

CCA-178

547.970.07:543.854.1

Synthetic Studies in the Polyene Series. II.* Synthesis of 15,15'-Dihydro- β -carotene

A. Markovac-Prpić** and D. Fleš

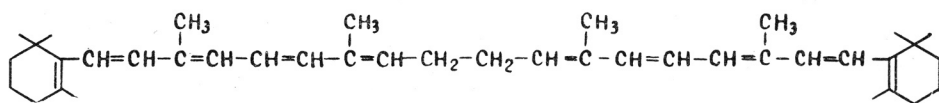
Research Department, »Pliva« Pharmaceutical and Chemical Works, Zagreb, Croatia, Yugoslavia

Received May 31, 1960

The compound mentioned in the title has been prepared by condensation of 3,8-dimethyl-3,8-dihydroxy-decadiyne-(1,9) with two moles of 4-[2',6',6'-trimethyl-cyclohexene-(1')-yl]-2-methyl-buten-(3)-al-(1), followed by dehydration and partial hydrogenation of acetylenic bonds. Intermediates and the final product were purified by absorption chromatography, and their structures were proved by spectroscopic and analytical methods.

The total synthesis of β -carotene, the most important of the provitamin A carotenoids was achieved several years ago by the three groups of workers.^{1,2,3} Many papers concerned with the synthetic chemistry of carotenoids have been published and several review articles summarizing these findings have appeared.⁴

Several carotenoid hydrocarbons more saturated than $C_{40}H_{56}$ have been isolated from various classes of fungus, but the structure of most of these compounds has not been established so far.⁵ A crystalline dihydro- β -carotene has been isolated from *Cyclamen persicum* and was proved by Karrer and Leumann⁶ to be 7,7'-dihydro- β -carotene (I). The same compound was prepared in 1940 by Karrer and Ruegger⁷ through reduction of β -carotene with aluminum amalgam.

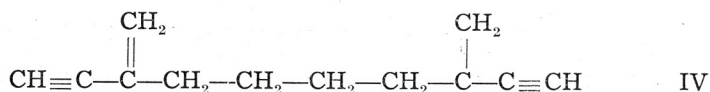
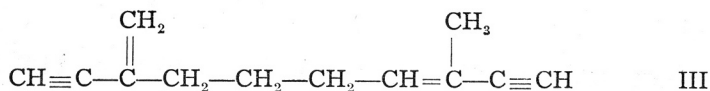
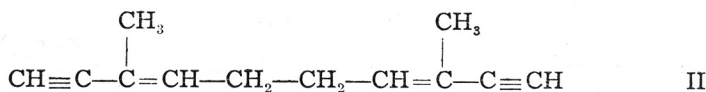


I

The total synthesis of 7,7'-dihydro- β -carotene was achieved by Inhoffen *et al.*⁸ in 1953. They have prepared the hydrocarbon I by condensing a mixture of C_{12} -hydrocarbons II, III and IV with two moles of 4-[2',6',6'-trimethyl-cyclohexene-(1')-yl]-2-methyl-buten-(3)-al-(1) (C_{14} -aldehyde). The acetylenic bonds of the mixture of C_{40} -diols were selectively reduced to double bonds and after

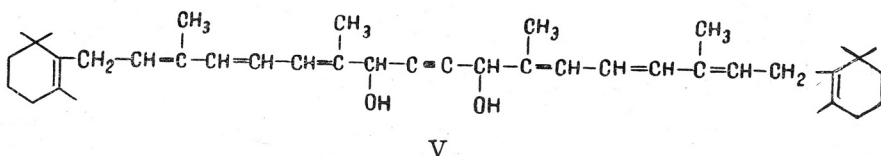
* Part I, D. Fleš, V. Tomašić, and A. Markovac-Prpić, *Croat. Chem. Acta*, **30** (1958) 69.

** Taken from the thesis submitted by A. Markovac-Prpić in partial fulfilment of the requirement for the degree of Doctor of Chemistry (equivalent to Ph. D.) at the University of Zagreb.

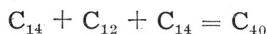


a double allylic shift and dehydration 7,7'-dihydro- β -carotene was obtained.

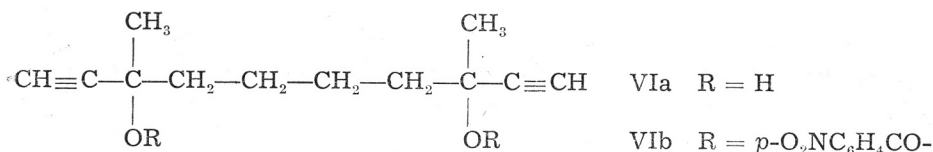
Isler and his associates⁹ have prepared the same hydrocarbon I in 1956, by applying the Nyler-Whiting reaction to acetylenic diol V.



