M — 2, 2.5%), 562 (M — 18, 3.5%), 474 (M — 106, 2.6%), 456 (M — 18 — 106, 3%), and 203 (100%) (Found: $M^{+\cdot}$, 580.391. $C_{40}H_{52}O_3$ requires M, 580.392).

For the mixture containing 88% of deoxyflexixanthin, obtained by autoxidation of natural flexixanthin, Aasen and Jensen [2] give m.p. 183.5—185°; $\lambda_{max.}$ (acetone) 479.5 and 505infl nm; $\nu_{max.}$ (KBr) 1 612 and *ca.* 1 540 cm^{-1}; δ see Table.

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