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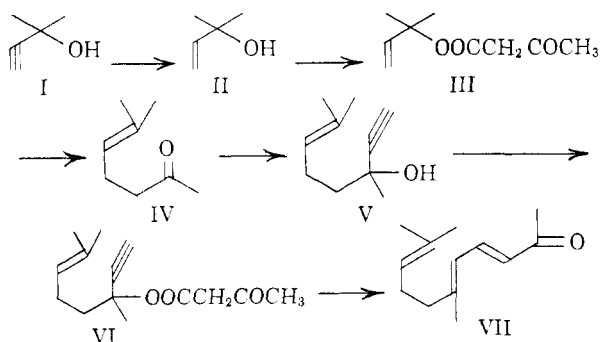
Total Synthesis of Pseudoionone and an Isomeric Ketone

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GEORGE O. CHASE, AND ALFRED OFNER

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A practical total synthesis of pseudoionone, from acetone, is described. The key step is a pyrolytic rearrangement of a disubstituted propargyl acetoacetate (dehydrolinalyl acetoacetate) to pseudoionone. In addition, an isomeric ketone is obtained, which has been identified as 4-(5-isopropenyl-2-methylcyclopenten-1-yl)butanone-2. A mechanism is suggested for the novel rearrangement.

A key starting material for the commercial production of vitamin A¹ (and of various carotenoids) is pseudoionone (VII), which is ordinarily prepared by the condensation of acetone with citral.² The source of the latter, a C-10 unsaturated aldehyde, is lemon grass oil, a natural product which varies widely in purity, availability, and price. In an attempt to eliminate this dependence on a natural product, a program was initiated to obtain a reasonably inexpensive synthesis for citral or pseudoionone. We now wish to report a practical synthesis for the latter, starting from acetone, and employing a novel rearrangement of a propargylic acetoacetate.



Synthesis of pseudoionone. 2-Methyl-3-butyn-2-ol (I) was obtained by condensation of acetone with

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

(2) A. Russell and R. L. Kenyon, *Org. Syntheses*, **23**, 78 (1943).

sodium acetylide,³ and was hydrogenated to the vinyl carbinol (II) in the presence of Lindlar catalyst.⁴ 2-Methyl-3-buten-2-yl acetoacetate (III) was prepared by the reaction of diketene with II. This reaction was effected, in virtually quantitative yield, at 25–30° in the presence of catalytic quantities of the sodium salt of II or sodium methoxide.⁵ Pyrolysis of III at 140–160° caused rearrangement to 6-methyl-5-hepten-2-one (IV), with simultaneous evolution of carbon dioxide. This allylic rearrangement represents an application of the reaction reported by Kimel and Cope in 1943.⁵ We have found that the yields of γ,δ -unsaturated ketones produced in this type of reaction may be increased by conducting the pyrolysis of the acetoacetate in the presence of small amounts of an aluminum alkoxide. In this instance, IV was obtained from III in 83% yield.

Ethynylation of IV afforded the acetylenic carbinol, dehydrolinalool (V).⁶ This was converted to dehydrolinalyl acetoacetate, VI, by reaction with diketene. On pyrolysis of VI at 170–190°, carbon dioxide was evolved and a mixture of ketones was produced. The chief product was pseudoionone

(3) (a) J. F. Froning and G. F. Hennion, *J. Am. Chem. Soc.*, **62**, 653 (1940); (b) cf. also H. S. Taylor and W. J. Shenk, *J. Am. Chem. Soc.*, **63**, 2756 (1941).

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

(5) W. Kimel and A. C. Cope, *J. Am. Chem. Soc.*, **65**, 1992 (1943).

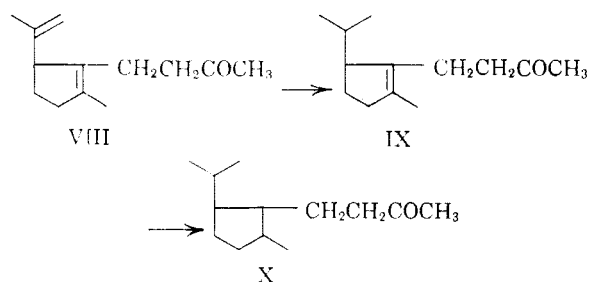
(6) L. Ruzicka and V. Fornasir, *Helv. Chim. Acta*, **2**, 182 (1919); cf. also H. Rupe and G. Lang, *Helv. Chim. Acta*, **12**, 1933 (1929).