In our studies on the preparation of carotenoids more saturated than β -carotene, we have prepared 15,15'-dihydro- β -carotene by the use of the following reaction scheme:

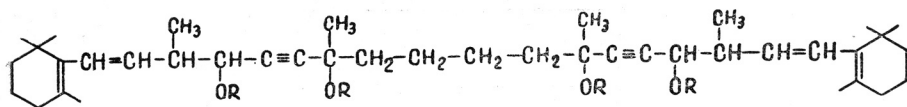


The central C_{12} -component was 3,8-dimethyl-3,8-dihydroxy-decadiyne-(1,9) (VIa), which was prepared by condensation of lithium acetylide with octanedione-(2,7)¹⁰ in liquid ammonia. C_{12} -Diol VIa was purified by vacuum distillation and cry-



stallised from a mixture of ether and petroleum ether. The structure of this compound was proved by analytical and spectroscopic methods and by preparation of a crystalline bis-(*p*-nitrobenzoate) (VIb).

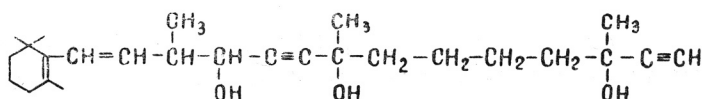
The phenyl-lithium condensation of C_{12} -diol VIa with two moles of C_{14} -aldehyde gave 1,18-bis[-2',6',6'-trimethyl-cyclohexene-(1')-yl]-3,7,12,16-tetramethyl-4,7,12,15-tetrahydro-octadecadiene-(1,17)-diyne-(5,13) (C_{44} -tetraol VIIa), which was contaminated with some low boiling material. The low boiling fractions were removed by high vacuum distillation, the air bath temperature not exceeding 80°. From the undistilled portions C_{40} -tetraol VIIa was isolated by repeated absorption chromatography on neutral aluminum oxide. The chro-



VIIa R = H

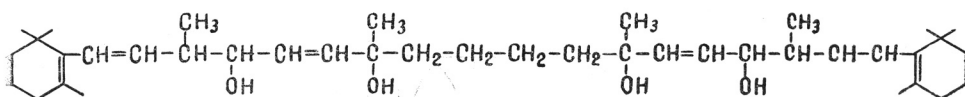
VIIb R = COCH₃

matogram was developed with a mixture of petroleum ether-ether giving six zones which were removed mechanically. The first three zones contained some low molecular weight materials, as indicated by molecular weight determination, while from the fourth zone was isolated a polyene compound corresponding to an empirical formula C₂₆H₄O₃, which was identified as 14-[2',6',6'-trimethyl-cyclohexene-(1')-yl]-3,8,12-trimethyl-3,8,11-trihydroxy-tetradecaene-(13)-diyne-(1,9) (C₂₆-triol VIII). The fifth zone contained a mixture of C₂₆-triol VIII and C₄-tetraol VIIa, while the sixth zone upon rechromatography gave the analytically pure C₄₀-tetraol VIIa.



VIII

The infrared spectrum of C₂₆-triol VIII shows the presence of terminal acetylenic bond at 3250 cm⁻¹, while the band at 2100 cm⁻¹ indicates the presence of —C≡C— group.¹¹ The active hydrogen and molecular weight determination are in agreement with the triol structure. The ultraviolet spectrum of C₄₀-tetraol



IX

in ethanol is given in Fig. 1 and shows a maximum at 2470 Å with an extinction value of 12120. The hydroxyl stretching frequency appears in infrared spectrum at 3350 cm⁻².¹² A tetraacetate VIIb and a partially hydrogenated C₄₀H₆₆O₇ tetraol IX were also prepared. The absorption bands of tetraacetate VIIb in infrared spectrum are located in the expected positions: 1750 cm⁻¹ (C=O stretching vibration) and 1250 cm⁻¹ (—C—O— stretching vibration).¹³

The stepwise dehydration of the C₄-tetraol VIIa with *p*-toluenesulfonic acid in toluene gave the crude mixture of C₄₀-hydrocarbons, from which 11,11'-dehydro-15,15'-dihydro-β-carotene (X) was isolated by the column chromato-

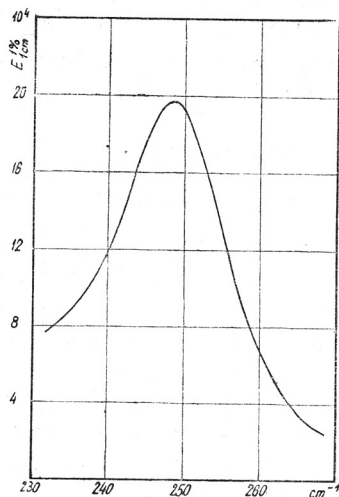
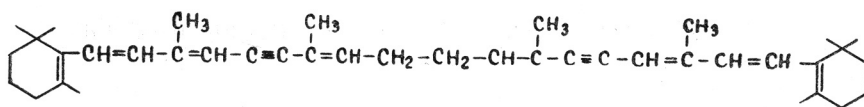


Fig. 1. The ultraviolet absorption spectrum of C_{40} -tetraol VIIa in ethanol.



