115. New Methods for the Synthesis of Oxygenated Carotenoids

by **J. D. Surmatis, A. Walser, J. Gibas, U. Schwieter** and **R. Thommen**

Technical Development Department
Hoffmann-La Roche Inc., Nutley, New Jersey, USA

Dedicated to Dr. *O. Isler* on his 60th birthday

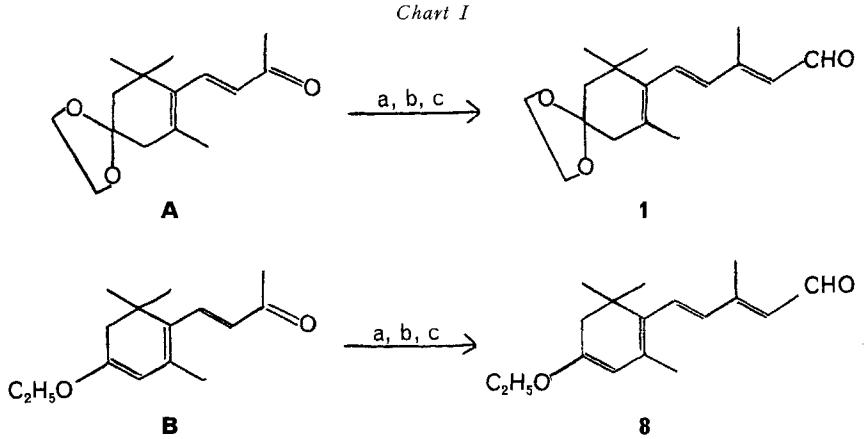
(15. V. 70)

Summary. Six keto carotenoids (**4**, **5**, **6**, **11**, **12**, and **22**) were synthesized from intermediates which were prepared from the condensation products of mesityl oxide and acetoacetic ester. Compounds **4** and **22** can serve as precursors for zeaxanthin, while **5** can be used as an intermediate for xanthophyll. Echinenone and canthaxanthin were prepared by a new approach from vitamin A. Two new types of keto carotenoids with the keto functions incorporated into the unsaturated chain were prepared.

The oxygenated carotenoids are very widely distributed in nature. Even though the structures of many of these compounds are well known, they are not readily available by total synthesis. We now wish to report on the synthesis of a number of keto carotenoids, some of which can serve as precursors to zeaxanthin and xanthophyll.

In a recent publication [1], we reported the total synthesis of two new oxygenated β-ionones, A and B, from a condensation product of mesityl oxide and acetoacetic ester. These ionones were readily converted to the corresponding ionylidene-acetaldehydes **1** and **8** by following the reaction steps indicated in Chart I.

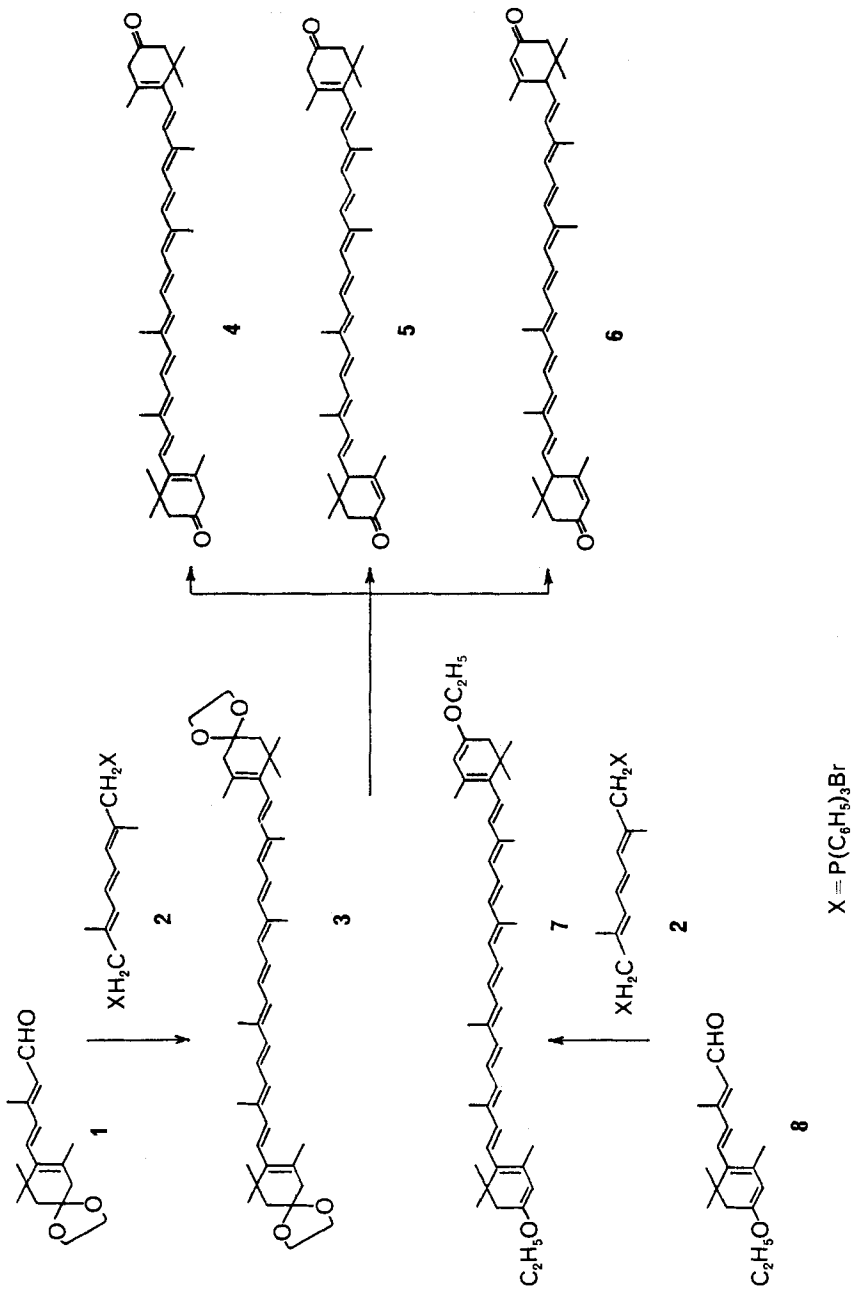
Chart I



a. $(C_2H_5O)_2POCH_2COOC_2H_5$ b. $LiAlH_4$ c. MnO_2

The synthesis of **3** and **7** followed a $C_{15} + C_{10} + C_{15}$ building scheme as shown in Chart II. When **3** was hydrolyzed with 10% aqueous sulfuric acid at the boiling temperature of methylene chloride-acetone, the product consisted of dihydrorhodoxanthin (**4**) and two minor products which were established as **5** and **6**. When **3**

Chart II



was hydrolyzed with 36% hydrochloric acid in methylene chloride and ethyl alcohol at room temperature, the main product consisted of **6**, and **4** and **5** were isolated and identified as the contaminants. Hydrolysis of **7** by either of the two methods described yielded **6** as the main reaction product.