(VII) and there was obtained also another ketone of the same empirical formula. The over-all yield of pseudoionone from acetone was about 35%. Considering the ready availability of inexpensive starting materials, this yield is sufficient to make the method attractive as a source of pseudoionone.

Structure of the isomeric ketone. Pyrolysis of dehydrolinalyl acetoacetate afforded, in addition to pseudoionone, another ketone, $C_{13}H_{20}O$, in appreciable quantities. The product was a methyl ketone, since iodoform was obtained on treatment with hypiodite. Total hydrogenation disclosed the presence of two double bonds, in addition to the ketone function. One double bond was easily hydrogenated, while the second was reduced with more difficulty. Further, the absence of any characteristic absorption in the ultraviolet indicated that the double bonds were neither conjugated with each other nor with the carbonyl group.

Ozonolysis of the ketone produced formaldehyde and no acetone—evidence of a methyldiene double bond. This was confirmed by the infrared spectrum (absorption at 1640, 887, and 3060 cm^{-1}). The absence of out-of-plane deformation frequencies in the 800 to 840 cm^{-1} range suggested that the second double bond was tetrasubstituted.⁷

These data (and the molecular refraction) were indicative of a monocyclic ketone. Numerous attempts at dehydrogenation (to an aromatic compound) of the hydrocarbon, $C_{13}H_{22}$, obtained by Wolff-Kishner reduction of the ketone, were unsuccessful. Thus, the possibility that the ketone was a cyclohexene derivative was rejected. From all the above-mentioned data, and in consideration of its formation from VI, formula VIII, with a cyclopentene ring, was deemed probable for the isomeric ketone.⁸ Its di- and tetra-hydro derivatives would be IX and X, respectively.

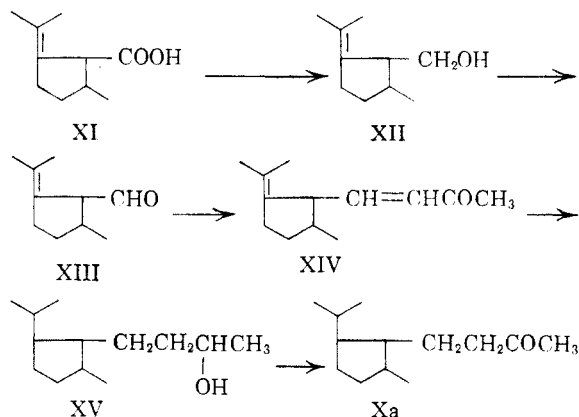


The structure for X, and thus, indirectly, for VIII, was confirmed by an independent synthesis of X starting with pulegenic acid, XI.⁹

(7) We are indebted to Dr. F. Forrester of these laboratories for help in interpretation of infrared data.

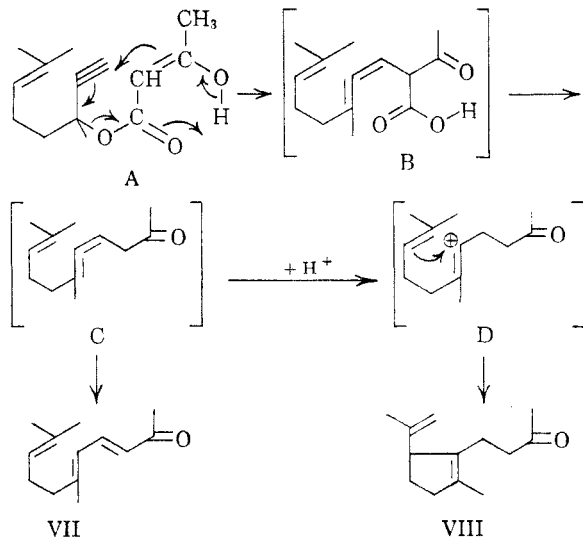
(8) The presence of a cyclopentenyl ring and the nature of the ketonic side chain were demonstrated by G. Saucy *et al.*, Roche Labs., Basle, Switzerland, from physical data and degradation experiments; to be published independently.