X

graphy on neutral aluminum oxide. The chromatogram was developed with a mixture of benzene and petroleum ether, and the third zone was rechromatographed to give analytically pure hydrocarbon X. The ultraviolet spectrum in

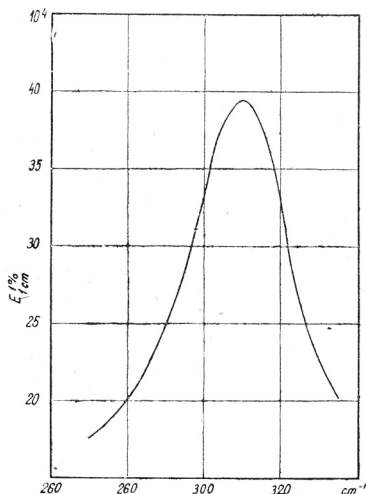
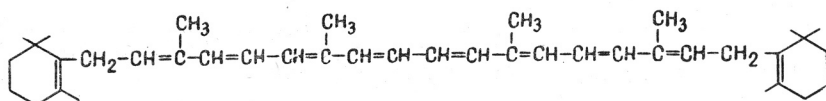


Fig. 2. The ultraviolet absorption spectrum of 11,11'-dehydro-15,15'-dihydro- β -carotene (X) in cyclohexane.

cyclohexane (Fig. 2) shows a maximum at 3100 Å which is in agreement with the proposed structure. This structure was also confirmed by perhydrogenation in the presence of Adams' catalyst.

The partial hydrogenation of 11,11'-dehydro-15,15'-dihydro- β -carotene X by the use of a Lindlar catalyst¹⁴ gave a mixture of hydrocarbons, which after



XI

rechromatography on neutral aluminum oxide of the activity III yielded three zones. The third zone was eluted with a mixture of ether and methanol, and rechromatographed through a column of aluminum oxide of the activity II. Chromatogram was developed with a mixture of petroleum ether and benzene. From the third, orange-yellow zone, 15,15'-dihydro- β -carotene (XI) was eluted

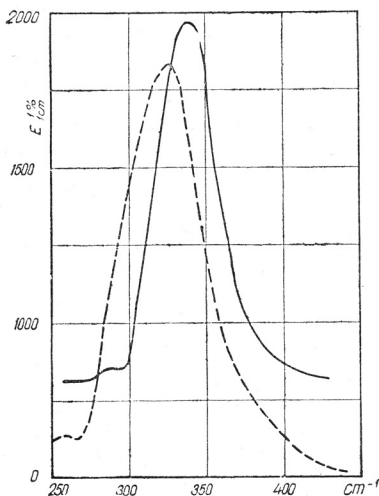


Fig. 3. The ultraviolet absorption spectra of 15,15'-dihydro- β -carotene (XI) in cyclohexane (—) and vitamin A¹⁶ (---)

with ether-methanol as an orange-yellow glassy solid. The product gave characteristic blue-violet color with the Carr-Price reagent.¹⁵ The ultraviolet spectrum of 15,15'-dihydro- β -carotene in cyclohexane shows maxima at 2880 Å and at 3400 Å with extinctions of $E_{1\text{cm}}^{1\%}$ 720 and 1900 respectively. The resemblance of the ultraviolet spectrum of 15,15'-dihydro- β -carotene and vitamin A¹⁶ is shown in the figure 3.

EXPERIMENTAL*

All chromatographic separations were performed under a stream of repurified nitrogen¹⁷ in the absence of the direct day-light. Aluminum oxide, standardized according to Brockmann, neutral, of the activity IV was used if not otherwise stated. The infrared spectra were recorded on a Perkin-Elmer Mod. 134 spectrophotometer, NaCl prisms, in Nujol, and ultraviolet spectra on Beckman Model DU spectrophotometer.

Octanedione-(2,7)

Thirteen grams of 1,8-bis-(diazoo)-octanedione-(2,7) were converted to octanedione-(2,7) following essentially the procedure used for the preparation of octene-(4)-dione-(2,7).¹⁸ Yield 9 g. (90%), b. p. 114° at 10 mm; m. p. 42°**

3,8-Dihydroxy-3,8-dimethyl-decadiyne-(1,9) (VIa)