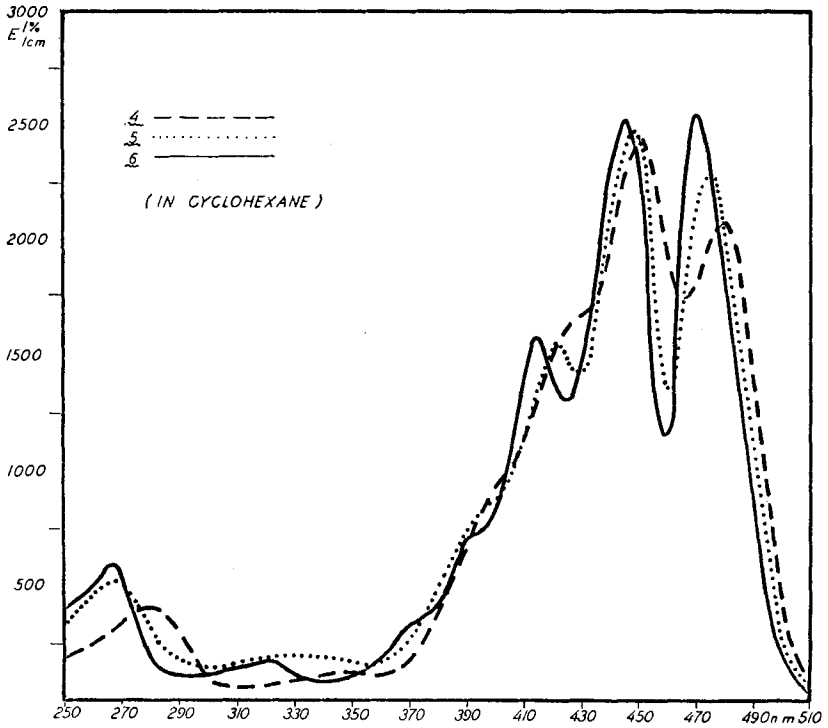


Fig. 1. *UV. Spectra of* **4**, **5**, *and* **6** *in Cyclohexane*

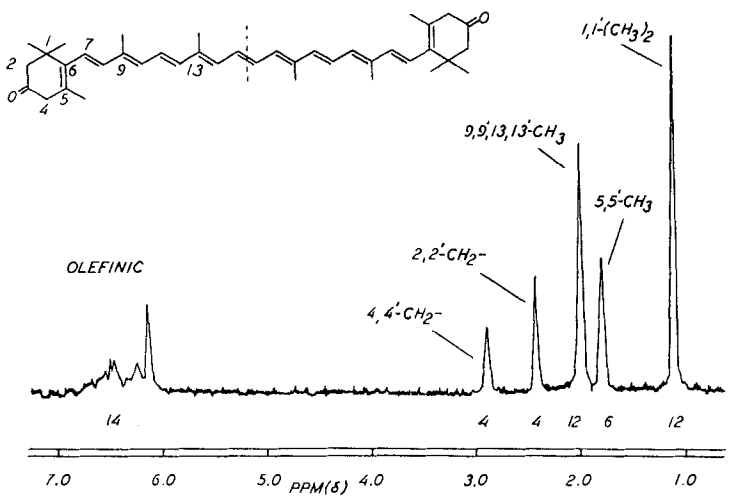


Fig. 2. *NMR. Spectrum of* **4**

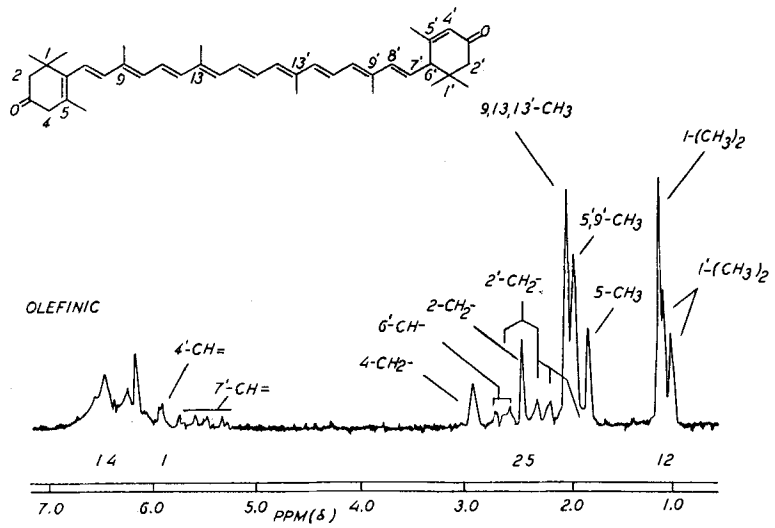


Fig. 3. *NMR. Spectrum of* **5**

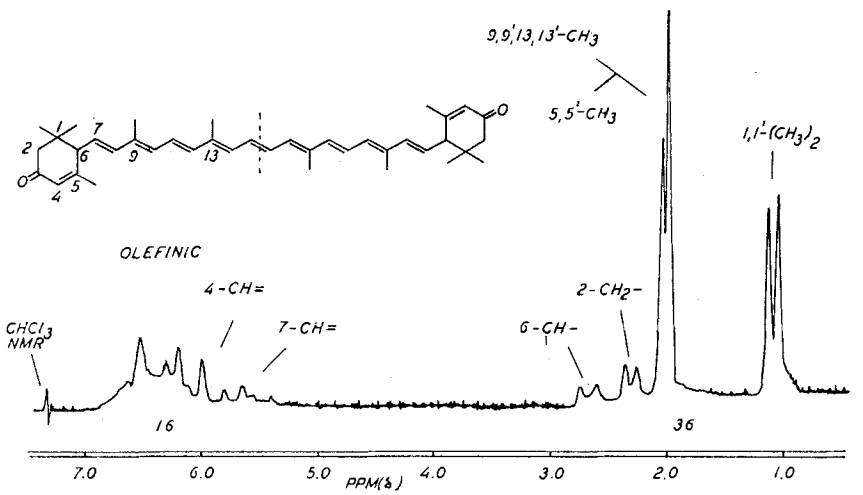


Fig. 4. *NMR. Spectrum of* **6**

By reacting a mixture of the ionylidene-acetaldehydes **1** and **9** with **2** by the same $C_{15} + C_{10} + C_{15}$ building scheme, an unsymmetrical carotenoid, **10**, was isolated by chromatography on silica gel. Hydrolysis of **10** yielded only one product, **11**, which was purified by silica gel chromatography. Some dehydrogenation of **11** occurred during the chromatography. Isolation and purification of the new product afforded a keto carotenoid, **12**, as dark violet crystals: mp. 176–178°; UV. max. 483 nm ($E^{1\%}_{1\,cm}$ = 2381) in cyclohexane.

Chart III

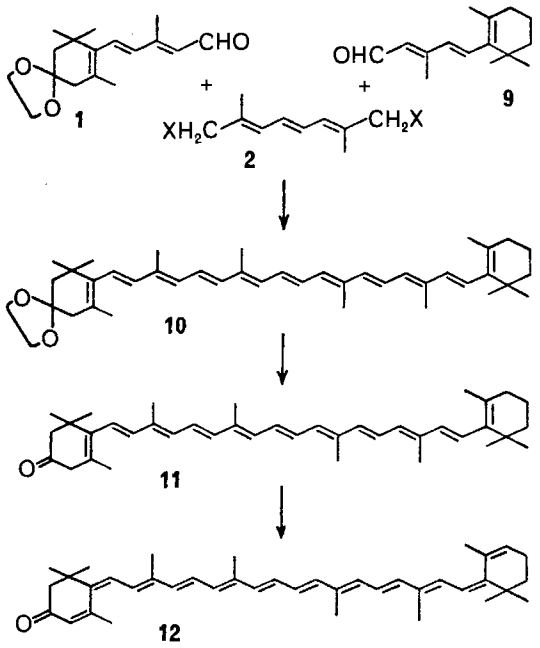
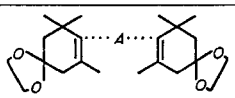
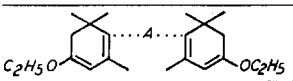
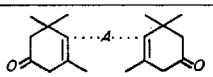
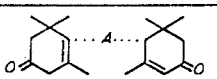
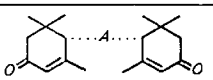
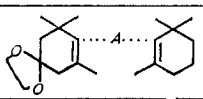
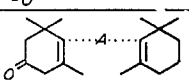
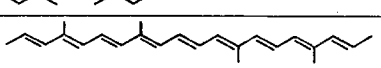


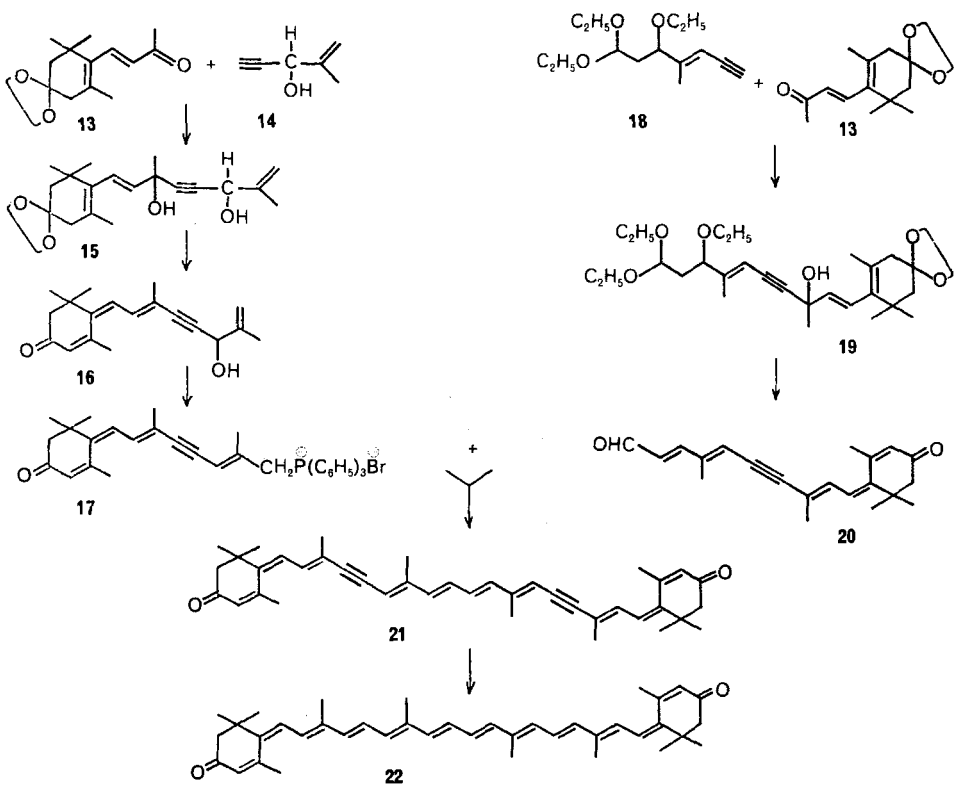
Chart IV. *Melting Points and UV. Data for* **3**, **7**, **4**, **5**, **6**, **10**, and **11**

