[CONTRIBUTION FROM THE TECHNICAL DEVELOPMENT DEPARTMENT OF HOFFMANN-LA ROCHE, INC.]

A New Synthesis of *trans*-β-Carotene and Decapreno-β-carotene[1]

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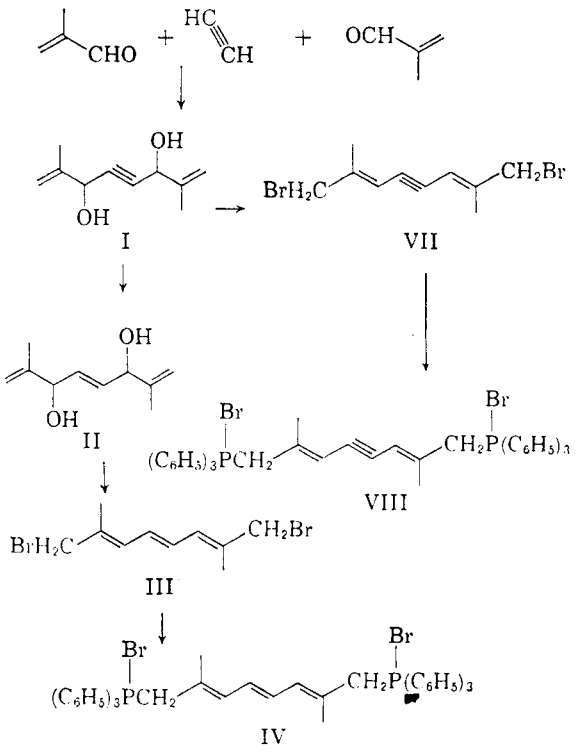
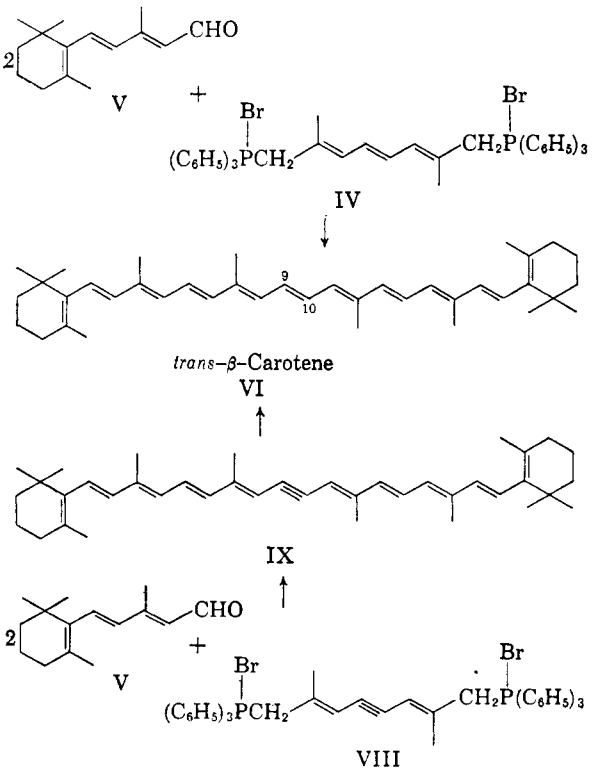
trans-β-Carotene was synthesized in good yield by following a $C_{15} + C_{10} + C_{15}$ building scheme using β-ionylideneacetaldehyde as the C_{15} component. When vitamin A aldehyde was substituted for β-ionylideneacetaldehyde, decapreno-β-carotene, a C_{50} carotenoid with no vitamin A activity, was obtained.