(9) H. Rupe and K. Schafer, *Helv. Chim. Acta*, 11, 463 (1928).



Pulegenic acid (XI) was reduced with lithium aluminum hydride to the corresponding alcohol (XII), and the latter was oxidized by chromic acid to the aldehyde (XIII). Condensation of XIII with acetone in the presence of alkali afforded the C-13 ketone (XIV). Hydrogenation of XIV with Pt-C at elevated pressure caused formation of the saturated carbinol (XV). Oxidation of XV gave the saturated ketone (Xa). This was proved identical with our tetrahydroketone (X) by mixed melting point of a derivative,¹⁰ and by identity of the infrared curves.

Mechanism of the reaction. Pyrolysis of dehydrolinalyl acetoacetate (as well as other substituted propargyl acetoacetates¹¹) results in formation of products in which inversion of the original propargyl group has occurred. This conforms with the findings for the corresponding allylic compounds,⁵ and hence the reaction is visualized as occurring by an intramolecular cyclic mechanism analogous to that proposed for the allylic rearrangement.



(10) It is worth noting that semicarbazones of the optically active Xa and racemic X have the same melting point.

(11) W. Kimel and N. W. Sax, U. S. Patent 2,661,368 (Dec. 1, 1953), and other unpublished results; *cf.* also R. N. Lacey, *J. Chem. Soc.*, 827 (1954); G. I. Samokhvalov, M. A. Miropolskaya, and N. A. Preobraghenskii, *Doklady Akad. Nauk U.S.S.R.*, 107, 103 (1956).

In this sequence, the starting material is represented in its enolic form (A). Under the influence of heat, the α -carbon atom of the substituted propargyl group becomes detached from the ester oxygen atom, and the propargylic γ -carbon atom becomes attached to the central methylene carbon atom of the acetoacetic ester. Simultaneously, electron pairs shift as illustrated to produce the substituted acetoacetic acid (B). The latter immediately decarboxylates to the allenic ketone (C). Presumably, this allenic compound is quite labile and rearranges, for the most part, to the more stable conjugated configuration represented by pseudoionone (VII).

Formation of the cyclopentene derivative (VIII) may commence with addition of a proton to the allenic intermediate C to give a carbonium ion D. This cyclizes, in a concerted fashion, with loss of a proton, whereby the isomeric ketone, VIII, is obtained.

Such a cyclic mechanism accounts well for the inversion of the substituted propargyl group which occurs. However, we have no assurance that such a mechanism is a necessary requisite for the reaction, especially since no allenic compounds were isolated.

Formation of pseudoionone from dehydrolinalyl acetoacetate is representative of a general reaction whereby unsaturated ketones are produced by pyrolysis of disubstituted propargyl acetoacetates.¹¹ Similar results are obtained by heating the corresponding propargyl-type alcohols with acetoacetic ester.¹² However, we would interpret this latter reaction as proceeding first by a trans-esterification to the propargyl acetoacetate, and then rearrangement of the ethynyl carbonyl ester.

EXPERIMENTAL¹³

2-Methyl-3-butyn-2-ol (I). This compound was prepared as described by Froning and Hennion.³ It was obtained in 90% yield; b.p. 104°; n_D^{25} 1.4182.

2-Methyl-3-buten-2-ol (II).¹⁴ To a solution of I (336 g., 4.0 moles) in an equal volume of petroleum ether were added quinoline (16.8 g.) and Lindlar catalyst⁴ (30 g.). The mixture was cooled to 10° and was shaken in a hydrogen atmosphere until four moles of hydrogen were consumed (about 3–5 hr.). Absorption of hydrogen had declined markedly at that point. The product was isolated by fractional distillation from a Fenske-type column packed with glass helices. II was obtained in yield of 323.3 g. (94%); b.p. 97–98°; n_D^{25} 1.4141; d_4^{25} 0.8200.

