residue afforded 17.8 g. of XV, b.p. 77–79° (0.1 mm.); $n_D^{25}$ 1.4590.

*Anal.* Calcd. for $C_{13}H_{26}O$: C, 78.72; H, 13.21. Found: C, 78.46; H, 12.97.

*4-(5-Isopropyl-2-methylcyclopentyl)butanone-2* (Xa). A solution of sodium dichromate (27 g.) and sulfuric acid (23 g.) in water (80 cc.) was added, dropwise, with vigorous stirring, to a solution of crude XV (17.8 g.) in benzene (50 cc.). The reaction temperature increased to 40°. Then the mixture was heated to reflux for 1 hr. The organic layer was separated, washed neutral, dried, and distilled. There were obtained 16 g. of Xa; b.p. 70–73° (0.6 mm.); $n_D^{25}$ 1.4532. It formed a semicarbazone, m.p. 123°, which was unchanged on admixture with the lower melting derivative of X. Further, there was no depression on admixture with the 156° derivative of X. Infrared curves of X and Xa were identical.

*Acknowledgment.* All microanalyses were performed by Dr. A. Steyermark and his staff of these laboratories. Infrared spectra were recorded by Dr. A. Motchane, using a Perkin-Elmer Model 21 spectrophotometer.

NUTLEY, N. J.

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

# Synthesis of Carotene Homologs

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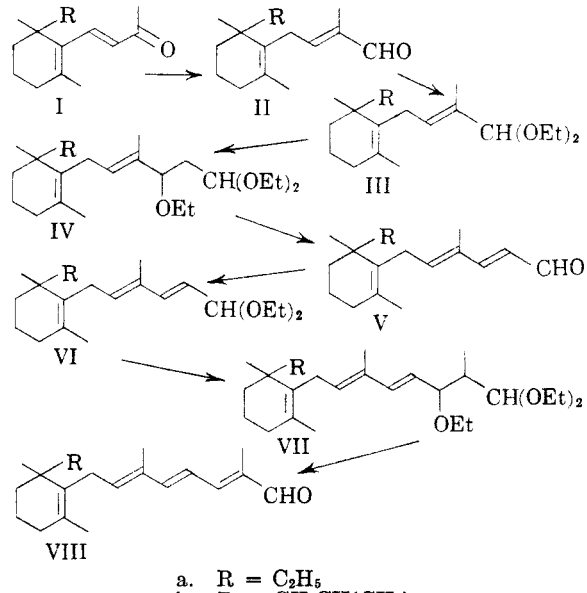
Three new carotene homologs were prepared by total synthesis. A C-41 hydrocarbon, 1-(2,6-dimethyl-6-ethylcyclohexen-1-yl)-18-(2,6,6-trimethylcyclohexen-1-yl)-3,7,12,16-tetramethyloctadecanonene-1,3,5,7,9,11,13,15,17 (XV) and a C-42 hydrocarbon, 1,18-bis(2,6-dimethyl-6-ethylcyclohexen-1-yl)-3,7,12,16-tetramethyloctadecanonene-1,3,5,7,9,11,13,15,-17 (XIa) showed considerable vitamin A activity. A C-46 hydrocarbon, 1,18-bis(2,6-dimethyl-6-isobutylcyclohexen-1-yl)-3,7,12,16-tetramethyloctadecanonene-1,3,5,7,9,11,13,15,17 (XIb) resembled *trans* β-carotene in color and other physical properties but had no vitamin A activity.

In a recent publication by Eugster *et al.*,[1] it was disclosed that 2,2′-dimethyl-β-carotene had about half of the vitamin A activity of β-carotene. The result is rather surprising in view of the fact that other changes in the ionone ring of vitamin A cause almost complete loss of activity.[2] Further study of the carotenoids with respect to relationship of chemical constitution to vitamin A activity aroused our interest. Accordingly, we now wish to report the total synthesis of three such homologs, involving substitution at the geminal methyl groups of the ionone rings.

The new compounds are: a C-41 hydrocarbon, 1-(2,6-dimethyl-6-ethylcyclohexen-1-yl)-18-(2,6,6-trimethylcyclohexen-1-yl)-3,7,12,16-tetramethyloctadecanonene-1,3,5,7,9,11,13,15,17 (XV); a C-42 hydrocarbon, 1,18-bis(2,6-dimethyl-6-ethylcyclohexen-1-yl)-3,7,12,16-tetramethyloctadecanonene-1,3,5,7,9,11,13,15,17 (XIa); and a C-46 compound, 1,18-bis(2,6-dimethyl-6-isobutylcyclohexen-1-yl)-3,7,12,16-tetramethyloctadecanonene-1,3,5,7,9,-11,13,15,17 (XIb). These compounds were prepared by a procedure reported by Isler *et al.*,[3] for the preparation of *trans*-β-carotene.

