50° for 3 hr. The excess reagent was removed *in vacuo* to give 1.8 g of a yellow oil. This material was dissolved in 50 ml of chloroform and added over 1 hr to a stirred solution of anthranilic acid N-methylamide (1.5 g, 0.01 mol) and pyridine (0.9 g, 0.011 mol) in 150 ml of chloroform at 0°. The solution was stirred overnight at room temperature, refluxed for 1 hr, washed with 1 *N* hydrochloric acid, 5% aqueous sodium bicarbonate, and water, and dried over sodium sulfate, and the solvent was removed *in vacuo*. Chromatography on silica gel and crystallization from ethyl acetate gave 1.2 g (41%) of **11** as fine needles: mp 182–185° dec; $\lambda_{max}^{C_2H_4OH}$ 302 nm (ϵ 7900), 249 (12,800); nmr (DMSO-d_6) δ 2.82 (3, d), 4.15 (2, s), 6.9–7.9 (9, m), 8.9–9.1 (2, br).

Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.9; H, 5.4; N, 9.5. Found: C, 69.0; H, 5.2; N, 9.4.

1-Acetyl-3-methylene-4,1-benzoxazepine-2,5-dione (7) was prepared from **1a** in acetic anhydride, by the method described,[2] in 70% yield: mp 95° (lit.[2] mp 95–96°).

Treatment of N-Pyruvoylanthranilic Acid N-Methylamide (1c) with Acetic Anhydride–Pyridine.—A solution of 0.5 g of **1c** in 5 ml of 1:1 acetic anhydride–pyridine was allowed to stand for 2 days at room temperature and then heated on a steam bath for 6 hr. The solution was diluted with ether, washed with 1 *N* hydrochloric acid, 5% aqueous sodium bicarbonate, and water, and dried over sodium sulfate. Chromatography on silica gel gave two major products: A [150 mg; mp 134–135°; M^+ 304; $\lambda_{max}^{CH_3OH}$ 294, 240, 221 nm; nmr ($CDCl_3$) δ 1.59 (3, s), 1.62 (3, s), 2.10 (3, s), 2.98 (3, s), 7.0–8.0 (4, m)] and B [65 mg; mp 157–159°; M^+ 304; $\lambda_{max}^{CH_3OH}$ 291, 240, 218 nm; nmr ($CDCl_3$) δ 1.65 (3, s), 1.78 (3, s), 2.00 (3, s), 3.00 (3, s), 7.1–8.2 (4, m)].

^{18}O Exchange of Ia.—Analytically pure N-pyruvoylanthranilic acid (**Ia**, 200 mg) was dissolved in 10 ml of dry tetrahydrofuran in a capped serum vial, 1 ml of $H_2{}^{18}O$ (1.71% ^{18}O) was added, and the solution was allowed to stand at room temperature for 72 hr. Aliquots (5 mg), taken periodically to measure the extent of exchange, were added to pyrolysis tubes and the solvent was removed immediately under a nitrogen stream. Succeeding exchanges were run for 24 hr only. Rigorously dried solvents and glassware were used through all ^{18}O experiments. The samples (5 mg) of the material to be analyzed were dried thoroughly under high vacuum and then pyrolyzed at 500° for 4 hr as previously described.[7] The pyrolysis tube was cooled in a methanol–Dry Ice bath and the resulting gases were examined on a mass spectrometer. Since the yield of carbon monoxide was insufficient for the purposes of analysis, the carbon dioxide peak was used. Background hydrocarbons were minimal and the analysis was straightforward. The ^{18}O content of the water was determined by equilibration of a sample with CO_2 in a pyrolysis tube at 500° followed by mass spectroscopy of the gas. The isotope content of the CO_2 was calculated from formula 1

$$^{18}O\ (\%) = \frac{[46]/([44] + [45]) \times 0.96}{2 + \{[46]/([44] + [45])\}} \times 100 \qquad (1)$$

where [44], [45], and [46] are the relative intensities of the *m/e* 44, 45, and 46 peaks.

Registry No.—**1a**, 14469-11-5; **1b**, 18326-62-0; **1c**, 20452-61-3; **1d**, 13748-93-1; **11**, 20453-01-4.

The Synthesis of 1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-18-(2,6,6-trimethyl-2-cyclohexen-1-ylidene)-3,7,12,16-tetramethyl-2,4,6,8,10,12,14,16,18-octadecanonaene and Its Rearrangement to *trans*-β-Carotene

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A novel synthesis of 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-18-(2,6,6-trimethyl-2-cyclohexen-1-ylidene)-3,7,12,-16-tetramethyl-2,4,6,8,10,12,14,16,18-octadecanonaene (**6**) and its rearrangement to *trans*-β-carotene are reported. A new type of carotenoid with a cross-conjugated keto function (**4**) was used as an intermediate for the synthesis of **6**.