		mp.	Absorption Maxima (Cyclohexane)					
			nm			$E^{1\%}_{1\,cm}$		
	**3**	178	481	453	430	1690	1950	1370
	**7**	149	491			1744		
	**4**	208	480	451	428	2100	2435	1695
	**5**	192	476	448	423	2278	2478	1570
	**6**	194	472	443	417	2550	2530	1605
	**10**	165	481	453	430	1888	2181	1545
	**11**	188	479	452	430	2296	2633	1870
A = 								

I. A Total Synthesis of Rhodoxanthin. – Rhodoxanthin is widely distributed in small quantities in nature. The ripe berries of the yew tree, *taxas baccata*, are a good source of the pigment. *Kuhn & Brockmann* [2] isolated the pigment from these berries and elucidated its chemical structure. *Karrer & Solmssen* [3] confirmed the constitution of rhodoxanthin by converting dihydrorhodoxanthin to zeaxanthin. *Isler* and coworkers [4] reported a total synthesis of rhodoxanthin in 1967 by a $C_{14} + C_{12} + C_{14}$ building scheme. We now report a total synthesis of rhodoxanthin from the substituted β-ionone **13** (= A) [1]. Compound **14**, which is readily available by ethynylation of methacrolein, was condensed with **13** by means of a *Grignard* reaction to yield the diol **15**. Dehydration of **15** by refluxing a methylene chloride solution with 5% sulfuric acid yielded 2,6-dimethyl-8-(4-oxo-2,6,6-trimethyl-2-cyclohexenylidene)-1,6-octadien-4-yn-3-ol (**16**). Condensation of **16** with triphenylphosphonium bromide [5] gave the *Wittig* compound **17**: mp. 212°.

4-Methyl-1,1,3-triethoxy-4-hepten-6-yne (**18**) was prepared by a condensation of C_6 acetal [6] with ethyl vinyl ether and a zinc chloride catalyst by a procedure described by *Isler et al.* [7]. Compound **18** was condensed with the substituted β-ionone

Chart V



13 by means of a *Grignard* reaction to form **19**, which was subsequently hydrolyzed with sodium acetate, acetic acid, and water to afford the aldehyde **20** as dark yellow needles: mp. 116°. Condensation of **20** with the *Wittig* salt **17** yielded 10,11,10',11'-

tetradehydro-rhodoxanthin (**21**) as dark red needles melting at 178°. Reduction of **21** with *Lindlar's* catalyst [8], followed by thermal isomerization (95° in heptane), afforded *trans*-rhodoxanthin (**22**) as dark violet colored crystals: mp. 217–219°; UV. max. 521 (1752), 491 (2386), 466 (1990) nm ($E^{1\%}_{1\,cm}$) in cyclohexane.

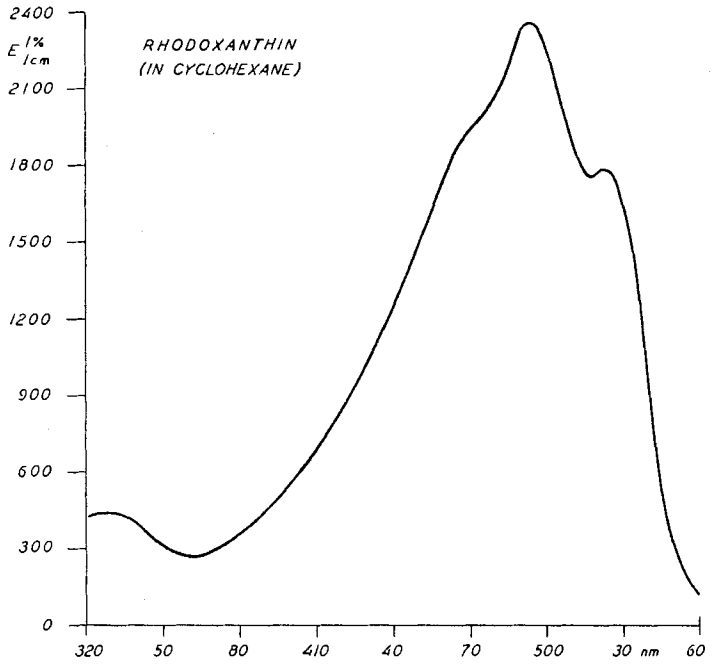


Fig. 5. *UV. Spectrum of Rhodoxanthin in Cyclohexane*

II. A Total Synthesis of Echinenone and Canthaxanthin. – Echinenone, 4-keto-β-carotene (**29**), is found in nature in echinoidae and in crustacea [9] [10]. Canthaxanthin, 4,4'-diketo-β-carotene (**32**), has been reported to be present in crustacea [10], in the feathers of several species of birds [11], in the organs of flamingos [12], in mushrooms [13], and in algae [14]. Echinenone has been synthesized from β-apo-8'-carotenal [15] and the best starting material for canthaxanthin has been β-carotene [16]. We now wish to report convenient syntheses of echinenone and canthaxanthin from vitamin A as illustrated in Chart VI.

Retinal (**24**), which was prepared in 85% yield by oxidation of vitamin A alcohol with manganese dioxide[1]) in methylene chloride, was reacted with N-bromosuccinimide in methylene chloride and acetic acid to yield 4-acetoxyretinal (**26**). Compound **26** was condensed with retinyltriphenylphosphonium sulfate to yield the acetate of isocryptoxanthin (**27**), which was saponified to isocryptoxanthin (**28**) and oxidized by the *Oppenauer* method to yield echinenone (**29**) in 55% yield (based on vitamin A aldehyde): mp. 178–179°; absorption max. 461 nm ($E^{1\%}_{1\,cm}$ = 2110) in cyclohexane.

[1]) Available from *General Metallic Oxides Corporation;* Jersey City, New Jersey (manganese hydrate, No. 37).