The appropriate substituted β-ionone[4] (I) was converted to the corresponding substituted C-14 aldehyde (II) by glycidation with ethyl chloroacetate followed by treatment of the glycidic ester with alkali.[5] The aldehyde (II) was converted to its acetal (III) in the conventional manner, and this was condensed with ethyl vinyl ether, in the presence of zinc chloride, to give an ether acetal (IV). When IV was heated with a solution of sodium acetate, water, and acetic acid, ethanol was eliminated from the α,β- position, the acetal was




a. R = $C_2H_5$
b. R = $CH_2CH(CH_3)_2$

(1) C. H. Eugster, A. H. Trivedi, and P. Karrer, *Helv. Chim. Acta*, **38**, 1359 (1955).

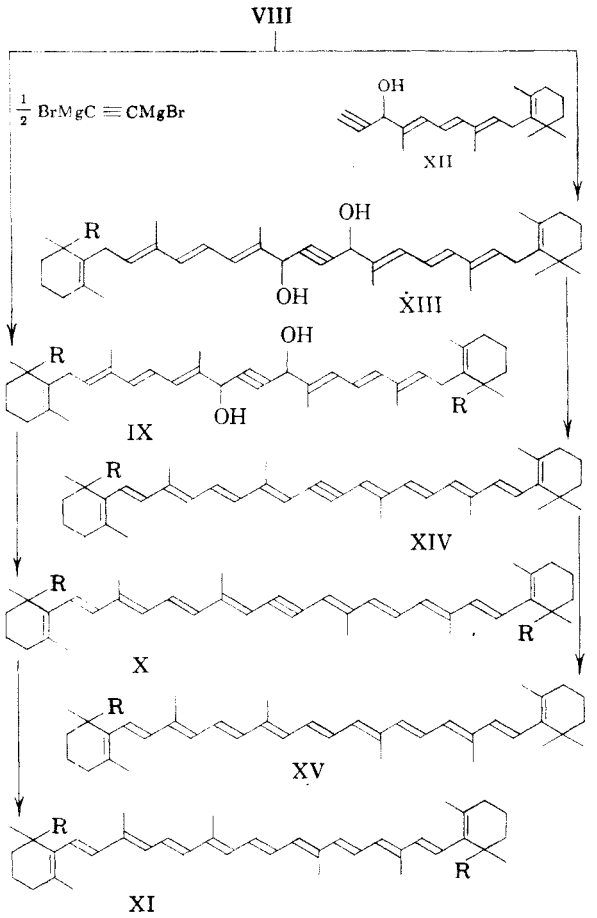
(2) W. Oroshnik, U. S. Patent **2,602,092**, July 1, 1952; B. C. L. Weedon and R. J. Woods, *J. Chem. Soc.*, 2687 (1951).

(3) O. Isler, H. Lindlar, M. Montavon, R. Ruegg, and P. Zeller, *Helv. Chim. Acta*, **39**, 249 (1956).

(4) Preparation to be described in a subsequent publication.

(5) See O. Isler, W. Huber, A. Ronco, and M. Kofler, *Helv. Chim. Acta*, **30**, 1911 (1947).

hydrolyzed, and a crystalline substituted C-16 aldehyde (V) was isolated. Repetition of the sequence of acetalization, vinyl ether condensation, and hydrolysis, but employing ethyl propenyl ether in place of ethyl vinyl ether, resulted in formation of a substituted C-19 aldehyde (VIII).




a. R = $C_2H_5$
b. R = $CH_2CH(CH_3)_2$

The process for conversion of a substituted C-19 aldehyde (VIII) to a symmetrical carotene homolog (XI) commenced with condensation of two moles of VIII with acetylene dimagnesium bromide, whereby the acetylenic diol (IX) was obtained. Rearrangement and, simultaneously, dehydration of IX to the acetylenic hydrocarbon (X) was effected by means of hydrogen chloride in ethanol. Partial hydrogenation of X in the presence of a poisoned palladium catalyst[6] afforded the corresponding ethylenic compound in which the double bond at carbon atom 9 was *cis*. However, this was readily converted to the *trans*-β-carotene homolog (XI) by heating at reflux in normal hexane. Both XIa and XIb were obtained as well defined easily crystallized solid compounds resembling β-carotene in color and crystalline form.