The first synthesis of 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-18-(2,6,6-trimethyl-2-cyclohexen-1-ylidene)-3,7,-12,16-tetramethyl-2,4,6,8,10,12,14,16,18-octadecanonaene (**6**) was reported in 1956.[1] In spite of its structural similarity to β-carotene, very little is known about this carotenoid; it has not been found in nature nor reported to play a role in the biosynthesis of naturally occurring carotenoids. The ease with which it was transformed into β-carotene may explain its absence in natural products. By using a readily available intermediate (**1**) of an industrial vitamin A synthesis,[2,3] **6** was prepared in high yield and rearranged to *trans*-β-carotene.

A search of the literature resulted in one reference[4] describing a carotenoid with a cross-conjugated keto function. Its structure had not been fully established yet, as the work was hampered by a lack of material and published data on this type of configuration. This was an "open-ring" carotenoid belonging to a class represented by lycopene.

The C-20 diol (**1**) was oxidized with manganese dioxide[5] in methylene chloride to afford a cross-conjugated keto aldehyde, **2** (65%), as yellow crystals, mp 74°. The condensation of **2** with retinylphosphonium sulfate (**3**) resulted in a new type of keto carotenoid, **4** (60%), mp 156°. Compound **4** crystallized as dark violet hexagonal prisms from benzene–methanol and as red rhombic crystals from heptane. The color of a solution of **4** in benzene or heptane was similar to that of *trans*-β-carotene of equal concentration. Compound **4** was approximately twice as soluble in heptane as *trans*-β-carotene.

The nuclear magnetic resonance (nmr) spectrum was compatible with the structure assigned to **4** (Figure 1).

The ultraviolet spectrum of **4** showed a weaker absorption than that of *trans*-β-carotene, and the curve exhibited only one maximum (Figure 2).

The retinyltriphenylphosphonium sulfate (**3**) was obtained as a yellow crystalline monohydrate on react-

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[1] O. Isler, M. Montavon, R. Ruegg, and P. Zeller, *Helv. Chim. Acta*, **39**, 454 (1956).

[2] O. Isler, A. Ronco, W. Guex, N. C. Hindley, W. Huber, K. Dialer, and M. Kofler, *ibid.*, **32**, 489 (1949).

[3] J. D. Surmatis, U. S. Patent 2,610,208 (1952).

[4] S. L. Jensen and K. Schmidt, *Arch. Mikrobiol.*, **46**, 138 (1963).

[5] Available from General Metallics Oxides Corp., Jersey City, N. J. (Manganese hydrate no. 37).

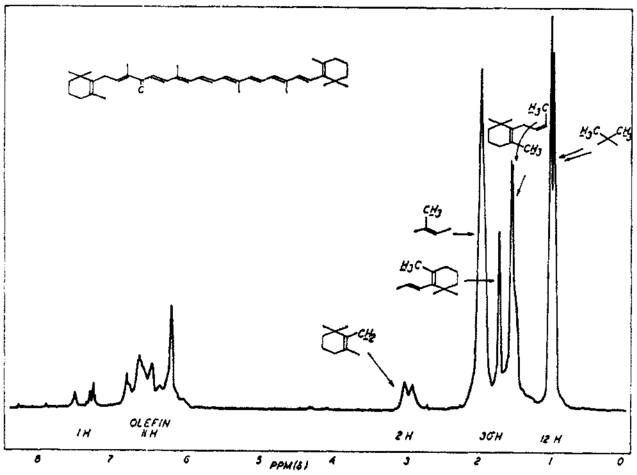

Figure 1.—Nuclear magnetic resonance spectrum of **4**.

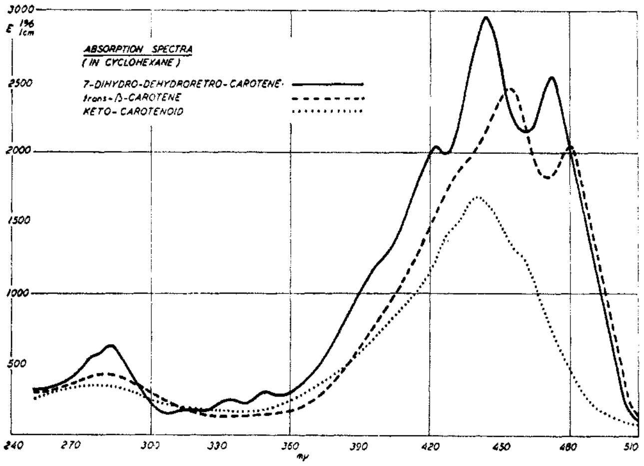

Figure 2.—Ultraviolet spectrum of **4**.