2-Methyl-3-buten-2-yl acetoacetate (III).¹⁵ To a solution of

II (430 g., 5.0 moles) in an equal volume of toluene was added sodium methoxide (5.0 g.). Diketene (462 g., 5.5 moles) was added, dropwise, during 2 hr. The reaction temperature was maintained at 25–30° by external cooling. The solution was stirred until there was no further evidence of heat evolution (about 5 hr.). Then the mixture was worked up by washing successively with dilute sulfuric acid, saturated sodium bicarbonate solution, and finally with water until neutral. Distillation at diminished pressure afforded III in yield of 825 g. (97%); b.p. 82–84° (8 mm.); n_D^{25} 1.4372; d_4^{25} 0.9850; M_D calcd. (keto form) 44.96, (enol form) 46.01, found 45.27.

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.55; H, 8.24. Found: C, 63.50; H, 8.24.

6-Methyl-5-hepten-2-one (IV).¹⁶ A 2-l. three necked flask, equipped with mechanical stirrer, thermometer, and condenser connected at the top to a gas meter *via* a Dry Ice trap, was charged with III (510 g., 3.0 moles) and aluminum isopropoxide (8.7 g.). The mixture was stirred vigorously and was heated to 140–160° for 5 hr., during which time 2.14 cu. ft. (90%) of carbon dioxide was evolved. Distillation of the residue afforded 314 g. (83%) of IV, b.p. 58–59° (10 mm.); n_D^{25} 1.4372; d_4^{25} 0.8610; 2,4-dinitrophenylhydrazone, m.p. 86–87°; semicarbazone, m.p. 135–136°. These physical constants are in agreement with those previously reported for this ketone.¹⁷

Dehydrolinalool (V). This compound was prepared essentially as described by Ruzicka and Fornasir,⁶ yield from IV, 95%; b.p. 88–90° (14 mm.); n_D^{25} 1.4608.

Dehydrolinalyl acetoacetate (VI). By the same procedure described above for the preparation of III, there was obtained from V (760 g., 5.0 moles) and diketene (462 g., 5.5 moles) a quantitative yield (1180 g.) of VI. The undistilled product was of sufficient purity for use in the next step. However, it could be distilled, in high vacuum, as a colorless liquid; 43–46° (0.007 mm.); n_D^{25} 1.4652; d_4^{25} 0.9785; M_D calcd. (keto form) 66.07, (enol form) 67.11, found 66.78.

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.32; H, 8.74.

Pseudoionone (VII). In an apparatus similar to that described for the preparation of IV, a mixture of VI (236 g., 1.0 mole), decalin (250 cc.), acetic acid (3.0 g.), and aluminum isopropoxide (0.2 g.) was heated to 175–190° for 2.5 hr. During that time, 0.666 cu. ft. of carbon dioxide (84%) was evolved. The residue was allowed to cool and was washed with dilute sulfuric acid, several times with saturated sodium bicarbonate solution, and finally with water until neutral. The organic portion was dried over calcium sulfate and the decalin was removed by concentration *in vacuo*. Fractionation of the residue gave 105.7 g. (55%) of VII; b.p. 90–95° (0.5 mm.); n_D^{25} 1.5272. Identity of the product was confirmed by preparation of its semicarbazone, m.p. 142°, and the 2,4-dinitrophenylhydrazone, m.p. 149.5°. There was no depression in m.p. of these derivatives on admixture with authentic samples prepared from pseudoionone obtained by condensation of citral with acetone.²

The pseudoionone obtained by the pyrolytic method was cyclized to β -ionone, using a mixture of sulfuric and acetic acids.¹⁸ From 200 g. of VII, there was obtained 152 g. of β -ionone, b.p. 91–93° (0.7 mm.); n_D^{25} 1.5187. The good yield of β -ionone attests to the high quality of pseudoionone employed.