The compounds were readily prepared free of the *cis* form by following the isomerization with a recrystallization from methylene chloride containing a trace of pyridine. These were then checked by ultraviolet absorption spectra. The presence of the *cis* isomer was easily noted by the typical "*cis* peak." Fig. 1 shows the ultraviolet absorption

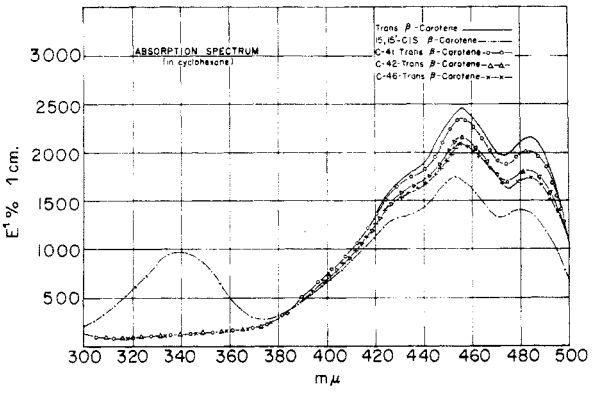



FIGURE 1

spectrum of the new compounds compared with *trans*-β-carotene and *cis*-β-carotene.[7]

The *cis* and *trans* forms of carotene can be also differentiated by the infrared spectrum in the

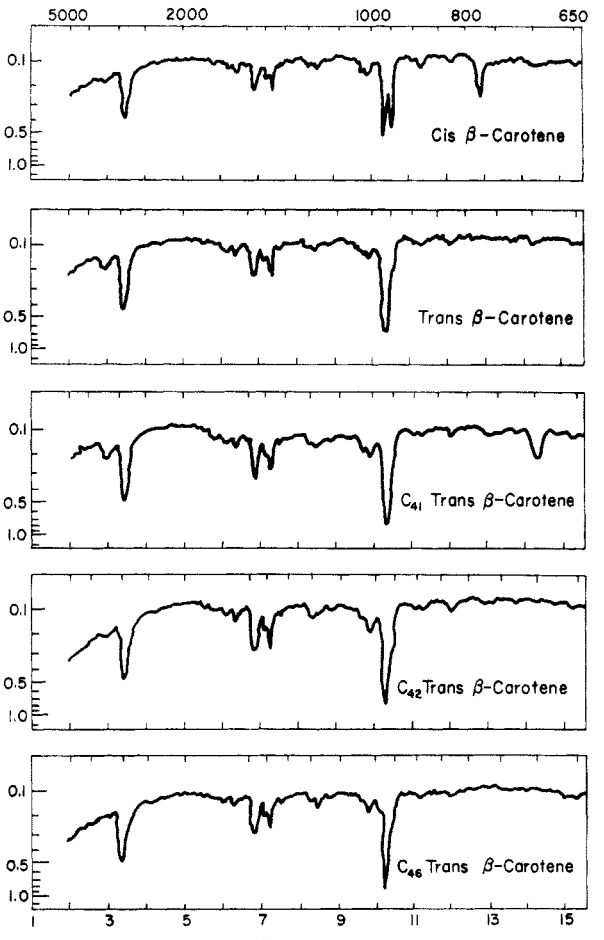
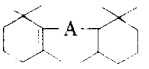
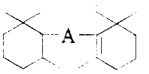
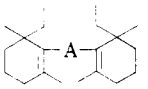
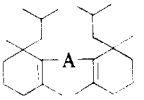


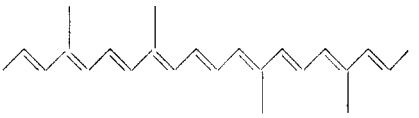

FIGURE 2

(6) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).

(7) The measurements were made with a Beckman spectrophotometer–Model DU.

TABLE I

| Compound | Structure | Vitamin A Liver Storage Assay | Vitamin A Liver and Kidney Storage Assay | Curative Growth Assay |
|---|---|---|---|---|
| β-Carotene |  | 100 | 100 | 100 |
| 1-Desmethyl-1-ethyl-β-Carotene (XV) |  | 53 | 82 | 56 |
| 1,1′-Bisdesmethyl-1,1′-bisethyl-β-Carotene (XIa) |  | 38 | 78 | 41 |
| 1,1′-Bisdesmethyl-1,1′-bisisobutyl-β-Carotene (XIb) |  | 0 | 0 | 0 |

A = 

10.3–10.6 micron range. The infrared curves are shown by Fig. 2.[8]

The unsymmetrical carotene homolog (XV) was obtained from the substituted C-19 aldehyde (VIIIa) by a slightly different sequence. A C-21 acetylenic carbinol (XII)[3] (obtained by reaction of C-19 aldehyde with lithium acetylide) was treated with two moles of ethyl magnesium bromide, and to the resultant Grignard complex was added VIIIa, whereby the unsymmetrical acetylenic diol (XIII) was obtained. Conversion of the diol to the acetylenic hydrocarbon (XIV) and thence to the β-carotene homolog (XV) paralleled the preparation of the corresponding symmetrical homolog (XI). The unsymmetrical compound (XV) was also an easily crystallized relatively stable substance, with a color similar to that of β-carotene.