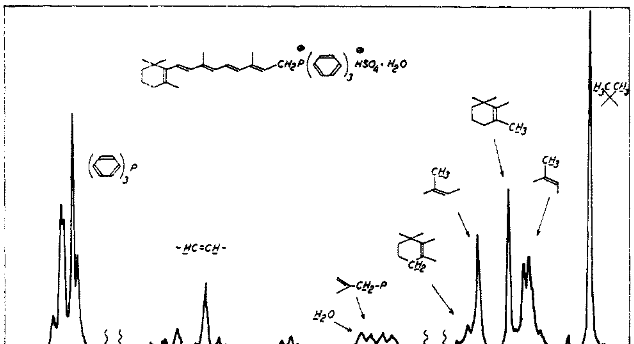

Figure 3.—Nuclear magnetic resonance spectrum of **3**.

ion of vitamin A acetate with triphenylphosphonium sulfate. The presence of a doublet of doublets in the nmr spectrum ($J_{CH,P} = 17.5$ cps; $J_{CH,CH_2} = 7.5$ cps) for the CH_2P group indicated the presence of the =CH-CH_2P moiety instead of the retro structure which results when vitamin A is treated with a mineral acid (Figure 3).

Reduction of **4** with sodium borohydride in methanol-pyridine afforded the hydroxy carotenoid (**5**). Samples of **4** and **5** were tested for biological activity in comparison with *trans*-β-carotene, using the rat liver storage[6,7] and curative-growth assays. Although both compounds supported growth at a dose level of 200 μg per day, the calculated vitamin A activities were only 60,000 and 130,000 USP units per gram for **4** and **5**, respectively.

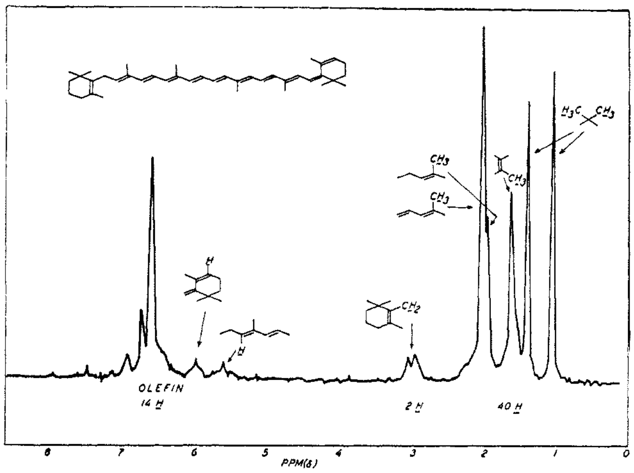

Figure 4.—Nuclear magnetic resonance spectrum of **6**.

When **5** was dehydrated by stirring an acetone solution at 25–30° for 4 hr in the presence of hydrobromic acid, *trans*-β-carotene was afforded in 70% yield; at 0°, a new carotenoid was obtained (73%), mp 168°. The uv spectrum showed three well-defined maxima with typical high absorption displayed by the retro structure (Figure 2). The nmr spectrum was compatible with the structure assigned to 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-18-(2,6,6-trimethyl-2-cyclohexen-1-ylidene)-3,7,12,16-tetramethyl-2,4,6,8,10,12,14,16,18-octadecanonaene (**6**) (Figure 4). Compound **6** was found to be unstable under acidic conditions. On stirring a suspension of **6** in acetone containing a trace of hydrobromic acid for 4 hr at 25–30°, *trans*-β-carotene (96%), mp 181°, was obtained (Chart I).

Experimental Section[8,9]

3,7-Dimethyl-6-oxo-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,7-nonatrienal (2).—C-20 diol **1** (609 g), CH_2Cl_2 (4.8 l.), and MnO_2 (2.4 kg) were placed in a 12-l., round-bottom flask fitted with a mechanical stirrer, and agitated for 24 hr under N_2. Additional MnO_2 (2.4 kg) was added, and the stirring was continued for 24 hr. The spent MnO_2 was filtered off and then washed with CH_2Cl_2. The solvent was removed from the combined filtrate and washings, and the residue was crystallized from hexane to give 390.6 g (65%) of **2** as pale yellow crystals, mp 74°; uv (C_2H_5OH), 290 mμ ($\epsilon^{1\%}_{1cm}$ 1014).

Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.90; H, 9.34.

Retinyltriphenylphosphonium Sulfate (3).—Triphenylphosphine (315 g), CH_3OH (3.0 l.), and concentrated H_2SO_4 (56 ml) were placed in a 5-l. flask and stirred for 30 min. Crystalline vitamin A acetate (328 g) was added all at once, and the reaction was stirred under N_2 for 24 hr. The solvent was removed by vacuum distillation, and the residue was crystallized by dissolving in 2.5 l. of boiling acetone and then cooling to 10° for 24 hr. The yellow crystalline product was filtered, washed with acetone, and dried in a vacuum oven at 50°. The retinyltriphenylphosphonium sulfate, which was obtained as a hydrate, weighed 380 g (58.7%), mp 202°.

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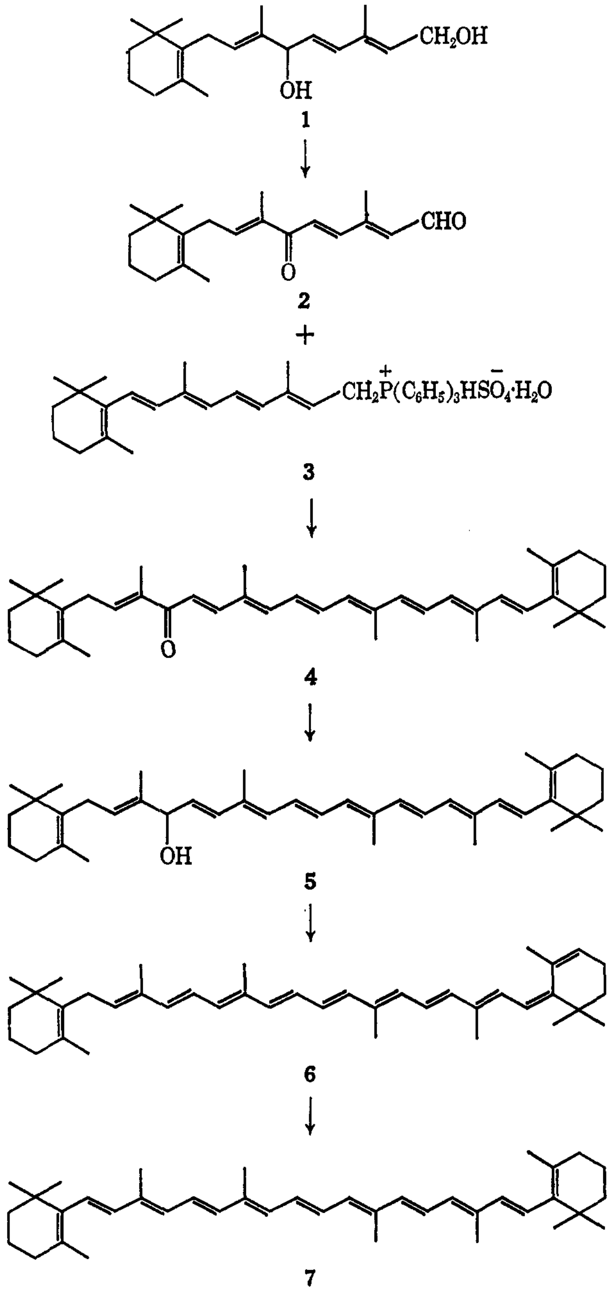
(6) J. R. Foy and K. Morgarlidge, *Anal. Chem.*, **20**, 304 (1948).

(7) K. Guggenheim and W. Koch, *Biochem. J.*, **38**, 256 (1944).

(8) The nuclear magnetic resonance (nmr) spectra were obtained with a Varian A-60 spectrometer using $CDCl_3$ as solvent and tetramethylsilane as the internal reference (δ = 0 ppm).

(9) The boiling and melting points are uncorrected; melting points were determined in vacuum capillaries.

CHART I



Anal. Calcd for $C_{38}H_{47}O_5PS$: C, 70.56; H, 7.32. Found: C, 70.86; H, 7.32.