A solution of 8 g. of octanedione-(2,7) in 50 ml. of ether was added during one hour with vigorous stirring into a solution of lithium acetylide prepared from 1.2 g. of lithium in 250 ml. of liquid ammonia. The mixture was stirred for an additional hour under a slow stream of acetylene. The complex was decomposed with 15 g. of ammonium chloride and ammonia allowed to evaporate overnight at room temperature. After working up the residue with ether and water, drying with magnesium sulfate and evaporating the solvent, 12 g. of the crude oily product was obtained. It contained 27% of C₁₂-diol VIa as determined by silver nitrate titration of ethynyl group according to Eglinton and Whiting.¹⁹ The crude carbinol was dissolved in 10 ml. of methanol and treated with a solution of semicarbazide acetate (prepared from 5.5 g. of semicarbazide hydrochloride, 8 g. of sodium acetate and 10 ml. of methanol). After standing overnight at room temperature, the semicarbazone fraction was removed by suction filtration and the mother liquor concentrated *in vacuo*. The oily residue was dissolved in 80 ml. of ether, washed with two 5-ml. portions of water, neutralized with sodium bicarbonate solution, dried and solvent evaporated to give 5.8 g. of a product containing 93.5% of C₁₂-diol VIa. This product was further purified by vacuum distillation at a temperature of 108–110° (bath temperature) and a pressure of 0.06 mm. yielding a colorless oil which solidified on standing; m. p. 86–89°. A sample was crystallised for analysis from a mixture of ether-petroleum ether (b. p. 40–60°) (1:1) and melted at 91°.

The infrared spectrum shows the bands at 3250 cm⁻¹ (≡CH), 2090 cm⁻¹ (—C≡C—) and 3400 cm⁻¹ (—OH).

Anal. 9.63 mg. subst.: 26.11 mg. CO₂, 7.90 mg. H₂O
C₁₂H₁₈O₂ (192.2) calc'd.: C 74.19; H 9.34%
found: C 73.99; H 9.18%
Active hydrogen: calc'd.: 2
found: 1.9

3,8-Dimethyl-3,8-bis-(p-nitrobenzoyloxy)-decadiyne-(1,9) (VIb)

A mixture of 0.5 g. of C₁₂-diol VIa and 0.5 g. of *p*-nitrobenzoyl chloride in 5 ml. of pyridine was heated for thirty minutes on a water bath. The reaction mixture was treated with a saturated sodium bicarbonate solution, the crystalline precipitate filtered off, washed with water, dried and recrystallised from a mixture of benzene-petroleum ether (b. p. 40–60°) (1:1) to give dibenzoyl derivative VIb; m. p. 170°.

Anal. 9.86 mg. subst.: 22.81 mg. CO₂, 4.08 mg. H₂O
C₂₆H₂₄O₈N₂ (492.47) calc'd.: C 63.41; H 4.91%
found: C 63.13; H 4.63%

1,18-Bis-[2',6',6'-trimethyl-cyclohexene-(1')-yl]-3,7,12,16-tetramethyl-4,7,12,15-tetrahydroxy-octadecadiene-(1,17)-diyne-(5,13) (C₄₀-tetraol) (VIIa)

A solution of 3.82 g. (0.02 mole) of C₁₂-diol VIa in 100 ml. of benzene was treated under vigorous stirring with 67 ml. of an ethereal solution of phenyl-lithium (0.56 g.,

* Melting points are uncorrected

** Reported m. p. 43°.¹⁰

0.08 mole). The yellow suspension which resulted, was refluxed for three hours at a bath temperature of 60–70°, while a slow stream of nitrogen was bubbled through. The reaction mixture was cooled to room temperature, a solution of 12.1 g. of C_{14} -aldehyde²⁰ in 50 ml. of ether was added and heating continued for an additional six hours. After cooling to room temperature the yellow suspension was poured on a mixture of 60 g. of ice and 6 ml. of phosphoric acid. The water layer was separated, extracted with three 50-ml. portions of ether, the total organic fraction washed with three 20-ml. portions of water, neutralized with three 15-ml. portions of a saturated sodium bicarbonate solution, dried over magnesium sulfate and solvent evaporated *in vacuo* to give 15 g. of a yellow oil. The crude condensation product was transferred into a short path distillation apparatus and the fraction distilling at 10^{-4} mm and 80–90° (bath temperature) was removed. Molecular weight of this fraction was 190 ± 15 (cryoscopic in dioxane). The residue which showed a molecular weight of 540 (cryoscopic in dioxane) (calc'd. for C_{40} -tetraol VIIa 606.9) was dissolved in 10 ml. of ether and poured on a column of neutral aluminum oxide (25×2.5 cm.), and the chromatogram developed with 500 ml. of a mixture of petroleum ether (b. p. 40–60°) and ether (10:1) to give six zones, which were separated mechanically. The first three zones were eluted with ether yielding 0.37 g., 0.3 g., and 0.5 g. of oily products having molecular weight of 284, 156 and 180 respectively (cryoscopic in dioxane) and were discarded. The fourth, yellow-brown zone was eluted with 400 ml. of a mixture of ether-methanol (10:1) yielding 0.45 g. of a dark-yellow oil with a molecular weight of 450. Purification of this product is described under the preparation of 14-[2,6,6'-trimethyl-cyclohexene-(1')-yl]-3,8,12-trimethyl-3,8,11-trihydroxy-tetradecaene-(13)-diyne-(1,9) (C_{26} -triol VIII). The fifth zone was eluted in the same manner giving 0.5 g. of a yellow oil with a molecular weight of 510. When treated with an aqueous silver nitrate solution, a slight turbidity occurred, indicating that some of the C_{26} -triol was still present. The fifth zone was not further purified. The elution of the sixth zone with 500 ml. of ether-methanol (10:1) gave 1.5 g. of a light-yellow oil, which had a molecular weight of 565 (cryoscopic in benzene). This fraction was dissolved in 20 ml. of ether and rechromatographed on aluminum oxide (25×2.5 cm.), the chromatogram developed with 500 ml. of a mixture of petroleum ether (b. p. 40–60°) and ether (10:1), and the two zones separated mechanically. The second zone was eluted with 300 ml. of a mixture of ether and methanol (10:1), the effluent washed with three 20-ml. portions of water, dried over magnesium sulfate and ether evaporated yielding 0.7 g. of C_{40} -tetraol VIIa as a viscous yellow oil.