Chart VI

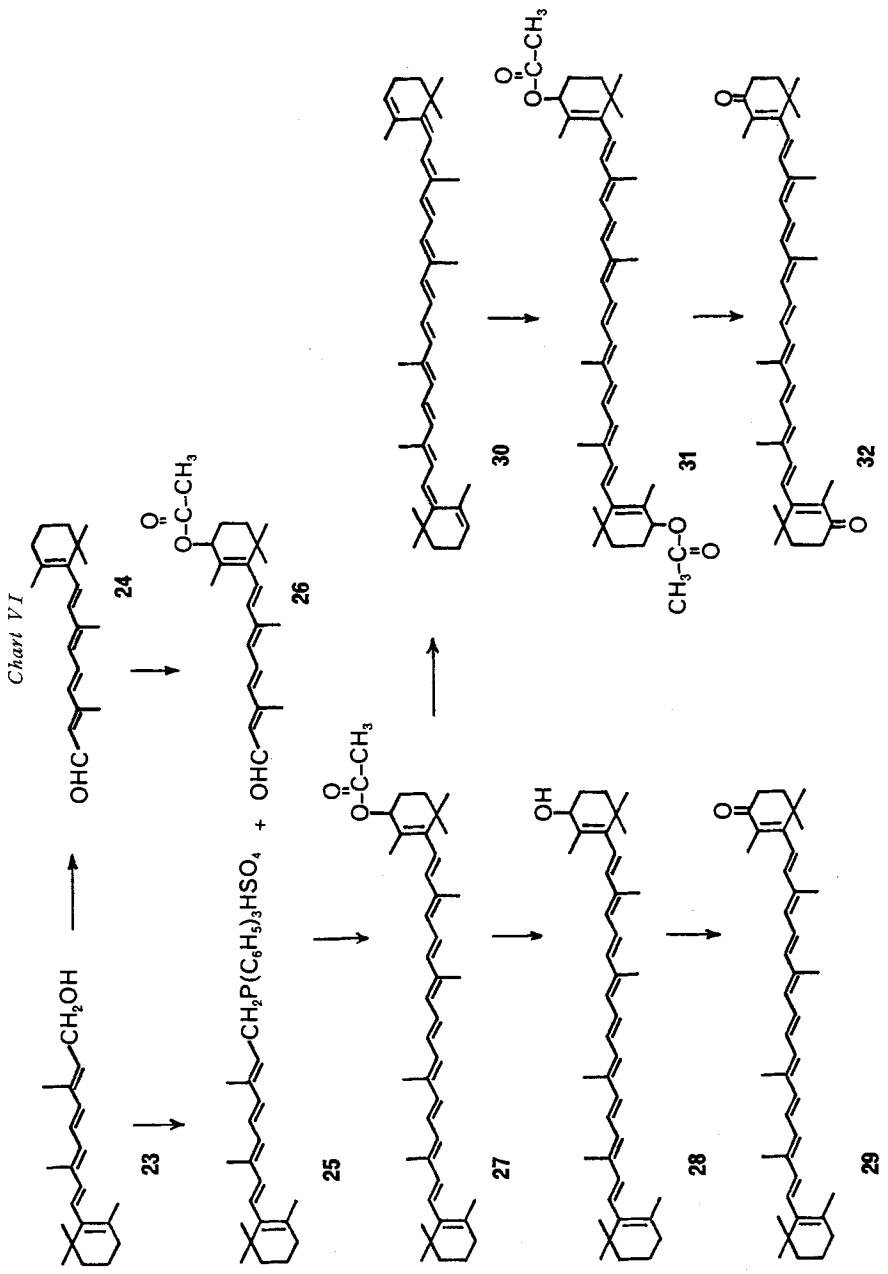
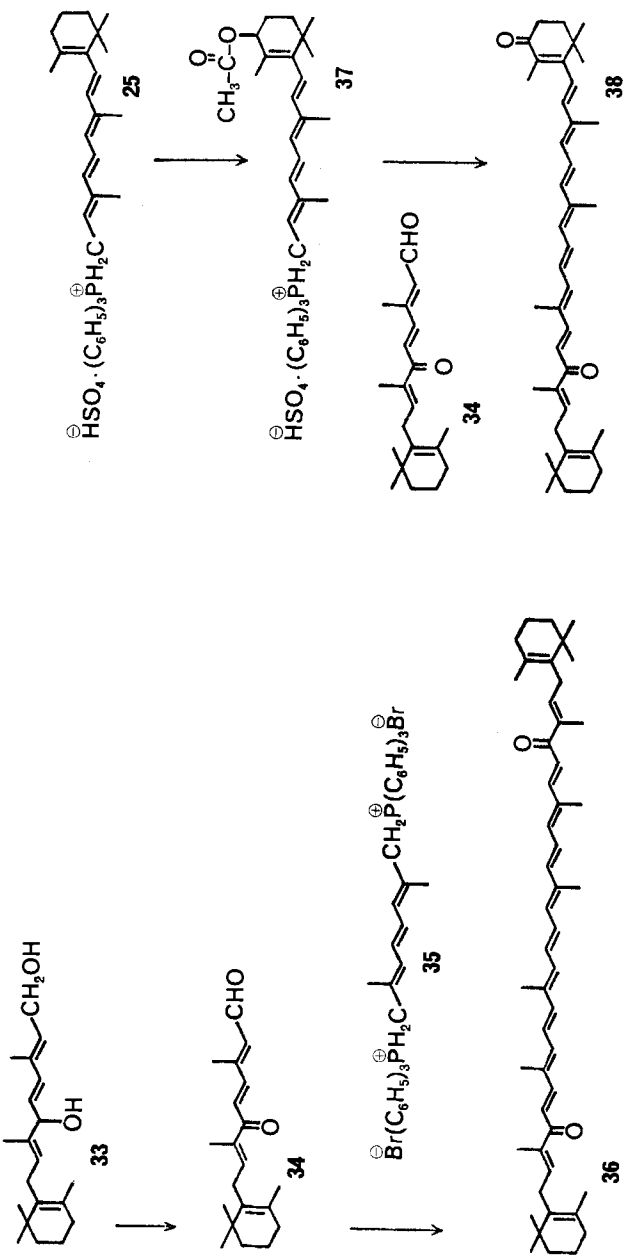