In 1907, Willstätter[2] proved that carotene found in green leaves is identical with that in carrots. Zechmeister[3] in 1928 established the presence of eleven conjugated double bonds and two ring systems in carotene. Karrer[4] by oxidative degradation determined the ring structure and four additional C-methyl groups. Application of the isoprene rule enabled him to establish the now accepted formula, which is made up of eight isoprene units. In 1950, Karrer,[5] Inhoffen,[6] and Milas[7] synthesized *trans*-β-carotene independently. The industrial manufacturing procedure developed by Isler and his group[8] followed the building principle of $C_{19} + C_2 + C_{19}$ of Inhoffen, whereas a later synthesis devised by Isler[13] used the intermediates $C_{14} + C_{12} + C_{14}$.

The synthesis presented here follows a $C_{15} + C_{10} + C_{15}$ building scheme. *trans*-β-Ionylideneacetaldehyde was condensed with a Wittig[9] compound prepared from a C_{10} diol.

To prepare the C_{10} Wittig compound (IV), methacrolein was treated with acetylenedimagnesium bromide according to the procedure of Strong[10] to give the acetylenic diol (I) in 70% yield. Reduction of I with Lindlar catalyst[11] afforded the ethylenic diol (II) in 80% yield. To form the dibromide (III), 48% hydrobromic acid was dropped into an alcoholic solution of II at −10°, whereby III was obtained in 90% yield. The Wittig compound (IV)





(1) Presented at the 137th National Meeting of the American Chemical Society, April 12, 1960, Cleveland, Ohio.

(2) R. Willstätter and W. Mieg, *Ann.*, **355**, 1 (1907).

(3) L. Zechmeister *et al.*, *Ber.*, **61**, 566 (1928); *Ber.*, **66**, 123 (1933).

(4) P. Karrer *et al.*, *Helv. Chim. Acta*, **12**, 1142 (1929); **13**, 1084 (1930); **14**, 1033 (1931).

(5) P. Karrer and C. H. Eugster, *Helv. Chim. Acta*, **33**, 1172 (1950).

(6) H. H. Inhoffen *et al.*, *Ann.*, **570**, 54–69 (1950).

(7) N. A. Milas *et al.*, *J. Am. Chem. Soc.*, **72**, 4844 (1950).

(8) O. Isler *et al.*, *Helv. Chim. Acta*, **39**, 294 (1956).

(9) G. Wittig, *Ber.*, **87**, 1318 (1954); G. Wittig and Geissler, *Ann.*, **580**, 44 (1953).

(10) F. M. Strong, *J. Am. Chem. Soc.*, **70**, 154 (1948).

(11) H. Lindlar, *Helv. Chim. Acta*, **35**, 442 (1952).

was made by dropping a benzene solution of the dibromide (III) into a stirred solution of triphenylphosphene also in benzene. The condensation proceeded smoothly at 40–45° in the presence of iodine catalyst. The crude Wittig compound (IV) crystallized from the reaction mixture in 90% yield.

To effect the condensation to *trans*-β-carotene, the Wittig compound (IV) was added to a stirred solution of phenyllithium in ethyl ether. Reaction with *trans*-β-ionylideneacetaldehyde (V) resulted in a 50.8% yield of pure *trans*-β-carotene (VI). The ultraviolet and visible absorption spectrum and the infrared spectrum for *trans*-β-carotene prepared by the new synthesis were identical with the spectra from an authentic sample of natural *trans*-β-carotene. There was no lowering of mixed melting points. When the Wittig compound of the acetylenic C_{10} diene (VIII) was used for the condensation with *trans*-β-ionylideneacetaldehyde (V), 9,10-dehydrocarotene[8] (IX) resulted in 55% yield. Hydrogenation in the presence of a poisoned palladium catalyst[11] afforded the corresponding ethylenic compound in which the double bond at carbon atom 9 was *cis*. This was readily converted to *trans*-β-carotene (VI) by heating at reflux temperature in normal hexane.