*Solubility*[9] *and biological activity.*[10] Samples of the C-41, C-42, and C-46 carotenoids were tested for biological activity by comparison to all-*trans*-β-carotene[11] using the rat liver storage[12,13] and curative growth assays. Kidney levels of vitamin A were also measured. Very similar results were obtained by the liver storage and curative growth methods. Although higher results were obtained using the combined liver and kidney vitamin A storage data, the biological activities must be assessed by the results of the curative growth test. The results are given in Table I.

Since the low solubility of *trans*-β-carotene, in edible oils, sometimes poses a problem for its application as a pigment, the solubilities of these carotene homologs in a variety of oils and solvents, were also determined.[14] The relative solubility in fifteen solvents are recorded in Table III.

It is interesting to observe that the vitamin A activity decreases with increasing substitution of the geminal methyl groups. Furthermore, this decrease in activity cannot be accounted for solubility characteristics because solubilities of our carotenoids increase with increasing substitution.

*Dependence of vitamin A activity on chemical structure.* The relative stability, crystalline nature, and ease of purification and characterization of synthetic carotenoids, compared with corresponding vitamin A homologs, make them attractive for study of the relationship between vitamin A activity and chemical structure. A comparison of the activities of the homologs reported in this paper with those previously reported for various other carotenoids, in which chemical changes have been introduced into the ionone rings, is presented in Table II.

3,4-Dehydro-β-carotene, 1-desmethyl-1-ethyl-β-carotene (XV) and cryptoxanthin would be expected to exhibit biological activity since the vitamin A moiety constitutes half of the molecule. However, even with compounds substituted in both ionone rings, such as 2,2′-dimethyl-β-carotene, and 1,1′-bisdesmethyl-1,1′-bisethyl-β-carotene (XIa), there is still considerable activity. This is true also of the compound containing an additional double bond in each ionone ring, 3,4,3′,4′-bisdehy-

(8) The infrared curves were made with potassium bromide disks by a Model 21 double beam spectrophotometer, Perkins–Elmer Corp.

(9) We are indebted to Dr. J. C. Bauernfeind for the solubility results.

(10) For determination of biological activities we are indebted to Mr. E. De Ritter of our Nutrition Department.

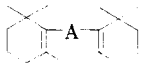
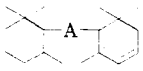
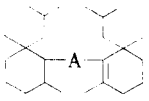
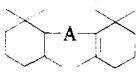
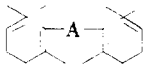
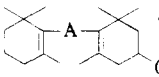
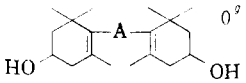
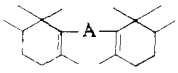
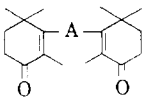
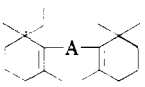
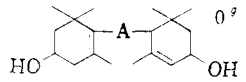
(11) Equimolar comparison to all *trans*-β-carotene.

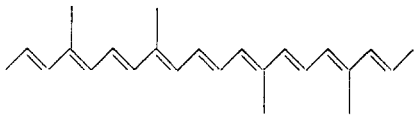
(12) J. R. Foy and K. Morgareidge, *Anal. Chem.*, **20**, 304 (1948).

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

(14) Details are given in the Experimental Part.

TABLE II

| Name | Structure | Activity[a] | Name | Structure | Activity[a] |
|---|---|---|---|---|---|
| β-Carotene |  | 100% | 3,4,3′,4′-Bisdehydro-β-Carotene |  | 38%[b,c,e] |
| 3,4-Dehydro-β-Carotene |  | 75%[b] | 1,1′-Bis-desmethyl-1,1′-Bis-isobutyl-β-Carotene (XIb) |  | 0 |
| 1-Desmethyl-1-Ethyl-β-Carotene (XV) |  | 56% | Lycopene |  | 0[f] |
| Cryptoxanthin |  | 50%[c] | Zeaxanthin |  | 0[g] |
| 2,2′-Dimethyl-β-Carotene |  | 50%[d] | Canthaxanthin |  | 0[h] |
| 1,1′-Bisdesmethyl-1,1′-Bisethyl-β-Carotene (XIa) |  | 41% | Xanthophyll |  | 0[g] |

A = 

[a] Activity in rats compared with β-carotene. [b] *Helv. Chim. Acta*, **39**, 274 (1956). [c] *Arch. Biochem.*, **7**, 447 (1945). [d] Ref. (1). [e] *Ann.*, **594**, 165 (1955). [f] *Helv. Chim. Acta*, **33**, 1349 (1950); *Helv. Chim. Acta*, **39**, 463 (1956). [g] *Helv. Chim. Acta*, **17**, 24 (1934). [h] *Biochem. J.*, **57**, 223 (1954).

dro-β-carotene. However, if the ionone rings are opened, as in lycopene, or if functional groups are introduced, as in zeaxanthin, canthaxanthin, or xanthophyll, there is complete loss of activity.