4-(5-Isopropenyl-2-methylcyclopenten-1-yl)butanone-2 (VIII). Redistillation of the foreruns obtained from the preparation of VII gave 27.0 g. (14%) of VIII, b.p. 59–61° (0.3 mm.); n_D^{25} 1.4810; d_4^{25} 0.9213; semicarbazone (from 50% alcohol), m.p. 136°. M_D calcd. 59.13, found 59.38.

Anal. Calcd. for $C_{13}H_{20}O$: C, 81.19; H, 10.48. Found: C, 80.77; H, 10.39.

(16) W. Kimel, U. S. Patent 2,638,484 (May 12, 1953).

(17) E. Guenther, *The Essential Oils*, D. Van Nostrand Co., Inc., New York, New York, 1949, Vol. II, p. 382.

(18) E. Royals, *Ind. Eng. Chem.*, **38**, 546 (1946).

(12) Y. R. Naves, *Compt. rend.*, **240**, 1437 (1955); Y. R. Naves, *Bull. soc. chim. France*, 672 (1956); Y. R. Naves and P. Ardizio, *Bull. soc. chim. France*, 1479 (1955); P. Teisseire, *Recherches*, **5**, 3 (1955).

(13) Boiling and melting points are uncorrected.

(14) For previous preparations of this compound see A. E. Favorskii and A. I. Lebedeva, *J. Gen. Chem. (U.S.S.R.)*, **8**, 879 (1938); (3, b); Commercial Solvents Corp., Brit. Patent 595,459 (Dec. 5, 1947); E. F. Smith, U. S. Patent 2,516,826 (July 25, 1956).

(15) W. Kimel, U. S. Patent 2,628,250 (Feb. 10, 1953).

Anal. of the semicarbazone. Calcd. for $C_{14}H_{23}N_3O$: C, 67.43; H, 9.29; N, 16.86. Found: C, 67.50; H, 9.12; N, 16.70.

A solution of VIII (19.2 g.) in acetic acid (58 g.) was ozonized several hours at 0°. The ozonide was decomposed by warming with water (150 cc.), zinc dust (20 g.), and a trace of hydroquinone. A portion of the solution was distilled and from the distillate a dimedone derivative was prepared;¹⁹ m.p. and mixed m.p. with formaldehyde dimedone 188°.

4-(5-Isopropyl-2-methylcyclopenten-1-yl)butanone-2 (IX). A solution of VIII (192.2 g.) in an equal volume of petroleum naphtha (60–80°) was hydrogenated at 25° at atmospheric pressure in the presence of Lindlar catalyst (19.2 g.). Uptake of hydrogen decreased sharply after consumption of 0.986 mole (about 4 hr.). Distillation, after removal of catalyst and solvent, gave IX, b.p. 94° (3 mm.); n_D^{25} 1.4681; d_4^{25} 0.9023. M_D calcd. 59.58, found 59.65.

Anal. Calcd. for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.84; H, 11.37.

The semicarbazone melted at 142°.

Anal. Calcd. for $C_{14}H_{23}N_3O$: C, 66.85; H, 10.02; N, 16.71. Found: C, 67.07; H, 9.73; N, 17.13.

4-(5-Isopropyl-2-methyl-1-cyclopentyl)butanone-2 (X). A mixture of VIII (250 g.), hexane (2000 cc.), and 5% palladium-calcium carbonate (25 g.) was hydrogenated in an autoclave at 500 lb. per sq. in. at 125° for 4 hr. The mixture was worked up in the usual manner, affording X, b.p. 75° (1 mm.), n_D^{25} 1.4536; d_4^{25} 0.8873; M_D calcd. 59.87, found 60.03.

Anal. Calcd. for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.61; H, 12.28.

The product, X, gave a mixture of semicarbazones, which could be separated by fractional crystallization from 70% isopropyl alcohol. The more soluble derivative (which predominated) melted at 123°, while the less soluble derivative had m.p. 156°. However, melting points of mixtures of the two fractions were not depressed, suggesting that the semicarbazones were derivatives of different stereoisomeric forms of X.²⁰

Anal. of the 123° semicarbazone. Calcd. for $C_{14}H_{27}N_3O$: C, 66.36; H, 10.74; N, 16.58. Found: C, 66.65; H, 10.38; N, 16.43.