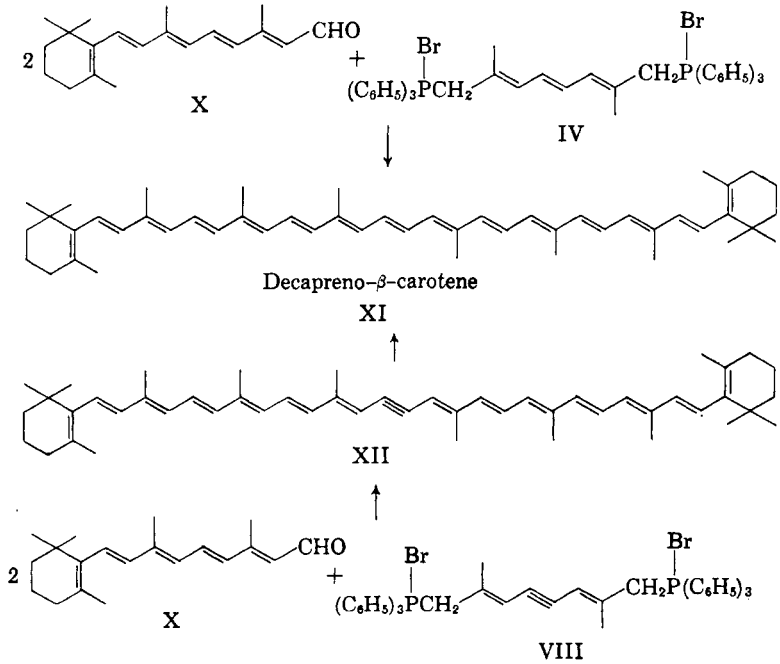
can be expected for the longer chain of conjugated double bonds. The decapreno-β-carotene showed a marked difference from carotene in the color of the pigment. Instead of the typical yellow, a dilute benzene solution showed a brilliant violet red.

Condensation of vitamin A aldehyde (X) with the acetylenic C_{10} compound (VIII) resulted in a dehydro C_{50} carotenoid (XII)[13] having absorption maxima at 481 and 512 mμ (petroleum ether). Selective reduction of XII followed by isomerization afforded decapreno-β-carotene (XI) which was identical in all respects with the sample obtained above. The decapreno β-carotene differs from *trans*-β-carotene by two isoprene units in the chain structure. It showed no vitamin A activity as determined by the rat liver storage test[14,15] and curative growth assay.

EXPERIMENTAL[16]

2,7-Dimethyl-1,7-octadien-4-yne-3,6-diol (I). Ethynylene magnesium bromide was prepared by bubbling dry acetylene for 24 hr. into ethylmagnesium bromide obtained from magnesium turnings (97.2 g.), ethyl bromide (436 g.), dry ethyl ether (1600 cc.), and toluene (800 cc.). Methacrolein (140 g.) was rapidly added to the stirred reaction, which was then refluxed for 1 hr. The resultant Grignard complex was poured onto crushed ice (500 g.), and dilute (5%) sulfuric acid was added until the mixture was faintly acid. The ether solution containing the product was washed to neutrality with sodium bicarbonate and then water, and dried over anhydrous calcium sulfate.

Removal of the solvent *in vacuo* afforded the crude diol.



When vitamin A aldehyde (X) was substituted for the C_{15} aldehyde, a C_{50} carotenoid (XI) resulted which was identified as decapreno-β-carotene.[12,13] It was obtained in 38% yield as a dark violet crystalline solid. The absorption spectrum showed maxima at 475, 501, and 537 mμ (petroleum ether) with the curve closely resembling that of *trans*-β-carotene except that it is shifted to the right, as

(12) P. Karrer, *Helv. Chim. Acta*, **34**, 28–35 (1951).
(13) O. Isler *et al.*, *Ann.*, **603**, 129 (1957).

(14) J. R. Foy and K. Morgareidge, *Anal. Chem.*, **20**, 304 (1948).
(15) K. Guggenheim and W. Koch, *Biochem. J.*, **38**, 256 (1944).
(16) The melting points were determined in vacuum capillaries. Uncorrected.

After recrystallization from toluene, there resulted I, in a yield 116 g. (70%) m.p. 88–91°.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26: H, 8.49. Found: C, 72.10; H, 8.45.