## EXPERIMENTAL[15]

*4-(2,6-Dimethyl-6-ethylcyclohexen-1-yl)-2-methylbuten-2-al-1* (IIa). 5-l. three-neck flask, equipped with an efficient stirrer, was charged with 4-(2,6-dimethyl-6-ethylcyclohexen-1-yl)-buten-3-one-2 (Ia)[4] (576.1 g.), ethyl chloroacetate (685 g.) and methanol (216 cc.). The solution was cooled to −20° and sodium methylate (377 g.) was added in small portions during 2 hr. The reaction temperature was maintained at −5° to −10° during the addition, and stirring was continued for an additional hour at 0°. Then, a solution of sodium hydroxide (278 g.) in methanol (1980 cc.) was cooled to 15°, and was poured, with stirring, into the reaction mixture. This caused an increase in temperature to 20°. Water (5 l.) was added, and stirring was continued for 1 hr. Finally, the product was extracted with petroleum ether, washed neutral, and isolated by distillation. IIa was obtained at b.p. 110° (0.35 mm.); $n_D^{25}$ 1.5112; yield, 514.8 g. (83.7%).

*Anal.* Calcd. for $C_{15}H_{24}O$: C, 81.77; H, 10.98. Found: C, 81.59; H, 10.60.

*6-(2,6-Dimethyl-6-ethylcyclohexen-1-yl)-4-methylhexadien-2,4-al-1* (Va). IIa was converted to its acetal (IIIa) by stirring for 4 hr., at 20–25°, a solution of IIa (292 g.), ethyl orthoformate (240 g.), and *p*-toluenesulfonic acid (0.3 g.) in ethanol (40 cc.). The mixture was allowed to stand overnight, and then a solution of zinc chloride (4 g.) in acetic acid (240 cc.) was added. The reaction flask was cooled by an ice bath and ethyl vinyl ether (112 g.) was introduced at 5–10° during 1 hr. Stirring was continued overnight at the same temperature. The product, 6-(2,6-dimethyl-6-ethylcyclohexen-1-yl)-4-methyl-1,1,3-triethoxyhexene-4 (IVa) was not isolated.

To the reaction mixture was added a solution of sodium acetate (160 g.) in water (120 cc.) and acetic acid (1000 cc.). The apparatus was arranged for distillation, and the solution was heated to 95–100° for 3 hr., whereby the low boiling components were eliminated. The residue was allowed to cool, and was diluted with water (1500 cc.). The oil layer was separated, dissolved in methanol (250 cc.), and was cooled to −10°, whereby the product crystallized. Recrystallization from petroleum ether afforded the aldehyde (Va) in yield of 189 g. (76%), as white crystals; m.p. 49–50°; $\epsilon$ = 29,480 at 284 mμ (95% ethanol).

*Anal.* Calcd. for $C_{17}H_{28}O$: C, 82.88; H, 10.64. Found: C, 83.16; H, 10.28.

*8-(2,6-Dimethyl-6-ethylcyclohexen-1-yl)-2,6-dimethyloctatrien-2,4,6-al-1* (VIIIa). The acetal 6-(2,6-dimethyl-6-ethylcyclohexen-1-yl)-1,1-diethoxy-4-methylhexadiene-2,4 (VIa) was obtained by stirring a solution of Va (50 g.), ethyl orthoformate (38 cc.), and *p*-toluenesulfonic acid (0.15 g.) in ethanol (16 cc.) for 18 hr. at room temperature. The mixture was cooled to 5°, and a solution of zinc chloride (1 g.) in acetic acid (110 cc.) was added, followed by dropwise addition of ethyl propenyl ether (29 cc.) during 1 hr. The reaction mixture was maintained at 5–10° for 18 hr. The resultant ether acetal (VIIa) was not isolated, but was used directly for the next step.

A solution of sodium acetate (33 g.) in water (25 cc.) and acetic acid (200 cc.) was introduced into the reaction flask and the mixture heated at 90–95° for 3 hr. in a nitrogen

(15) Boiling and melting points are uncorrected. The melting points were determined in vacuum capillaries.

atmosphere. The solution was allowed to cool and was diluted with water, whereby an oil separated. It was washed with water, and was ultimately crystallized by dissolving in petroleum ether (100 cc.) and cooling to −20°. Repeated recrystallization afforded the C-20 aldehyde (VIIIa) as white crystals; yield, 25.8 g. (45%); m.p. 39–40°; $\epsilon$ = 43,420 at 329 m$\mu$ (95% ethanol).

*Anal.* Calcd. for $C_{20}H_{30}O$: C, 83.86; H, 10.55. Found: C, 83.84; H, 10.30.