CH2OH
OHC
CH2P(C6H5)3HSO4
+
O
O–C–CH3
CH3–C–O
23
24
25
26
27
28
29
30
31
32
OH

Chart VII



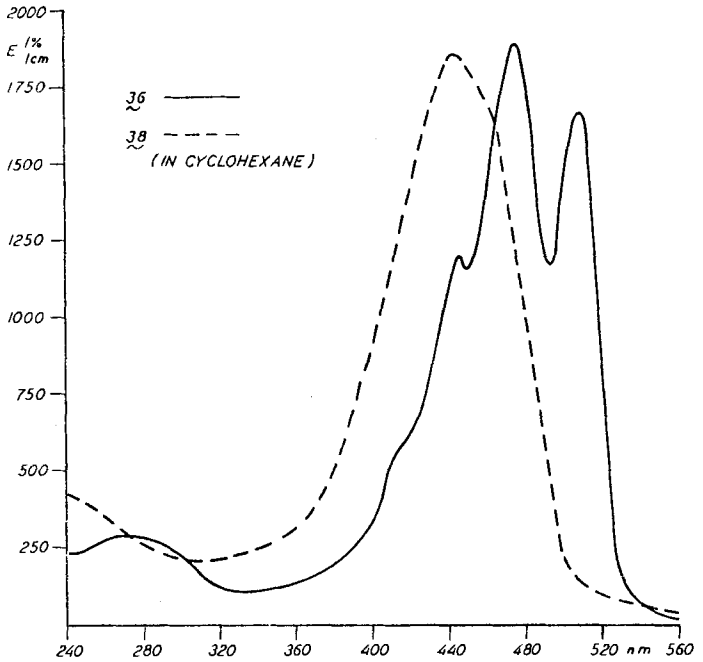


Fig. 6. *UV. Spectra of* **36** *and* **38** *in Cyclohexane*

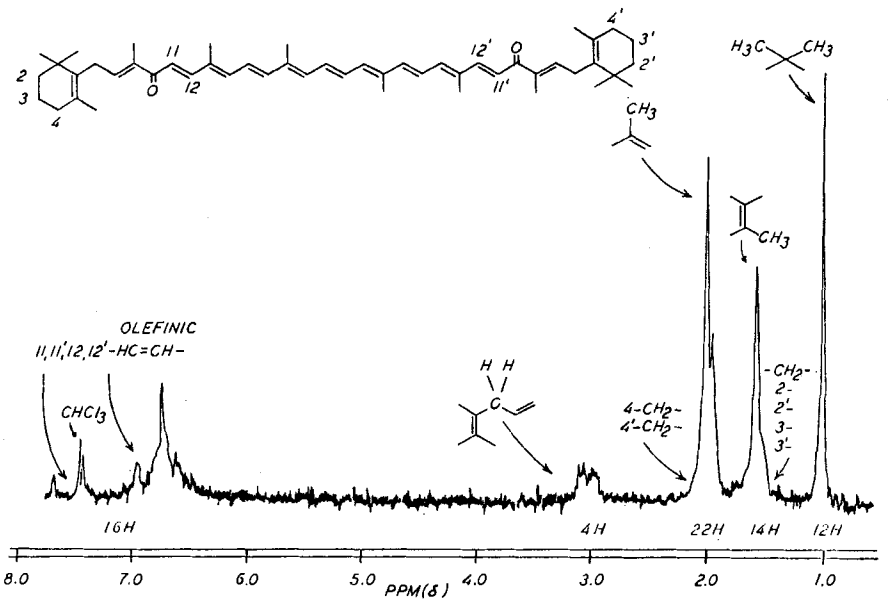


Fig. 7. *NMR. Spectrum of* **36**

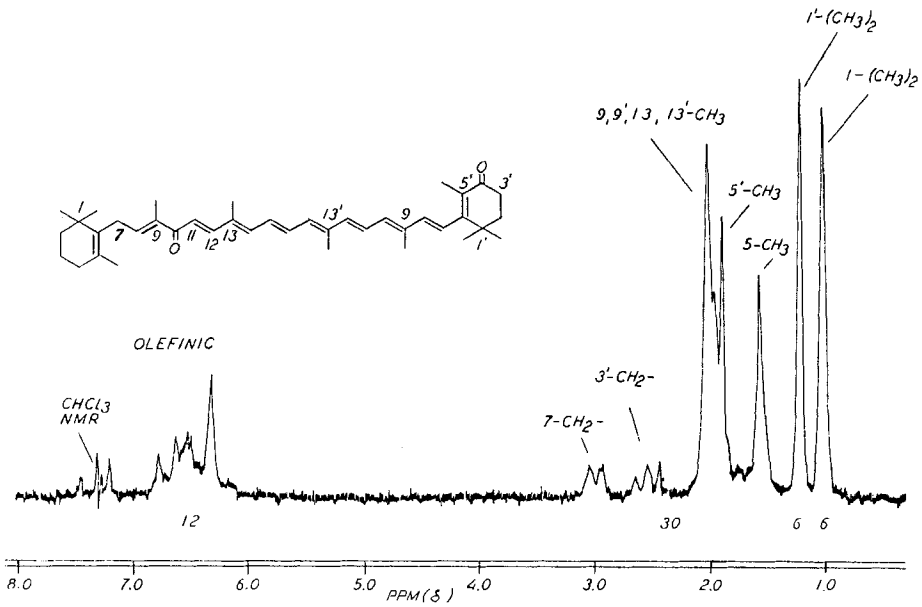


Fig. 8. *NMR. Spectrum of* **38**

Treatment of **27** with 68% hydrobromic acid at −45°, gave dehydro-retro-carotene (**30**) (30.7% based on retinene): mp. 196–197°; UV. max. 447 (2260), 473 (3130), 504 (2460) nm ($E^{1\%}_{1\,cm}$).

Reaction of **30** with N-bromosuccinimide in chloroform and acetic acid yielded the acetate of isozeaxanthin (**31**). Saponification, followed by oxidation with aluminium isopropoxide, resulted in a 74% yield of canthaxanthin (**32**) based on **30**: mp. 212–213°; UV. max. 469 nm ($E^{1\%}_{1\,cm}$ = 2200) in cyclohexane.

III. Synthesis of Chain-Substituted Keto Carotenoids 36 and 38. – Until recently, nothing was known about cross-conjugated keto carotenoids in which the keto functions are incorporated into the unsaturated chain. The first compound of this nature was reported in 1969 [17]. Because of the interest in the physical properties of such compounds, two new carotenoids of this type are described in this communication. See Chart VII.

3,7-Dimethyl-6-oxo-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,7-nonatrienal (**34**), which was prepared by oxidation of **33** with manganese dioxide in methylene chloride [17], was condensed with **35** in a methyl alcohol solution of potassium hydroxide to give 1,26-bis-(2,6,6-trimethyl-1-cyclohexenyl)-3,7,11,16,20,24-hexamethylhexacosa-2,5,7,9,11,13,15,17,19,21,24-undecaen-4,23-dione (**36**) in 40% yield: mp. 190°; UV. max. 473 nm ($E^{1\%}_{1\,cm}$ = 1898) in cyclohexane.

For the preparation of 1-(2,6,6-trimethyl-1-cyclohexenyl)-18-(2,6,6-trimethyl-3-oxo-1-cyclohexenyl)-3,7,12,16-tetramethyloctadeca-2,5,7,9,11,13,15,17-octaen-4-one (**38**), compound **25** was treated with N-bromosuccinimide in the presence of

acetic acid, and the resulting acetoxy *Wittig* compound **37** was condensed with the substituted aldehyde **34** to form **38** in 35% yield: mp. 195°; UV. max. 438 nm ($E^{1\%}_{1\,cm}$ = 1864) in cyclohexane.

Experimental Part[2])

5-(4,4-Ethylenedioxy-2,6,6-trimethyl-1-cyclohexen-1-yl)-3-methyl-2,4-pentadienal (**1**). – (a) α-Diethylphosphono-ethyl acetate (90 g) was added to a suspension of sodium amide (16 g) in ethyl ether (500 ml), and the mixture was stirred for 4 h. 3,3-Ethylenedioxy-β-ionone [1] (51 g) dissolved in ethyl ether (200 ml) was dropped into the stirred reaction in 15 min, and the stirring was continued for 18 h at room temperature. The reaction mixture was poured into cold water (5°) and extracted with hexane. The extract was washed with water until neutral and dried over sodium sulfate, and the solvent was removed under vacuum. The residue consisted of 58 g (88.9%) of 5-(4,4-ethylenedioxy-2,6,6-trimethyl-1-cyclohexen-1-yl)-3-methyl-2,4-pentadienoic acid ethyl ester. An analytical sample, which was purified by chromatography on silica gel G using a (2:1) hexane-ethyl ether solvent system, had bp. 124–125°/0.1 Torr; $n_D^{25} = 1.5395$; UV. max. (ethanol): 295 (514), 258 (439) nm ($E^{1\%}_{1\,cm}$).

$C_{19}H_{28}O_4$ (320.43) Calcd. C 71.22 H 8.81% Found C 71.39 H 8.71%

(b) A solution of 5-(4,4-ethylenedioxy-2,6,6-trimethyl-1-cyclohexen-1-yl)-3-methyl-2,4-pentadienoic acid ethyl ester (50 g) in ethyl ether (200 ml) was added to a suspension of lithium aluminium hydride (7.5 g) in ethyl ether (150 ml) at – 10 to 0° over a period of 30 min. Stirring was continued for an additional 2 h at 0 to 5°. The reaction mixture was decomposed by the dropwise addition of 40 ml of water at 15°. The precipitated inorganic salt was filtered, and the solvent was removed under vacuum to yield 42 g (96.7%) of 5-(4,4-ethylenedioxy-2,6,6-trimethyl-1-cyclohexen-1-yl)-3-methyl-2,4-pentadienol as a colorless, viscous oil; $n_D^{25} = 1.5405$.

$C_{17}H_{26}O_3$ (278.40) Calcd. C 73.34 H 9.41% Found C 73.16 H 9.39%

(c) Manganese dioxide (500 g) was added in 3 portions to a solution of 5-(4,4-ethylenedioxy-2,6,6-trimethyl-1-cyclohexen-1-yl)-3-methyl-2,4-pentadienol (42 g) in benzene (1 l) over a period of 9 h. The reaction mixture was stirred under an atmosphere of nitrogen for 24 h. The spent manganese dioxide was filtered, and the solvent was removed by distillation under vacuum. The residue (**1**) was a pale yellow oil which weighed 36 g (86.4%). An analytical sample, which was purified by chromatography over silica gel G using a (1:1) ethyl ether-hexane solvent system, had $n_D^{25} = 1\,573$; UV. max. (ethanol): 315 (520), 277 (445) nm ($E^{1\%}_{1\,cm}$).

$C_{17}H_{24}O_3$ (276.38) Calcd. C 73.88 H 8.75% Found C 73.75 H 8.60%

5-(2,6,6-Trimethyl-4-ethoxy-1,3-cyclohexadien-1-yl)-3-methyl-2,4-pentadienal (**8**). – (a) α-Diethylphosphono-ethyl acetate (22 g) was added to a suspension of sodium amide (4 g) in ethyl ether (150 ml), and the mixture was stirred for 3 h under an atmosphere of nitrogen. 3-Ethoxy-3,4-dehydro-β-ionone (12 g) dissolved in ethyl ether (50 ml) was added to the reaction mixture in 30 min, and stirring was continued at reflux temperature for 18 h. At the end of this period, unreacted ionone was present in the reaction mixture as determined by TLC., so an additional 10 g of phosphonate and 2.3 g of sodium amide were added, and the refluxing was continued for an additional 24 h. The reaction mixture was diluted with cold water (5°) and extracted with hexane. The extract was dried over sodium sulfate, and the solvent removed under vacuum. The product, a yellow oil, weighed 16.5 g. An analytical sample, purified over silica gel G using a (1:1) hexane-ethyl ether solvent system, had UV. max. (ethanol): 375 (604), 260 (400) nm ($E^{1\%}_{1\,cm}$).

$C_{19}H_{28}O_3$ (304.43) Calcd. C 74.96 H 9.27% Found C 75.11 H 9.45%

(b) A solution of 5-(2,6,6-trimethyl-4-ethoxy-1,3-cyclohexadien-1-yl)-3-methyl-2,4-pentadienoic acid ethyl ester (14 g) in ethyl ether (50 ml) was dropped into a suspension of lithium aluminium hydride (1.5 g) in ethyl ether (100 ml) in 30 min at – 5°. Stirring was continued for 3 h at 0 to – 5°. The reaction mixture was decomposed by dropwise addition of 10 ml of water at 15°. The precipitated solid was filtered, and the filtrate was dried over sodium sulfate. The solvent was

[2]) The bp.'s and mp.'s are uncorrected; mp.'s are determined in vacuum capillaries.

removed under vacuum to yield 11.2 g of product as a colorless viscous oil which was oxidized without further purification.