2,7-Dimethyl-1,4,7-octatriene-3,6-diol (II). A solution of I (83 g.) in toluene (500 cc.) was hydrogenated in the presence of poisoned palladium catalyst[11] until 1 molar equivalent of hydrogen was consumed. The catalyst was filtered off and washed thoroughly with additional portions of hot toluene. Finally the filtrate was concentrated *in vacuo*. The crystalline product remaining in the flask was redissolved in hot petroleum ether (b.p. 60–80°) and allowed to crystallize in a refrigerator. Filtration and drying afforded 67 g. (80%) of II, m.p. 69–70°.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.69; H, 9.65.

1,8-Dibromo-2,7-dimethyl-2,4,6-octatriene (III). A solution of II (36.6 g.) in 95% ethyl alcohol (100 cc.) was placed in a 1-l., round bottom flask fitted with a thermometer, mechanical stirrer, and a dropping funnel. The solution was cooled to −10°, then 48% hydrobromic acid (250 cc.) was added from the dropping funnel with vigorous stirring, in 30 min. The reaction was stirred cold (0° to −10°) for an additional 15 min., then the crystalline dibromide was filtered by suction under a blanket of nitrogen. The product was washed on the filter with sodium bicarbonate (5%) and dried *in vacuo* at 35°. There was obtained 53 g. (90%) of III, m.p. 80–82°.

Anal. Calcd. for $C_{10}H_{14}Br_2$: C, 40.84; H, 4.79. Found: C, 40.91; H, 4.65.

2,7-Dimethyl-2,4,6-octatrienylenebis(triphenylphosphonium bromide) (IV). A solution of triphenylphosphene (131 g.) in benzene (400 cc.) was placed in a 1-l., round bottom flask. A solution of III (53 g.) and iodine (0.1 g.) in benzene (400 cc.) was placed in the dropping funnel and added to the stirred reaction at 40–45° in 2 hr. The reaction was stirred while warm for 4 hr., then allowed to stand at room temperature overnight. The product was filtered by suction, washed with petroleum ether (200 cc.), and dried *in vacuo* at 50°. The product (IV) was obtained in yield of 133 g. (90%). An analytical sample after repeated recrystallization from methyl alcohol-ethyl acetate, melted at 280°.

Anal. Calcd. for $C_{46}H_{44}Br_2P_2$: C, 67.49; H, 5.42. Found: C, 66.98; H, 5.93.

trans β-Carotene (VI). To a solution of phenyllithium (0.22 mole) in ethyl ether (300 cc.), there was added 92 g. of IV during 30 min. with vigorous stirring. This caused the color of the reaction mixture to become a deep violet-red, while the temperature rose from 22° to 34°. The reaction was tested for completeness by means of the Gilman test.[17] A solution of β-ionylideneacetaldehyde (48 g.) in ethyl ether (200 cc.) was added from a dropping funnel in 1 hr. The reaction was stirred while heating at reflux for 8 hr. It was then cooled to −10° and methyl alcohol (400 cc.) was added. After cooling for an additional 4 hr. at −5° to −10°, the violet crystals of VI were filtered off by suction, washed with 95% ethyl alcohol (200 cc.), and petroleum ether (200 cc.). Recrystallization from benzene and drying *in vacuo*, yielded 29.6 g. (50.8%) of *trans*-β-carotene melting at 181°. The infrared and ultraviolet absorptions of VI and from an authentic sample of *trans*-β-carotene were identical. There was no lowering of mixed melting point.

Anal. Calcd. for $C_{40}H_{56}$: C, 89.48; H, 10.52. Found: C, 89.45; H, 10.40.

(17) H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

1,8-Dibromo-2,7-dimethyl-2,6-octadien-4-yne (VII). This was prepared in the same manner as III from 2,7-dimethyl-1,7-octadien-4-yne-3,6-diol (I) (200 g.) and 48% hydrobromic acid (1000 cc.) in yield of 279 g. (79%); m.p. 40°. This compound was not reliably stable, so it was used for the next step without further purification.