The ultraviolet absorption spectrum of C_{40} -tetraol VIIa in ethanol shows absorption maximum at 2470 Å (ϵ 12120) (Fig. 1).

Anal. 9.23 mg. subst.: 26.93 mg. CO_2 , 8.41 mg. H_2O
 $C_{40}H_{62}O_4$ (606.9) calc'd.: C 79.26; H 10.30%
 found: C 79.62; H 10.19%
 Molecular weight (cryoscopic in benzene): calc'd.: 606.9
 found: 590
 Active hydrogen (Zerewitinoff): calc'd.: 4
 found: 3.9

Perhydrogenation. A sample of C_{40} -tetraol VIIa (50 mg.) was hydrogenated over Adams' catalyst in a mixture of cyclohexane-acetic acid (1:1), and absorbed 13.9 ml. of hydrogen (S. T. P.); calc'd. 14.7 ml.

Active hydrogen (Zerewitinoff): calc'd.: 4
 found: 3.9

1,18-Bis-[2',6',6'-trimethyl-cyclohexene-(1')-yl]-3,7,12,16-tetramethyl-4,7,12,15-tetraacetoxy-octadecadiene-(1,17)-diyne-(5,13) (VIIb)

A solution of 0.48 g. of C_{40} -tetraol VIIa in 5 ml. of benzene and 5 ml. of pyridine was cooled to -5° and under vigorous stirring, treated with 0.37 ml. of acetyl chloride. The reaction mixture was stirred for one hour at 0° , then heated for an additional hour at 60° and kept overnight at room temperature. The reaction mixture was poured on 5 ml. of 5% sulfuric acid, water layer separated, extracted with three 5-ml. portions of benzene, the total benzene fraction washed with water, neutralized with a saturated sodium bicarbonate solution, dried and evaporated

in vacuo yielding 0.5 g. of a pale yellow oil. Crude tetraacetate was dissolved in 5 ml. of ether, poured on a column of aluminum oxide (10×2 cm.), and the chromatogram developed with 200 ml. of petroleum ether (b.p. $40-60^\circ$) giving two yellow zones. Elution with 200 ml. of benzene afforded 0.15 g. of viscous, colorless oil. The analytical sample was dried for 5 hours at 25° and 10^{-4} mm. The compound had no free hydroxyl group as indicated by active hydrogen determination and infrared spectrum. The bands at 1750 cm^{-1} and 1230 cm^{-1} are attributed to C=O and C—O— stretching vibrations.

Anal. 11.82 mg. subst.: 32.19 mg. CO_2 , 9.86 mg. H_2O
 $\text{C}_{48}\text{H}_{70}\text{O}_8$ (775.04) calc'd.: C 74.33; H 9.10%
 found: C 74.32; H 9.33%
 Active hydrogen (Zerewitinoff): calc'd.: 0
 found: 0.1

1,18-Bis-[2',6',6'-trimethyl-cyclohexene-(1')-yl]-3,7,12,16-tetramethyl-4,7,12,15-tetrahydroxy-octadecatetraene-(1,5,13,17) (IX)

A sample of analytically pure tetraol VIIa (80 mg.) was dissolved in 7 ml. of dioxane and hydrogenated in the presence of a Lindlar catalyst.¹⁴ Approximately theoretical amount of hydrogen for partial reduction of triple bonds (5.6 ml., calc'd. 5.9 ml. S.T.P.) was consumed in 5 hours, when the uptake of hydrogen stopped completely. The catalyst was separated by filtration, dioxane evaporated *in vacuo*, and the oily residue dried for analysis for 5 hours at 25° and 10^{-4} mm.