*4,8-Dimethyl-10-(2,6,6-trimethylcyclohexen-1-yl)-decatrien-4,6,8-yne-1-ol-3* (XII). This compound was obtained by the action of lithium acetylide on 2,6-dimethyl-8-(2,6,6-trimethylcyclohexen-1-yl)-octatrien-2,4,6-al-1 (VIII, R = H) as described by Isler *et al.*[3]; yield, 80%; b.p. 100° (0.025 mm.); $n_D^{25}$ 1.5750.

*1-(2,6-Dimethyl-6-ethylcyclohexen-1-yl)-18-(2,6,6-trimethylcyclohexen-1-yl)-3,7,12,16-tetramethyloctadecahexen-2,4,6,12,14,16-yn-9-diol-8,11* (XIII). To ethylmagnesium bromide, prepared in the usual manner from magnesium turnings (5.0 g.), ethyl bromide (27 g.), and ether (100 cc.), was added, dropwise, a solution of XII (27 g.) in ether (50 cc.). The mixture was heated to reflux for 3 hr. Then, VIIIa (26.5 g.) in ether (100 cc.) was introduced, and refluxing was continued for 2 hr. The resultant Grignard complex was poured, cautiously, onto crushed ice (500 g.), and dilute (5%) sulfuric acid was added until the mixture was faintly acid. The ether solution of the diol was separated, washed to neutrality, and dried over calcium chloride. Removal of the solvent by distillation *in vacuo* afforded the C-41 diol, XIII, as a waxy, yellow solid, in quantitative yield. The crude product was of sufficient purity for use in the next step.

*1-(2,6-Dimethyl-6-ethylcyclohexen-1-yl)-18-(2,6,6-trimethylcyclohexen-1-yl)-3,7,12,16-tetramethyloctadecaocten-1,3,5,7,11,13,15,17-yne-9* (XIV). The crude diol (XIII) was dissolved in ethyl acetate (400 cc.) and ethanol (80 cc.), and to it was added a solution (40 cc.) of 6*N* hydrogen chloride in ethanol. After several minutes, crystals of the acetylenic hydrocarbon (XIV) appeared. The mixture was stirred for about 30 min., and was then stored overnight at 0°. Finally, the product was filtered in an inert atmosphere, and was washed successively with cold alcohol, water, and cold alcohol again. There was obtained, in this manner, 34.8 g. (70%) of XIV, m.p. 136°. Recrystallization from ethyl acetate afforded a product of m.p. 142°.

*Anal.* Calcd. for $C_{41}H_{56}$: C, 89.72; H, 10.28. Found: C, 89.61; H, 10.34.

*1-(2,6-Dimethyl-6-ethylcyclohexen-1-yl)-18-(2,6,6-trimethylcyclohexen-1-yl)-3,7,12,16-tetramethyloctadecanonene-1,3,5,7,9,11,13,15,17* (XV). A suspension of XIV (10 g.) in hexane (100 cc.) was hydrogenated in the presence of a poisoned palladium catalyst[6] until one molar equivalent of hydrogen was consumed. The suspension was heated to boiling before filtration of the catalyst, and the latter was washed thoroughly with additional portions of hot hexane. Finally, the filtrate was concentrated until a pasty mass remained. This was heated at 90° for 16 hr. in an inert atmosphere to effect a transformation to the *trans* compound. Filtration, and recrystallization from benzene-methanol, afforded 7.0 g. (70%) of XV, m.p. 168°.

$\lambda_{max}$ 455–456 m$\mu$ ($E^{1\%}_{1\,cm}$ 2350); $\lambda_{max}$ 484–486 m$\mu$ $E^{1\%}_{1\,cm}$ 2010). (Cyclohexane).

*Anal.* Calcd. for $C_{41}H_{58}$: C, 89.39; H, 10.61. Found: C, 89.17; H, 10.51.

*1,18-Bis(2,6-dimethyl-6-ethylcyclohexen-1-yl)-3,7,12,16-tetramethyloctadecahexen-2,4,6,12,14,16-yn-9-diol-8,11* (IXa). Ethynbis(magnesium bromide) was prepared[16] by bubbling dry acetylene for 20 hr. into the Grignard reagent from magnesium (12 g.), ethyl bromide (65 g.), and ether (250 cc.). A solution of VIIIa (60 g.) in ether (150 cc.) was added rapidly, and the mixture was heated to reflux for 2 hr. The resultant complex was decomposed by pouring onto ice and acidifying with dilute (5%) sulfuric acid. The ether layer was separated, was washed with sodium bicarbonate solution and then with water until neutral, and was dried over calcium chloride. Upon removal of the ether *in vacuo* there remained 63 g. of crude IXa, a white, waxy solid which was used in the next step without further purification.