Anal. of the 156° semicarbazone. Calcd. for $C_{14}H_{27}N_3O$: C, 66.36; H, 10.74; N, 16.58. Found: C, 66.31; H, 10.99; N, 16.79.

2-Butyl-3-isopropenyl-1-methylcyclopentene. VIII (400 g.) was dissolved in diethylene glycol (1500 cc.) and was reduced in the presence of hydrazine hydrate (200 cc.) and potassium hydroxide (336 g.) according to the method of Huang-Minlon.²¹ The hydrocarbon, 2-butyl-3-isopropenyl-1-methylcyclopentene was obtained in yield of 261 g. (70%), b.p. 76–78° (7 mm.); n_D^{25} 1.4661; d_4^{25} 0.8312; M_D calcd. 59.12, found 59.42.

Anal. Calcd. for $C_{13}H_{22}$: C, 87.56; H, 12.44. Found: C, 87.85; H, 12.07.

Numerous attempts were made to dehydrogenate the hydrocarbon, $C_{13}H_{22}$, to an aromatic compound. Among the conditions employed were: (1) refluxing with palladinized barium sulfate;²² (2) heating in the vapor phase over palladinized charcoal;²³ (3) treatment with *N*-bromsuccinimide;²⁴ (4)

heating with iodine;²⁵ (5) refluxing with sulfur or selenium. In all trials, either no reaction or extensive decomposition occurred; in no case was an aromatic compound obtained.

Pulegenic Acid (XI). The source of pulegone was commercial pennyroyal oil. XI was prepared from pulegone by the method described by Rupe and Schafer,⁹ and had b.p. 95–97° (0.45 mm.); n_D^{25} 1.4780.

2-Hydroxymethyl-3-isopropylidene-1-methylcyclopentane (XII). A solution of XI (336 g.) in ether (600 cc.) was added dropwise, during 2 hr., to a stirred suspension of lithium aluminum hydride (91.2 g.) in ether (2000 cc.). The mixture was heated to reflux for an additional hour and then was cooled to room temperature. Excess reducing agent was destroyed by the cautious addition of alcohol (400 cc.) and water (200 cc.). Then 15% aqueous sulfuric acid (1000 cc.) was added, with ice cooling. The ether layer was separated and was washed with 5% aqueous sodium bicarbonate solution and with water until neutral. Concentration *in vacuo* gave crude XII, which was purified by fractional distillation. It was obtained as a colorless liquid in yield of 260 g. (84.5%) with b.p. 76–77° (0.9 mm.); n_D^{25} 1.4830.

Anal. Calcd. for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.46; H, 11.54.

The *p*-nitrobenzoate melted at 90°.

Anal. Calcd. for $C_{17}H_{21}O_4N$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.25; H, 7.02; N, 4.72.

5-Isopropylidene-2-methylcyclopentanecarboxaldehyde (XIII). To a well stirred mixture of XII (154 g.), benzene (500 cc.), acetic acid (750 cc.), and water (1,000 cc.) was added, in 100 cc. increments, a solution of potassium dichromate (294 g.) and sulfuric acid (245 g.) in water (1000 cc.). Addition was made at a rate such that the reaction temperature did not exceed 40°. Stirring was continued for 30 min. after addition was complete; then the benzene layer was separated and was washed with sodium bicarbonate solution and water until neutral. The product, XIII, was obtained by fractional distillation as a colorless liquid with b.p. 74–77° (8 mm.); n_D^{25} 1.4632; yield, 50.0 g. (33%); semicarbazone (needles from 50% ethanol), m.p. 202°.

A satisfactory C and H analysis was not obtained for XIII. The values observed for C were invariably too low. However, no difficulty was experienced with the *semicarbazone*.

Anal. Calcd. for $C_{11}H_{19}ON_3$: C, 63.12; H, 9.15; N, 20.08. Found: C, 63.38; H, 9.00; N, 20.30.