(c) The product from the above reduction was placed in a flask with benzene (300 ml) containing 1% of pyridine and manganese dioxide (150 g), and the reaction mixture was stirred under an atmosphere of nitrogen for 18 h. The spent manganese dioxide was filtered, and the filtrate was evaporated under reduced pressure to yield 10 g of crude **8**. Purification by chromatography on silica gel G, using the solvent system benzene-ethyl ether (9:1), yielded 6.5 g of pure **8**; UV. max. (ethanol): 412 (677), 280 (400) nm $(E^{1\%}_{1\,cm})$.

$C_{17}H_{24}O_2$ (260.38) Calcd. C 78.42 H 9.29% Found C 78.30 H 9.30%

3,3,3',3'-Bis-(ethylenedioxy)-trans-*β-carotene* (**3**). 2,7-Dimethyl-2,4,6-octatrienylene-bis-(triphenylphosphonium bromide) (**2**) (45 g) was condensed with 27.6 g of **1** as already reported [18]. After recrystallization from benzene-methanol, the product (**3**) weighed 13 g (42%); mp. 179°; IR. (KBr): 1085 (*s*), 975 cm^{-1} (*s*); UV. max. (cyclohexane): 481 (1690), 453 (1950), 430 (1370) nm $(E^{1\%}_{1\,cm})$. $C_{44}H_{60}O_2$ (620.96) Calcd. C 80.94 H 9.26% Found C 80.82 H 9.38%

3,3'-Dioxo-trans-*β-carotene* (**4**). 3,3,3',3'-Bis-(ethylenedioxy)-*trans*-*β*-carotene (**3**) (2.0 g), methylene chloride (60 ml), acetone (60 ml), and 10% sulfuric acid (12 ml) were refluxed in an atmosphere of nitrogen for 3 h. The cooled reaction mixture was diluted with water and extracted with methylene chloride. The combined extracts were washed with sodium bicarbonate solution, then with water, and were dried over sodium sulfate. On removing the solvent under vacuum and crystallizing the residue from acetone-methanol, there was obtained 1.6 g of crude **4**. After purification over silica gel G using the solvent system methylene chloride-ethyl ether (9:1), 1.3 g of **4** was obtained: mp. 208°; UV. max. (cyclohexane): 480 (2100), 451 (2435), 428 (1695) nm $(E^{1\%}_{1\,cm})$.

$C_{40}H_{52}O_2$ (564.86) Calcd. C 85.05 H 9.25% Found C 85.16 H 9.43%

3,3'-Dioxo-trans-*α-carotene* (**5**). This compound was isolated as the more strongly absorbed component during the chromatography of the hydrolysis product of **3** with 10% sulfuric acid. On recrystallization from methyl alcohol-benzene, there resulted 100 mg of **5**; mp. 192°; UV. max. (cyclohexane): 476 (2278), 448 (2478), 423 (1570) nm $(E^{1\%}_{1\,cm})$.

$C_{40}H_{52}O_2$ (564.86) Calcd. C 85.05 H 9.25% Found C 85.10 H 9.32%

3,7,12,16-Tetramethyl-1,18-bis-(2,6,6-trimethyl-4-oxo-2-cyclohexen-1-yl)-1,3,5,7,9,11,13,15,17-octadecanonaene (**6**). 3,3,3',3'-Bis-(ethylenedioxy)-*trans*-*β*-carotene (**3**) (750 mg) was stirred with a mixture of methylene chloride (50 ml), ethyl alcohol (25 ml), water (1 ml), and 36% hydrochloric acid (2 ml) under an atmosphere of nitrogen for 6 h at room temperature. The reaction mixture was diluted with water and extracted with methylene chloride. The combined extracts were washed with sodium hydrogen carbonate solution, and the solvent was removed under vacuum. The residue crystallized from benzene-methanol to yield 450 mg of crude **6**. An analytical sample was prepared by chromatography on silica gel G with (9:1) methylene chloride-ethyl ether as the solvent system: mp. 194°; UV. max. (cyclohexane): 472 (2550), 443 (2530), 417 (1605) nm $(E^{1\%}_{1\,cm})$.

$C_{40}H_{52}O_2$ (564.86) Calcd. C 85.05 H 9.25% Found C 84.83 H 9.42%

3,3-Diethoxy-3,3',4,4'-tetradehydro-trans-*β-carotene* (**7**). This preparation was carried out by a procedure identical with that described for the preparation of **3**, except that 2.5 g of **8** was reacted with 4 g of **2** to yield 450 mg of **7** after recrystallization from ethanol-benzene; mp. 149°; UV. max. (ethanol): 491 nm $(E^{1\%}_{1\,cm} = 1744)$.

$C_{44}H_{60}O_2$ (620.96) Calcd. C 85.11 H 9.74% Found C 85.05 H 9.60%

3,3-Ethylenedioxy-trans-*β-carotene* (**10**). A condensation, carried out by the same procedure used for the preparation of **3**, was applied to a mixture of 6 g of *β*-ionylidene-acetaldehyde (**9**), 9 g of 5-(4,4-ethylenedioxy-2,6,6-trimethyl-1-cyclohexen-1-yl)-3-methyl-2,4-pentadienal (**1**), and 25 g of **2**. The product was purified by chromatography on 450 g of silica gel G with benzene. The 3,3-ethylenedioxy-*trans*-*β*-carotene (**10**) was obtained in the fraction which followed the *trans*-*β*-carotene. Recrystallization from benzene-methanol afforded 1.2 g of **10**; mp. 165°; UV. max. (cyclohexane): 481 (1888), 453 (2181), 430 (1545) nm $(E^{1\%}_{1\,cm})$.

$C_{42}H_{58}O_2$ (594.92) Calcd. C 84.79 H 9.83% Found C 84.62 H 9.73%

2,6,6-Trimethyl-1-[3,7,12,16-tetramethyl-18-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,5,7,9,11,13,15,17-octadecanonaenyl]-1-cyclohexen-4-one (**11**). A mixture of 3,3-ethylenedioxy-*trans*-β-carotene (**10**) (300 mg), methylene chloride (50 ml), acetone (50 ml), and 10% sulfuric acid (10 ml) was heated at reflux temperature under an atmosphere of nitrogen for 4 h. The reaction mixture was diluted with water and extracted with methylene chloride. The extract was washed with water and dried over sodium sulfate, and the solvent was removed under vacuum. The crystalline product was purified by chromatography on silica gel G with methylene chloride to yield 180 mg of **11**; mp. 188°; UV. max. (cyclohexane): 479 (2296), 452 (2633), 430 (1870) nm $(E^{1\%}_{1\,cm})$.

$C_{40}H_{54}O$ (550.87) Calcd. C 87.21 H 9.88% Found C 87.19 H 9.75%

2,6,6-Trimethyl-1-[3,7,12,16-tetramethyl-18-(2,6,6-trimethyl-2-cyclohexen-1-ylidene)-2,4,6,8,10,12,14,16-octadecaoctaenylidene]-2-cyclohexen-4-one (**12**). Compound **11** was slowly dehydrogenated during purification by chromatography over silica gel. The violet-red colored region was eluted and rechromatographed over silica gel using benzene-ethyl ether (9:1) as the solvent system. This afforded 30 mg of **12** as dark violet crystals; mp. 176–178°; IR. (KBr): 1670 (*s*), 975 (*s*), 950 cm^{-1} (*s*); UV. max. (cyclohexane): 483 nm $(E^{1\%}_{1\,cm} = 2381)$; mass spectrum: $M^+ = 548$, *m/e* 456 and 442 (*s*).