Anal. 14.00 mg. subst.: 40.54 mg. CO_2 , 13.76 mg. H_2O
 $\text{C}_{40}\text{H}_{66}\text{O}_4$ (610.93) calc'd.: C 78.63; H 10.89%
 found: C 79.02; H 11.00%
 Active hydrogen (Zerewitinoff): calc'd.: 4
 found: 3.87

14-[2',6',6'-trimethyl-cyclohexene-(1')-yl]-3,8,12-trimethyl-3,8,11-trihydroxy-tetradecaene-(13)-diyne-(1,9) (C_{26} -triol) (VIII)

The fourth zone of the purification of C_{40} -tetraol VIIa (0.45 g.) was dissolved in 100 ml. of ether and treated with three 20-ml. portions of a 10% silver nitrate solution. The white precipitate was removed by suction filtration, washed with water, suspended in 100 ml. of ether and under vigorous shaking treated with 10% hydrochloric acid until most of the silver acetylide dissolved. The ether layer was removed, washed with water, dried and the solvent evaporated *in vacuo*, yielding 250 mg. of a yellow oil, which was dissolved in 10 ml. of ether and chromatographed on aluminum oxide (2×10 cm.). The chromatogram was developed with 200 ml. of a mixture of petroleum ether (b.p. $40-60^\circ$) and ether (10:1) and two zones which separated were cut mechanically. The second zone contained C_{26} -triol VIII, and was eluted with 200 ml. of a mixture of ether-methanol (10:1). The effluent was washed with three 20-ml. portions of water, dried over magnesium sulfate and evaporated *in vacuo* giving 0.1 g. of compound VIII as a viscous yellow oil. Analytical sample was dried for 5 hours at 25° and 10^{-4} mm.

The infrared spectrum showed the bands at 3250 cm^{-1} ($\equiv\text{CH}$), 2100 cm^{-1} ($-\text{C}\equiv\text{C}-$) and 3380 cm^{-1} ($-\text{OH}$).

Anal. 10.41 mg. subst.: 29.81 mg. CO_2 , 9.19 mg. H_2O
 $\text{C}_{26}\text{H}_{40}\text{O}_3$ (400.58) calc'd.: C 77.95; H 10.07%
 found: C 78.15; H 9.87%
 Active hydrogen (Zerewitinoff): calc'd.: 3
 found: 3.05

Perhydrogenation. A sample of C_{26} -triol VIII (20 mg.) was hydrogenated in 10 ml. glacial acetic acid in the presence of 20 mg. of Adams' catalyst, and absorbed 5.9 ml. of hydrogen (S. T. S.); calc'd 6.7 ml.

1,18-Bis[2',6',6'-trimethyl-cyclohexene-(1')-yl]-3,7,7,12,16-tetramethyloctadeca-hexaene-(1,3,7,11,15,17)-diyne-(5,13)(11,11'-dehydro-15,15'-dihydro- β -carotene) (X)

To a boiling solution of 2.9 g. of tetraol VIIa in 170 ml. of toluene was added under a stream of purified nitrogen a solution of 0.244 g. of anhydrous *p*-toluenesulfonic acid in 10 ml. of boiling toluene. The reaction mixture was refluxed for two minutes, cooled in an ice-bath and neutralized with a saturated sodium bicarbonate solution. The aqueous layer was separated, extracted with three 20-ml. portions of petroleum ether (b. p. 40–60°) and organic fractions extracted with four 20-ml. portions of 90% methanol, followed by two 20-ml. portions of water. After drying with magnesium sulfate, solvents were evaporated *in vacuo* to give 2 g. of a brown oil, which showed a value of 1.7 active hydrogen. The partially dehydrated product (2 g.) was treated with another portion of *p*-toluenesulfonic acid in the same manner as previously described. Evaporation of toluene-petroleum ether gave 1.2 g. of a viscous oil, which contained no active hydrogen. The crude hydrocarbon was dissolved in 10 ml. of petroleum ether (b. p. 40–60°) and poured on a column of aluminum oxide (2.5×30 cm., activity II). The chromatogram was developed with 300 ml. of a mixture of petroleum ether (b. p. 40–60°) and benzene (10:1) giving three zones, which were separated mechanically. Elution of the first two zones with ether-methanol (9:1) gave a product with molecular weight of 1500 (cryoscopic in benzene) and was discarded. The third zone was eluted with 500 ml. of ether-methanol (9:1), effluent washed with three 20-ml. portions of water, dried and ether evaporated *in vacuo* to give 0.8 g. of a yellow viscous oil. This was dissolved in 5 ml. of petroleum ether (b. p. 40–60°) and rechromatographed on aluminum oxide (2×30 cm., activity II). The chromatogram was developed with 500 ml. of petroleum ether (b. p. 40–60°) and three zones which separated were cut mechanically. The second zone contained 11,11'-dehydro-15,15'-dihydro- β -carotene, and was eluted with 300 ml. of a mixture of ether-methanol (10:1), effluent washed with water, dried over magnesium sulfate and solvent evaporated yielding 0.35 g. of a viscous yellow oil. The analytical sample was dried for 5 hours at 25° and 10⁻⁴ mm.