3,7,12,16-Tetramethyl-1,18-bis(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,5,7,9,11,13,15,17-octadecaoctaen-4-one (4).—To a cold (10°) solution of retinyltriphenylphosphonium sulfate (64 g) in CH_3OH (1200 ml), a solution of the C-20 aldehyde 2 (30 g) in a mixture of CH_3OH (200 ml) and pyridine (10 ml) and a solution of KOH (10 g) in CH_3OH (100 ml) were added simultaneously with vigorous stirring over a period of 2 hr. The cooling bath then was removed and the reaction mixture was stirred for 12 hr under N_2. The resulting red crystalline solid was filtered and washed with CH_3OH (1000 ml), H_2O (1000 ml), and finally with CH_3OH (500 ml). The crude product was dried in a vacuum oven (20 mm) at 50° and recrystallized from heptane to obtain 33.2 g (50%) of 4, mp 156°; uv (cyclohexane) 438 mμ ($\epsilon_{1\,\mathrm{cm}}^{1\%}$ 1682).

Anal. Calcd for $C_{40}H_{56}O$: C, 86.90; H, 10.23. Found: C, 86.25; H, 10.23.

3,7,12,16-Tetramethyl-1,18-bis(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,5,7,9,11,13,15,17-octadecaoctaen-4-ol (5).—A solution of 5 (60 g) in CH_3OH (600 ml) and pyridine (600 ml) was reduced with sodium borohydride (15 g) by stirring for 24 hr under N_2 at room temperature. The reaction mixture was poured into ice–water (2 l.) in a separator provided with a stirrer, and the product was extracted with CH_2Cl_2. The extract was washed with H_2O and concentrated to a syrup *in vacuo* at 50°. The hydroxy carotenoid 5 was obtained as a yellow resinous solid (58 g), uv (cyclohexane), 405 mμ ($\epsilon_{1\,\mathrm{cm}}^{1\%}$ 1613).

Anal. Calcd for $C_{40}H_{58}O$: C, 86.57; H, 10.53. Found: C, 86.16; H, 10.40.

The Dehydration of 5 to *trans*-β-Carotene.—A solution of 63% HBr (20 ml) in acetone (150 ml) was dropped into a solution of the hydroxy carotenoid 5 (55.5 g) in acetone (800 ml) at 25–30° in 30 min. Stirring then was continued under N_2 for 4 hr. The red crystalline solid which was formed was filtered and washed with 5% aqueous $NaHCO_3$ and then with acetone. Recrystallization of the crude product from CH_2Cl_2 afforded 37.6 g (70%) of *trans*-β-carotene, mp 181°; uv (cyclohexane) 456 mμ ($\epsilon_{1\,\mathrm{cm}}^{1\%}$ 2500).

1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-18-(2,6,6-trimethyl-2-cyclohexen-1-ylidene)-3,7,12,16-tetramethyl-2,4,6,8,10,12,14,16,-18-octadecanonaene (6).—To a stirred solution of 5 (316 g) in acetone (3000 ml), 63% HBr (100 ml) dissolved in 500 ml of acetone was added dropwise at 0° over a period of 1 hr. The crystalline solid that formed was filtered, washed with 5% $NaHCO_3$ solution, and then washed with acetone. Recrystallization from benzene–methanol containing 0.1% of pyridine gave 251 g (72.8%) of 6, mp 168°; uv (cyclohexane) 444 mμ ($\epsilon_{1\,\mathrm{cm}}^{1\%}$ 2936).

Anal. Calcd for $C_{40}H_{56}$: C, 89.48; H, 10.52. Found: C, 89.22; H, 10.37.

Rearrangement of 1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-18-(2,6,6-trimethyl-2-cyclohexen-1-ylidene)-3,7,12,16-tetramethyl-2,4,6,8,10,12,14,16,18-octadecanonaene (6) to *trans*-β-Carotene (7).—To a suspension of 6 (100 g) in acetone (1.5 l.), a solution of 63% HBr (5 ml) in acetone (500 ml) was added all at once, and the mixture was stirred for 4 hr at room temperature (25–30°). The red crystalline solid was filtered, washed with 5% $NaHCO_3$ solution and then washed with acetone (2 l.), and dried *in vacuo* (20 mm) at 50°. Recrystallization from CH_2Cl_2 afforded 96 g (96%) of *trans*-β-carotene, mp 181°; 456 uv (cyclohexane) 456 mμ ($\epsilon_{1\,\mathrm{cm}}^{1\%}$ 2495).

Registry No.—**2,** 20843-63-4; **3,** 20930-45-4; **4,** 20941-64-4; **5,** 20843-65-6; **6,** 20843-64-5; **7,** 116-32-5.

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