$C_{40}H_{52}O$ (548.86) Calcd. C 87.53 H 9.55% Found C 87.50 H 9.42%

2,6-Dimethyl-8-(4-oxo-2,6,6-trimethyl-2-cyclohexenylidene)-1,6-octadien-4-yn-3-ol (**16**). Isopropenylethynylcarbinol (**14**) (9.6 g) was dropped into ethylmagnesium bromide prepared from 6.1 g of magnesium, 27 g of ethyl bromide, and 200 ml of ethyl ether. After refluxing for 45 min, 3,3-ethylenedioxy-β-ionone (**13**) (20 g) in ethyl ether (100 ml) was dropped into the reaction mixture over a period of 1 h at 10°. Stirring was continued for 1 h; then the reaction mixture was poured into cold water and the precipitated solid was dissolved in 5% sulfuric acid. The organic layer was separated, washed with water, and dried over sodium sulfate. On removing the ether under vacuum, there was obtained 31 g of the diol **15** which was dehydrated by stirring and refluxing with 100 ml of methylene chloride and 20 ml of 5% sulfuric acid under an atmosphere of nitrogen for 2 h. The oily layer was washed with water until neutral and dried over sodium sulfate, and the solvent was removed under vacuum: 27 g of **16** as an oil. An analytical sample was purified on silica gel G using hexane-ethyl ether (1:1) as the solvent system. The purified product had UV. max. (EtOH): 346 nm $(E^{1\%}_{1\,cm} = 978)$; IR. (film): 3400 (*s*), 2175 (*w*), 1680–1630 (*s*), 1580 (*s*), 900 (*s*) cm^{-1}.

$C_{19}H_{24}O_2$ (284.40) Calcd. C 80.24 H 8.50% Found C 80.15 H 8.28%

[2,6-Dimethyl-8-(4-oxo-2,6,6-trimethyl-2-cyclohexenylidene)-2,6-octadien-4-ynyl]-triphenylphosphonium bromide (**17**). Triphenylphosphonium bromide (9 g) was added to a solution of **16** (5 g) in methylene chloride (200 ml). After stirring for 16 h, the solution was washed with water and the methylene chloride was removed under vacuum. The residue was triturated with ethyl acetate to yield 9 g of **17**. An analytical sample which was recrystallized from ethyl acetate-methanol melted at 210–212°.

$C_{37}H_{38}BrPO$ (609.61) Calcd. Br 13.11% Found Br 12.93%

4,8-Dimethyl-10-(4-oxo-2,6,6-trimethyl-2-cyclohexenylidene)-2,4,8-decatrien-6-ynal (**20**). 4-Methyl-1,1,3-triethoxy-4-hepten-6-yne (**18**) (24 g) was dropped into a solution of ethylmagnesium bromide prepared from 2.7 g of magnesium, 14 g of ethyl bromide, and 150 ml of ethyl ether. After stirring the reaction mixture at reflux temperature for 30 min, 20 g of **13** in ethyl ether (100 ml) was added at 5°. The reaction mixture was stirred for 2 h at room temperature and then decomposed with cold water. The ether layer was separated, dried over sodium sulfate, and concentrated under vacuum. The residue, **19**, was heated on a steam bath for 3 h with glacial acetic acid (250 ml), water (30 ml), and sodium acetate (40 g). The reaction mixture was diluted with water and extracted with ether. The combined extracts were washed with water, with sodium hydrogen carbonate solution, and again with water. After drying over sodium sulfate, the solvent was removed under vacuum: 22 g of crude **20**. An analytical sample, which was purified by chromatography on silica gel with benzene-ethyl ether as the solvent system (3:2), melted at 114–116°;

UV. max. (EtOH): 389 (1244), 310 (910), 256 (482) nm ($E^{1\%}_{1\,cm}$); IR. (KBr): 2150 (*w*), 1680–1650 (*s*), 1600 (*m*), 1575 (*m*), 1120 (*s*), 975 (*m*), 965 (*m*), 895 (*m*) cm^{-1}.

$C_{21}H_{24}O_2$ (308.42) Calcd. C 81.78 H 7.84% Found C 81.97 H 8.03%

10,11,10',11'-Tetradehydro-rhodoxanthin (**21**). Compound **20** (1.2 g) and 2.6 g of the *Wittig* salt **17** were dissolved in 20 ml of methyl alcohol. Sodium methoxide (1 g) was added to the solution, and stirring was continued at 0 to 5° under an atmosphere of nitrogen. The precipitated carotenoid was filtered and recrystallized from benzene-methanol to yield 650 mg of **21** as dark red needles; mp. 176–178°; UV. max. (cyclohexane): 442 (1418), 383 (810), 325 (910) nm ($E^{1\%}_{1\,cm}$); IR. (KBr): 2150 (*w*), 1665 (*s*), 980 (*m*) cm^{-1}.

$C_{40}H_{46}O_2$ (558.81) Calcd. C 85.97 H 8.30% Found C 85.71 H 8.38%

Rhodoxanthin (**22**). Tetradehydro-rhodoxanthin (**21**) (500 mg) was dissolved in benzene (50 ml) and reduced in the presence of 100 mg of *Lindlar's* catalyst [8] and 0.1 ml of 1% solution of quinoline in acetone. After the theoretical quantity of hydrogen had been consumed, the sample was filtered and concentrated under vacuum. The residue was sealed in a tube with 2.5 ml of benzene and 5 ml of heptane and heated on a steam bath for 24 h. The dark violet crystals which separated from the solution were filtered and recrystallized from benzene-heptane. There was obtained 350 mg of *trans*-rhodoxanthin (**22**); mp. 217–219°; UV. max. (cyclohexane): 521 (1752), 491 (2386), 466 (1990) nm ($E^{1\%}_{1\,cm}$); IR. (KBr): 1665 (*s*), 1580 (*m*), 950 (*m*) cm^{-1}.

$C_{40}H_{50}O_2$ (562.84) Calcd. C 85.36 H 8.96% Found C 85.30 H 8.99%

4-Acetoxyvitamin A aldehyde (**26**). A solution of crystalline retinal (**24**) (142.2 g) in methylene chloride (1.2 l) was cooled to – 10° and added to a cooled suspension (– 10°) of N-bromosuccinimide (137.5 g) in methylene chloride (2.5 l) and glacial acetic acid (350 ml). Stirring was continued for 10 min and N,N-dimethylaniline (200 ml) was added. The cooling bath was removed and stirring was continued for 4 h. The reaction mixture was poured into cold 5% sulfuric acid (4 l), and the methylene chloride layer was separated and washed with cold (5°) 5% sulfuric acid (2 l), with water (3 l), with 2% sodium hydrogen carbonate solution (2 l), and finally with water (2 l). The oily layer was dried over sodium sulfate, and the solvent was removed under vacuum. The crude 4-acetoxyvitamin A aldehyde (**26**) weighed 203 g and had UV. max. at 375 nm ($E^{1\%}_{1\,cm} = 924$) in cyclohexane. An analytical sample of **26**, purified on silica gel G, had UV. max. at 375 nm ($E^{1\%}_{1\,cm} = 1235$). The crude material was used for the next reaction step.

Echinenone (**29**). To a solution of the crude 4-acetoxyvitamin A aldehyde (**26**) (101.5 g) in benzene (500 ml), there were added simultaneously, from two dropping funnels, a benzene solution of retinyltriphenylphosphonium sulfate (**25**) (from 70 g of vitamin A alcohol) and a solution of sodium (6 g) in methanol (120 ml), at 25°. The reaction mixture was stirred for 4 h at 40°. A solution of 60 g of potassium hydroxide in 400 ml of methyl alcohol was added and the stirring was continued for an additional 2 h.

The reaction mixture was poured into ice water and extracted with ethyl ether, and the extract was washed with water. After drying over sodium sulfate, the solvent was removed under vacuum. The residue was dissolved in benzene (1 l) and acetone (400 ml); aluminium isopropoxide (120 g) was added, and the mixture was heated at reflux temperature for 16 h under an atmosphere of nitrogen.

The cooled reaction mixture was diluted with methylene chloride (3 l), washed with cold (5°) 5% sulfuric acid and then with water, and finally dried over sodium sulfate. The solvent was removed under vacuum and replaced with 200 ml of heptane, and this solution was heated at 95° for 16 h under nitrogen. The product was filtered and then crystallized from heptane-methanol at 0°. A second crop was obtained by reisomerization of the concentrated mother liquor by heating in heptane for 16 h at 95°. On recrystallization from methylene chloride-methanol, there was obtained 75.7 g of echinenone (**29**) (55% based on vitamin A aldehyde); mp. 178–179°; UV. max. (cyclohexane): 461 nm ($E^{1\%}_{1\,cm} = 2110$).

$C_{40}H_{54}O$ (550.87) Calcd. C 87.21 H 9.88% Found C 87.11 H 9.80%

Dehydro-retro-carotene (**30**). 4-Acetylisocryptoxanthin (**27**) was prepared from 50.5 g of crude 4-acetoxyvitamin A aldehyde by the procedure used in the preparation of echinenone except that, after completion of the *Wittig* reaction, the hydrolysis step was omitted and the reaction mixture was poured into ice water and extracted with ethyl ether. The ether extract was washed with water, dried over sodium sulfate, and the solvent removed under vacuum.