The ultraviolet absorption spectrum of the hydrocarbon X in cyclohexane showed absorption maximum at 3100 Å (ϵ 208500) (Fig. 2).

Anal. 10.16 mg. subst.: 33.25 mg CO₂, 9.13 mg. H₂O
 C₄₀H₅₄ (534.83) calc'd.: C 89.82; H 10.18%
 found: C 89.30; H 10.05%

Perhydrogenation. A sample of 11,11'-dehydro-15,15'-dihydro- β -carotene X (53 mg.) was hydrogenated in 10 ml. of a mixture of cyclohexane and acetic acid (1:1) in the presence of Adams' catalyst, and an approximately theoretical amount of hydrogen (26.0 ml. S. T. P.) was absorbed in six hours. (Calc'd. 26.9 ml.).

1,18-Bis-[2',6',6'-trimethyl-cyclohexene-(1')-yl]-3,7,12,16-tetramethyloctadeca-octaene-(1,3,5,7,11,13,15,17) (15,15'-Dihydro- β -carotene) (XI)

11,11'-Dehydro-15,15'-dihydro- β -carotene X (250 mg.) was dissolved in 5 ml. of purified dioxane and refluxed for 5 minutes with 100 mg. of platinum oxide catalyst. Platinum oxide was removed by filtration and the filtrate transferred to a semimicro hydrogenation apparatus. The hydrogenation was performed at a normal pressure in the presence of 200 mg. of a Lindlar catalyst. Two mole equivalents of hydrogen (20.7 ml., calc'd. 21.1 ml. S. T. P.) were consumed in four hours. Catalyst was removed by filtration and dioxane evaporated *in vacuo* (bath temperature below 40°) to give 200 mg. of the crude dihydro- β -carotene XI. This product was dissolved in 3 ml. of petroleum ether (b. p. 40–60°), poured on a column of aluminum oxide (25×2.5 cm.), eluted with 250 ml. of petroleum ether (b. p. 40–60°), followed by 250 ml. of benzene. The three zones which separated, were cut mechanically and the third zone eluted with 300 ml. of a mixture of ether-methanol (10:1). Evaporation of solvent gave 0.15 g. of a viscous oil, which was dissolved in 3 ml. of petroleum ether (b. p. 50–70°) and rechromatographed using neutral aluminum oxide of the activity II. The chromatogram was developed with 250 ml. of a mixture of benzene-petroleum ether (b. p. 50–70°) (1:1) into three zones, which were separated mechanically. The third zone which was the main fraction (12 cm. compared with 1 cm. of the first and the second zone) was eluted with 200 ml. of ether containing 10% of methanol. The eluate was

washed with three 20-ml. portions of water, dried over magnesium sulfate and evaporated *in vacuo* yielding 100 mg. of 15,15'-dihydro- β -carotene in the form of an orange-yellow glassy solid, which could be pulverized to a yellow powder. A characteristic blue-violet color with the Carr-Price reagent was obtained. An analytical sample was dried for 5 hours at 25° and 10⁻⁴ mm.

The ultraviolet absorption spectrum of this compound (in cyclohexane) showed absorption maxima at 2880 Å ($E_{1\text{cm}}^{1\%}$ 720) and 3400 Å ($E_{1\text{cm}}^{1\%}$ 1990) (Fig. 3).

Anal. 11.2 mg. subst.: 35.92 mg. CO₂, 10.44 mg. H₂O
 C₄₀H₅₈ (538.87) calc'd.: C 89.15; H 10.84%
 found: C 89.55; H 10.65%

Perhydrogenation. A sample of 15,15'-dihydro- β -carotene IX (13.6 mg.) was hydrogenated in 3 ml. of a mixture of cyclohexane-acetic acid (1:1) in the presence of 20 mg. of Adams' catalyst. Approximately ten mole equivalents of hydrogen (4.9 ml.) were consumed in three hours (calc'd. for ten double bonds 5.5 ml. S. T. P.).

Acknowledgments. The authors are grateful to Professor Viktor Hahn from the University of Zagreb, for his continued interest in this work. The helpful suggestions of Professor Nicholas A. Milas from the Massachusetts Institute of Technology, Cambridge, Mass., are acknowledged gratefully. Thanks are also due to Mrs. Marija Milohnoja and Mrs. Ljubica Loborec from this Laboratory for their capable technical assistance. The numerous spectral measurements and microanalyses were performed in the Physico-chemical Laboratory of the Institute »Ruder Bošković« and in the microanalytical Laboratory of »Pliva«.