*1,18-Bis(2,6-dimethyl-6-ethylcyclohexen-1-yl)-3,7,12,16-tetramethyloctadecaocten-1,3,5,7,11,13,15,17-yne-9* (Xa). By the same procedure described for the preparation of XIV, there was obtained from the crude diol, IXa, the acetylenic hydrocarbon, Xa, in yield of 37.7 g. (64%); m.p. (from ethyl acetate), 128°.

*Anal.* Calcd. for $C_{42}H_{58}$: C, 89.61; H, 10.39. Found: C, 89.84; H, 10.25.

*1,18-Bis(2,6-dimethyl-6-ethylcyclohexen-1-yl)-3,7,12,16-tetramethyloctadecanonene-1,3,5,7,9,11,13,15,17* (XIa). Xa was hydrogenated to the corresponding *cis* carotenoid as described for XV, and conversion to the *trans* compound, XIa, was effected by heat. XIa was obtained in yield of 75.8%, m.p. 162°.

$\lambda_{max}$ 456 m$\mu$ ($E^{1\%}_{1\,cm}$ 2170); $\lambda_{max}$ 483–484 m$\mu$ ($E^{1\%}_{1\,cm}$ 1800) (Cyclohexane).

*Anal.* Calcd. for $C_{42}H_{60}$: C, 89.29; H, 10.71. Found: C, 89.42; H, 10.47.

*4-(2,6-Dimethyl-6-isobutylcyclohexen-1-yl)-2-methylbuten-2-al-1* (IIb). This was obtained, in the same manner as IIa, from 4-(2,6-dimethyl-6-isobutylcyclohexen-1-yl)-buten-3-one-2 (Ib)[4] (542 g.) and chloroacetic ester (644 g.) in yield of 389 g. (67.7%); b.p. 117° (0.45 mm.); $n_D^{25}$ 1.506.

*Anal.* Calcd. for $C_{17}H_{28}O$: C, 82.19; H, 11.36. Found: C, 82.02; H, 11.18.

*6-(2,6-Dimethyl-6-isobutylcyclohexen-1-yl)-4-methylhexadien-2,4-al-1* (Vb). The acetal (IIIb) was obtained from IIb (160 g.) and orthoformic ester (120 g.), and was converted to the ether acetal IVb, and thence to the unsaturated aldehyde (Vb) in the same manner described for preparation of Va from IIa. The C-19 aldehyde (Vb) was obtained in yield of 139 g. (78.6%) with m.p. 48–52°. After repeated recrystallization from petroleum ether, the m.p. was 55–56°; $\epsilon$ 29,350 at 283–284 m$\mu$ (95% ethanol).

*Anal.* Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 82.97; H, 10.68.

*8-(2,6-Dimethyl-6-isobutylcyclohexen-1-yl)-2,6-dimethyloctatrien-2,4,6-al-1* (VIIIb). By the same procedure previously described for the preparation of VIIIa from Va, there was obtained from Vb (55 g.) using the processes of acetalization, condensation with ethyl propenyl ether (29 cc.) and hydrolysis, the C-22 unsaturated aldehyde (VIIIb). The product was crystallized from petroleum ether after long cooling in a Dry Ice–acetone bath. However, the crystals melted below room temperature. Therefore, the product was again cooled, and was filtered rapidly through a cooled sintered glass funnel. Then the crystals were allowed to melt, and the yellow oil was dried *in vacuo;* yield, 44 g. (70%). The product was purified further by distillation; b.p. 110° (0.025 mm.); $n_D^{25}$ 1.5795; ultraviolet max. at 328–329 m$\mu$ (95% ethanol).

*Anal.* Calcd. for $C_{22}H_{34}O$: C, 84.01; H, 10.90. Found: C, 83.94; H, 10.68.

*1,18-Bis(2,6-dimethyl-6-isobutylcyclohexen-1-yl)-3,7,12,16-tetramethyloctadecahexen-2,4,6,12,14,16-yn-9-diol-8,11* (IXb). In similar fashion to the preparation of IXa, there was obtained by the action of VIIIb (65 g.) on the ethynbis-(magnesium bromide) from 12 g. of magnesium, a yellow waxy product (IXb) in yield of 68 g. This crude diol was of sufficient purity for use in the next step.