The residue was dissolved in methylene chloride (500 ml) and cooled to $-45°$. Hydrobromic acid (68%) (20 ml) was then added to the reaction mixture which was stirred for 15 min. Saturated sodium carbonate solution (250 ml) was added, and stirring continued at room temperature for 30 min. The methylene chloride layer was washed with water, dried over sodium sulfate, and the solvent removed under vacuum. After isomerizing the residue by refluxing for 6 h in 100 ml of hexane, the product **30** was crystallized at $-10°$. Recrystallization from benzene-methanol afforded 20.5 g (30.7% based on vitamin A aldehyde (**24**)); mp. 196–197°; UV. max. (cyclohexane): 447 (2260), 473 (3130), 504 (2460) nm ($E^{1\%}_{1\,cm}$).

$C_{40}H_{54}$ (534.87) Calcd. C 89.82 H 10.17% Found C 89.79 H 10.22%

Canthaxanthin (**32**). A solution of dehydro-retro-carotene (**30**) (18.4 g) in chloroform[a]) (2.4 l) and glacial acetic acid (80 ml) was cooled to $-50°$. N-bromosuccinimide (6.8 g) was added to the stirred reaction, and, after stirring for 7 min, N,N-diethylaniline (140 ml) was added, and stirring was continued for 2 h at 0°. The reaction mixture was poured into ice water and extracted with ethyl ether. The ether extract was washed with cold (5°) 5% sulfuric acid, with water, and finally with 5% sodium carbonate solution. The dried extract was dried over sodium sulfate, and the solvent removed under vacuum.

The residue was stirred with benzene (600 ml) and 10% potassium hydroxide in methanol (200 ml) at 40° for 2 h. The reaction mixture was poured into water and extracted with ethyl ether. The extract was washed with water, dried over sodium sulfate, and the solvent was removed under vacuum. The residue, crude isozeaxanthin, was dissolved in benzene (600 ml), aluminium isopropoxide (60 g) and acetone (200 ml) were added, and the mixture was stirred at reflux temperature for 16 h under an atmosphere of nitrogen.

The reaction was poured into a mixture of cold (5°) 5% sulfuric acid and methylene chloride, and the product was extracted with more methylene chloride. The combined extracts were washed with water and the solvent was removed under vacuum. Hexane (200 ml) was added to the residue, and this solution was refluxed for 6 h under an atmosphere of nitrogen. The product crystallized at 0°. After recrystallization from methylene chloride-methanol, there was obtained 14.4 g (74%) of canthaxanthin (**32**); mp. 212–213°; UV. max. (cyclohexane): 469 nm ($E^{1\%}_{1\,cm} = 2200$).

$C_{40}H_{52}O_2$ (564.86) Calcd. C 85.05 H 9.28% Found C 85.10 H 9.25%

C_{50} *Keto carotenoid* (**36**). 2,7-Dimethyl-2,4,6-octatrienylene-bis-(triphenylphosphonium bromide) (**35**) [18] (70.0 g) was mixed with 3,7-dimethyl-6-oxo-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,7-nonatrienal (**34**) [17] (50.0 g), methanol (800 ml), and pyridine (40 ml). A solution of potassium hydroxide (18 g) in methanol (200 ml) was added from a dropping funnel at 10° in 30 min while the reaction mixture was stirred vigorously under an atmosphere of nitrogen. After stirring for 6 h the resulting red crystalline product was filtered, washed with water, then with methanol, and recrystallized from benzene to yield 23.4 g (40%) of **36**: mp. 190°; UV. max. (cyclohexane): 473 nm ($E^{1\%}_{1\,cm} = 1898$).

$C_{50}H_{68}O_2$ (701.09) Calcd. C 85.66 H 9.77% Found C 85.60 H 9.72%

1-(2,6,6-Trimethyl-1-cyclohexenyl)-18-(2,6,6-trimethyl-3-oxo-1-cyclohexenyl)-3,7,12,16-tetramethyl-octadeca-2,5,7,9,11,13,15,17-octaen-4-one (**38**). Retinyltriphenylphosphonium sulfate **25** (126 g) was dissolved in methylene chloride (2 l), and the solution was cooled to $-45°$. N-bromosuccinimide (50 g), dissolved in methylene chloride (1.5 l), and acetic acid (200 ml) (20°) were added to the vigorously stirred reaction mixture (during a period of 5 min). Dimethylaniline (200 ml) was added and the solution stirred for an additional 30 min. The reaction mixture was washed with 4 l of cold (5°) 6% sulfuric acid and then with water, and dried over sodium sulfate. On removal of

[a]) Alcohol-free chloroform was used (prepared by washing technical chloroform with water and drying over calcium sulfate).

the solvent under vacuum, the crude *Wittig* compound **37** was obtained as a brown syrup and used without further purification.

Crude **37** dissolved in 1.2 l of benzene was mixed with 48 g of **34**, and the solution was cooled to 10°. A solution of potassium hydroxide (100 g) in methanol (400 ml) was added from a dropping funnel in 30 min at 10° and the mixture stirred for 6 h at room temperature. The reaction mixture was poured into 1 l of water, and the benzene layer was separated, washed with water, and concentrated to a syrup under vacuum. The residue was dissolved in benzene (400 ml), acetone (400 ml) and aluminium isopropoxide (100 g) were added, and the mixture was stirred at reflux temperature for 12 h under an atmosphere of nitrogen.

The cooled reaction mixture was poured into water (2 l), and 5% hydrochloric acid was stirred into the resulting suspension until the precipitate was dissolved. The oily layer was separated, washed with water, and concentrated to a syrup. The thick red syrup was stirred with ethanol (500 ml) and cooled in a refrigerator overnight to give a red crystalline product which was filtered and recrystallized from benzene to yield 31.7 g (35%) of **38**; mp. 195°; UV. max. (cyclohexane): 438 nm ($E^{1\%}_{1\,cm} = 1864$).

$C_{40}H_{34}O_2$ (546.71) Calcd. C 84.73 H 9.60% Found C 84.84 H 9.88%

BIBLIOGRAPHY

[1] *J. D. Surmatis, A. Walser, J. Gibas & R. Thommen*, J. org. Chemistry *35*, 1053 (1970).
[2] *R. Kuhn & H. Brockmann*, Ber. deutsch. chem. Ges. *66*, 828 (1933).
[3] *P. Karrer & U. Solmssen*, Helv. *18*, 477 (1935).
[4] *H. Mayer, M. Montavon, R. Rüegg & O. Isler*, Helv. *50*, 1607 (1967).
[5] *J. D. Surmatis & A. Ofner*, J. org. Chemistry *28*, 2735 (1963).
[6] *R. Rüegg, H. Lindlar, M. Montavon, G. Saucy, S. F. Schaeren, U. Schwieter & O. Isler*, Helv. *42*, 847 (1959).
[7] *O. Isler, H. Lindlar, M. Montavon, R. Rüegg & P. Zeller*, Helv. *39*, 249 (1956).
[8] *H. Lindlar*, Helv. *35*, 446 (1952).
[9] *E. Lederer*, C. r. Soc. Biol. *117*, 411 (1934); *T. W. Goodwin & M. M. Taha*, Biochem. J. *47*, 244 (1950).
[10] *H. Thommen & H. Wackernagel*, Naturwissenschaften *51*, 87 (1964).
[11] *O. Volker*, Naturwissenschaften *48*, 581 (1961). – *D. L. Fox*, Compar. Biochemistry Physiol. *5*, 31 (1962); *6*, 305 (1962).
[12] *H. Thommen*, Biochem. biophys. Acta *69*, 387 (1963). – *D. L. Fox*, Compar. Biochemistry Physiol. *6*, 1 (1962).
[13] *F. Haxo*, Botan. Gaz. *112*, 228 (1950).
[14] *F. C. Czygen*, Experientia *20*, 573 (1964).
[15] *M. Akhtar & B. C. L. Weedon*, J. chem. Soc. *1959*, 4058; *C. K. Warren & B. C. L. Weedon, ibid. 1958*, 3972.
[16] *F. J. Petracek & L. Zechmeister*, J. Amer. chem. Soc. *78*, 1427 (1956). – *C. Gansser & L. Zechmeister*, Helv. *40*, 1757 (1957). – *R. Entschel & P. Karrer*, Helv. *41*, 402 (1958).
[17] *J. D. Surmatis, J. Gibas & R. Thommen*, J. org. Chemistry *34*, 3039 (1969).
[18] *J. D. Surmatis & A. Ofner*, J. org. Chemistry *26*, 1171 (1961).