2,7-Dimethyl-2,6-octadien-4-ynylenebis(triphenylphosphoniumbromide) (VIII). In a similar fashion to the preparation of IV, there was obtained by the action of triphenylphosphene (400 g.) in benzene (1200 cc.) on VII (175 g.) and iodine (0.2 g.) in benzene (1200 cc.) 472 g. (90%) of VIII melting at 223–227°. An analytical sample, after repeated recrystallizations from methyl alcohol–ethyl acetate, melted at 256–258°.

Anal. Calcd. for $C_{46}H_{42}Br_2P_2$: C, 67.65; H, 5.18. Found: C, 67.58; H, 5.31.

9,10-Dehydrocarotene (IX). By the same procedure described for the preparation of VI, there was obtained from VIII (100 g.) and β-ionylideneacetaldehyde (48 g.), 31.5 g. (55%) of IX, m.p. 154° after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{40}H_{54}$: C, 89.82; H, 10.18. Found: C, 89.80; H, 10.10.

trans-β-Carotene by reduction of IX. A suspension of IX (20 g.) in hexane (200 cc.) was hydrogenated in the presence of poisoned palladium catalyst[11] until 1 molar equivalent of hydrogen was consumed. The suspension was heated to boiling before filtration of the catalyst, and the latter was washed with additional hot hexane. The filtrate was concentrated until a pasty mass remained. This was heated at 90° for 16 hr. in an inert atmosphere to effect the transformation to the *trans*-compound. Filtration and recrystallization from benzene afforded 15 g. (75%) of VI, m.p. 181°. The identity of VI was confirmed by ultraviolet and infrared absorption spectra.

3,7,11,16,20,24-Hexamethyl-1,26-bis(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,5,7,9,11,13,15,17,19,21,23,25-hexacosatridecaene (XI). By a procedure similar to that for the preparation of VI, IV (42.6 g.) and vitamin A aldehyde (28.4 g.) were allowed to react to yield 14.8 g. (38%) of XI as a black colored crystalline solid, after recrystallization from methylene chloride and methyl alcohol. The melting point was 191°. The absorption spectrum had maxima at 327 mμ, $E^{1\%}_{1cm}$ = 692, 399 mμ, $E^{1\%}_{1cm}$ = 497, 475 mμ, $E^{1\%}_{1cm}$ = 2100, 501 mμ, $E^{1\%}_{1cm}$ = 2737, and 537 mμ, $E^{1\%}_{1cm}$ = 2243 (in heptane.)

Anal. Calcd. for $C_{50}H_{68}$: C, 89.76; H, 10.24. Found: C, 89.70; H, 10.15.

3,7,11,16,20,24-Hexamethyl-1,26-bis(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,5,7,9,11,15,17,19,21,23,25-hexacosadodecaen-13-yne (XII). XII was obtained in the same manner as XI from VIII (85 g.) and vitamin A aldehyde (56.8 g.) in yield of 32.8 g. (42%); m.p. 189°; absorption maxima at 328 mμ, $E^{1\%}_{1cm}$ = 623, 481 mμ, $E^{1\%}_{1cm}$ = 2467, and 512 mμ, $E^{1\%}_{1cm}$ = 1879.

Anal. Calcd. for $C_{50}H_{66}$: C, 90.03; H, 9.97. Found: C, 89.88; H, 10.02.

Decapreno-β-carotene XI *by partial reduction of* XII. A suspension of XII (5.0 g.) in hexane (50 cc.) was hydrogenated by a procedure similar to that described for the reduction of IX. After recrystallization from methylene chloride–methyl alcohol, there was obtained 3.5 g. of XI, m.p. 191°. The ultraviolet and infrared absorption spectra were identical with those obtained from X. There was no lowering of mixed melting point.

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