REFERENCES

1. P. Karrer and C. H. Eugster, *Compt. rend.* **230** (1950) 1920; *Helv. Chim. Acta* **33** (1950) 1172.
2. H. H. Inhoffen, F. Bohlmann, K. Bartram, and H. Pommer, *Chem. Ztg.* **74** (1950) 285; *Abh. Braunschweig. Wiss. Ges.* **2** (1950) 75.
3. N. A. Milas, P. Davis, I. Belič, and D. Fleš, *J. Am. Chem. Soc.* **72** (1950) 4844.
4. P. Karrer and E. Jucker, *Carotenoids*, Elsevier Publishing Co., New York 1950; N. A. Milas, in *The Vitamins*, Vol. I., p. 4., Academic Press Inc., New York 1954; H. H. Inhoffen and H. Siemer in *Progress in the Chemistry of Organic Natural Products*, Vol. IX, p. 1., Springer, Wien, 1952.
5. F. T. Haxo, in *Progress in the Chemistry of Organic Natural Products*, Vol. XII., p. 169., Springer, Wien, 1955.
6. P. Karrer and E. Leumann, *Helv. Chim. Acta* **34** (1951) 1412.
7. P. Karrer and A. Ruegger, *Helv. Chim. Acta* **23** (1940) 955; P. Karrer and R. Morf, *Helv. Chim. Acta* **14** (1931) 833.
8. H. H. Inhoffen, H. Pommer, and E. G. Meth, *Ann.* **572** (1951) 151.
9. O. Isler, M. Montavon, R. Ruegg, and P. Zeller, *Helv. Chim. Acta* **39** (1956) 454.
10. Marshal and Perkin, *J. Chem. Soc.* **57** (1908) 241.
11. J. H. Wotiz and F. A. Miller, *J. Am. Chem. Soc.* **71** (1949) 3441.
12. L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, p. 179, John Wiley and Sons, Inc., New York, 1954.
13. E. J. Hartwell, R. E. Richards, and H. W. Thompson, *J. Chem. Soc.* **1948**, 1436; H. W. Thompson and P. Torkington, *J. Chem. Soc.* **1945**, 640.
14. H. Lindlar, *Helv. Chim. Acta* **35** (1952) 446.
15. F. H. Carr and E. A. Price, *Biochem. J.* **20** (1926) 497.
16. H. R. Cama, F. D. Collins, and R. A. Morton, *Biochem. J.* **50** (1951) 48.
17. R. P. Linstead, J. A. Elvidge, and M. Whalley, *A Course in Modern Techniques of Organic Chemistry*, p. 139—141, Butterworths Scientific Publication, London, 1955.
18. D. Fleš, V. Tomašić, and A. Markovac-Prpić, *Croat. Chem. Acta* **30** (1958) 69.
19. G. E. Eglinton and M. C. Whiting, *J. Chem. Soc.* **1953** 3052.
20. O. Isler, W. Huber, A. Ronco, and M. Kofler, *Helv. Chim. Acta* **30** (1947) 1911.

IZVOD

Sintetske studije u redu poliena. II. Sinteza 15,15'-dihidro- β -karotina

A. Markovac-Prpić i D. Fleš

Kondenzacijom 3,8-dimetil-3,8-dihidroksi-dekadiina-(1,9) (VIa) sa dva mola 4-[2',6',6'-trimetil-cikloheksen-(1')-il]-2-metil-buten-(3)-ala-(1) (C_{14} -aldehid) priređen je 1,18-bis-[2',6',6'-trimetil-cikloheksen-(1')-il]-3,7,12,16-tetrametil-4,7,12,15-tetrahidroksioktadekadien-(1,17)-diin-(5,13) (C_{40} -tetraol VIIa), koji je dehidratacijom i parcijalnom redukcijom pripadnog 1,18-bis-[2',6',6'-trimetil-cikloheksen-(1')-il]-3,7,12,16-tetrametil-oktadekaheksaen-(1,3,7,11,15,17)-diina-(5,13) (X) preveden u 15,15'-dihidro- β -karotin (XI). Meduproducti kao i konačni produkt čišćeni su višestrukum apsorpcionom kromatografijom na neutralnom aluminijskom oksidu, a struktura je utvrđena analitičkim i spektroskopskim metodama. 15,15'-Dihidro- β -karotin je izoliran kao praškasta, žuto-narančasta tvar, koja daje karakteristično obojenje sa Carr-Price-ovim reagensom i pokazuje maksimume apsorpcije u ultraljubičastom svijetlu kod 2880 Å i 3400 Å sa $E_{1\text{ cm}}^{1\%}$ 720 i 1900. Raspored dvostrukih vezova u 15,15'-dihidro- β -karotinu utvrđen je uspoređivanjem UV spektra sa spektrom vitamina A (sl. 3).

ISTRAŽIVAČKI INSTITUT
»PLIVA« TVORNICA FARMACEUTSKIH I
KEMIJSKIH PROIZVODA
ZAGREB

Primljeno 31. svibnja 1960.