*1,18-Bis(2,6-dimethyl-6-isobutylcyclohexen-1-yl)-3,7,12,16-tetramethyloctadecaocten-1,3,5,7,11,13,15,17-yne-9* (Xb). The crude diol (IXb) (above), was dissolved in ethyl acetate (500 cc.) and ethanol (100 cc.), and was treated with 6*N* hydrogen chloride in ethanol (50 cc.). By working up in the

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TABLE III

| Solvent | Solubility, g./100 g. *Trans*-β-Carotene | C-41 *Trans*-β Carotene | C-42 *Trans*-β-Carotene | C-46 *Trans*-β-Carotene |
|---|---|---|---|---|
| Corn oil | 0.053 | 0.064 | 0.071 | 0.177 |
| Cottonseed oil | 0.060 | 0.063 | 0.068 | 0.210 |
| Olive oil | 0.053 | 0.065 | 0.069 | 0.192 |
| Safflower oil | 0.049 | 0.063 | 0.067 | 0.175 |
| Glyceryl trioleate | 0.059 | 0.069 | 0.082 | 0.224 |
| Preinoleyl alcohol | 0.049 | 0.013 | 0.023 | 0.170 |
| Aldol 40 | ... | 0.013 | 0.034 | ... |
| Aldol 11 | 0.025 | 0.033 | 0.042 | 0.315 |
| Ethyl laurate | 0.180 | 0.180 | 0.199 | 0.250 |
| Ethyl oleate | 0.082 | 0.132 | 0.161 | 0.287 |
| Ethyl myristate | 0.096 | 0.174 | 0.177 | ... |
| Ethyl acetate | 0.057 | 0.075 | 0.102 | ... |
| Propylene glycol | Trace | Trace | Trace | Trace |
| 95% Ethanol | 0.0021 | 0.0019 | 0.0018 | ... |
| Aldol 10 | 0.025 | 0.033 | 0.041 | 0.087 |
| Solubility ratio | 1.0 | 1.2 | 1.3 | 3.5 |

same manner as XIV, there was obtained Xb in yield of 39 g. (61%); m.p. (from ethyl acetate), 154°.

*Anal.* Calcd. for $C_{46}H_{68}$: C, 89.25; H, 10.75. Found: C, 89.12; H, 10.61.

*1,18-Bis(2,6-dimethyl-6-isobutylcyclohexen-1-yl)-3,7,12,16-tetramethyloctadecanonene-1,3,5,7,9,11,13,15,17* (XIb). This compound was prepared in the same manner as XV in yield of 80%, m.p. 164° (from benzene methanol); $\lambda_{max}$ 457 mμ ($E^{1\%}_{1\,cm.}$ 2090); 485–486 mμ ($E^{1\%}_{1\,cm}$ 1650) in cyclohexane.

*Anal.* Calcd. for $C_{46}H_{68}$: C, 88.96; H, 11.04. Found: C, 88.73; H, 10.61.

*Determination of carotenoid solubilities.* The relative solubilities for our synthetic homologs and for carotene, in 15 different solvents, were compared. The solubilities were determined by agitating an excess of the crystalline compound with the desired solvent in a 5-cc. screwcap vial sealed under carbon dioxide for 5 days[17] in a rotating shaker (30 r.p.m.). The samples were then centrifuged, and the supernatant liquid was analyzed by ultraviolet spectroscopy. The results are given in Table III.

*Acknowledgment.* Microanalyses were made by Dr. A. Steyermark and his staff of these laboratories. Ultraviolet and infrared spectra were taken by Dr. F. Forrester of these laboratories.

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(17) A. A. Mikhailovinina and B. G. Savinov, *Ukrain. Khim. Zhur.*, **16**, 183–7 (1950).

[CONTRIBUTION FROM BAKER LABORATORY, CORNELL UNIVERSITY]

# Derivatives of Homopseudopelletierine: Completely Enolic β-Ketoesters

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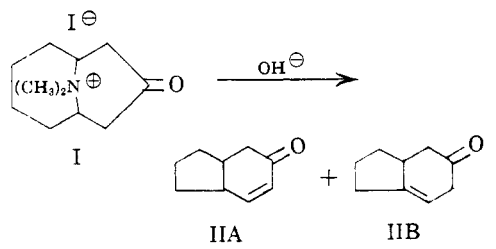
Syntheses of the homopseudopelletierine derivatives IIIC, VIIIB, and VIIIC are described. The infrared spectra of these compounds show them to be completely enolized, both in the solid state and in solution. This conclusion is supported by ultraviolet spectral data.

The degradative rearrangement of homopseudopelletierine methiodide (I) in base has been shown to yield the hydrindenone, IIA, along with an isomeric product, probably IIB.[2] Three types of mechanism have been suggested to rationalize this transformation.[2] None of these mechanisms could be operative in the case of the dibenzo derivative of I (IIIA), and it was therefore hoped that this compound might give rise to the unrearranged structure IV under elimination conditions. Efforts to prepare IIIA in order to test this reasoning have been unsuccessful and have now been discontinued. We wish, however, to report some incidental findings related to this problem.




I IIA IIB

The synthesis of compounds of the type III *via* the Robinson-Schöpf biogenetic technique required

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(2) J. Meinwald and M. Koskenkyla, *Chemistry & Industry*, 476 (1955).