4-(5-Isopropylidene-2-methylcyclopentan-1-yl)buten-3-one-2 (XIV). A solution of XIII (45 g.) in acetone (100 cc.) was added, dropwise, to 3*N* sodium hydroxide (50 cc.) in acetone (100 cc.), causing a temperature rise from 22° to 30°. Stirring was continued for 40 hr. at room temperature. The mixture was then diluted with several volumes of water and was extracted with petroleum ether. The organic layer was washed neutral, dried over calcium sulfate, and concentrated *in vacuo*. The crude ketone was purified *via* Girard's reagent and was distilled at diminished pressure. XIV was obtained in yield of 19.8 g. (34.8%); b.p. 73–76° (0.2 mm.); n_D^{25} 1.4960.

Anal. Calcd. for $C_{13}H_{20}O$: C, 81.19; H, 10.48. Found: C, 80.79; H, 10.51.

The *4-phenylsemicarbazone*, crystallized from ethanol, melted at 149–150°.

Anal. Calcd. for $C_{20}H_{27}N_3O$: C, 74.04; H, 8.08; N, 12.95. Found: C, 73.76; H, 8.20; N, 13.23.

4-(5-Isopropyl-2-methylcyclopentyl)butanol-2 (XV). A mixture of XIV (19.8 g.), acetic acid (150 cc.), and 5% platinum-charcoal (3 g.) was placed in autoclave and hydrogenated at 1000 lb. per sq. in. at 90° for 2 hr. Three moles of hydrogen were consumed. The catalyst was removed by filtration and the filtrate was diluted with several volumes of water and was extracted with petroleum ether. Distillation of the

(19) W. Weinberger, *Ind. Eng. Chem., Anal. Ed.*, **3**, 365 (1931).

(20) A more complete discussion of the stereochemical considerations involved here will be presented in a forthcoming publication of Dr. G. Saucy.

(21) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

(22) H. E. Eschinazi and E. D. Bergmann, *J. Am. Chem. Soc.*, **72**, 5651 (1950).

(23) R. P. Linstead and S. L. S. Thomas, *J. Chem. Soc.*, 1134 (1940).

(24) R. A. Barnes and G. R. Buckwalter, *J. Am. Chem. Soc.*, **73**, 3858 (1951).

(25) V. N. Ipatieff, H. Pines and R. C. Olberg, *J. Am. Chem. Soc.*, **67**, 694 (1945).

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.

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

Synthesis of Carotene Homologs

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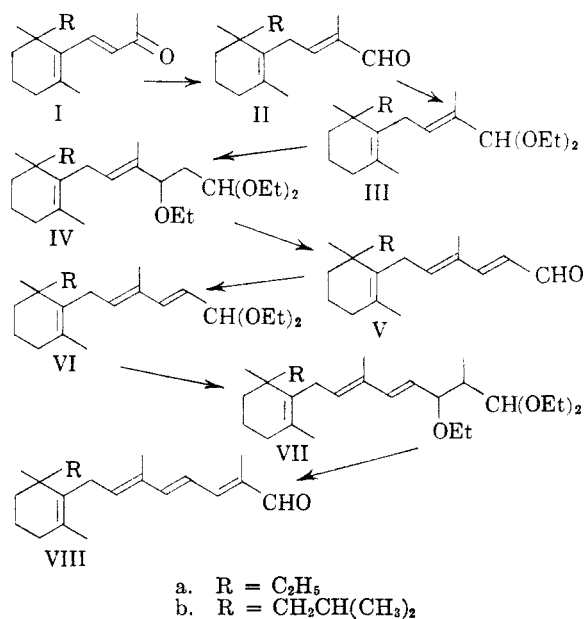
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Three new carotene homologs were prepared by total synthesis. A C-41 hydrocarbon, 1-(2,6-dimethyl-6-ethylcyclohexen-1-yl)-18-(2,6,6-trimethylcyclohexen-1-yl)-3,7,12,16-tetramethyloctadecanonene-1,3,5,7,9,11,13,15,17 (XV) and a C-42 hydrocarbon, 1,18-bis(2,6-dimethyl-6-ethylcyclohexen-1-yl)-3,7,12,16-tetramethyloctadecanonene-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 -ionone⁴ (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

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

(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.