pending the latter in petroleum ether and either passing through it hydrogen sulfide or adding ammonium thiocyanate. The polyvinylacetylene was recovered and distilled under reduced pressure and the fraction boiling at 55–60° (10^{-4}–10^{-5} mm.) collected and analyzed. It had an ultraviolet absorption spectrum with a maximum at 2860 Å., $E^{1\%}_{1\ cm.}$ 760 and an inflection at 3050 Å., $E^{1\%}_{1\ cm.}$, 404.

Anal. Calcd. for $C_{16}H_{22}$: C, 89.65; H, 10.35; active hydrogen (Zer.), 1.0; unsaturation, 5.0 ═. Found: C, 88.5; H, 10.1; active hydrogen (Zer.), 0.96; unsaturation, 4.78, 4.95 ═.

The polyvinylacetylene is very unstable and darkens on standing, even under nitrogen.

Acknowledgment.—The authors are indebted to Mrs. Alice R. Lowry, Mrs. Silvia P. Solar, Miss Margaret A. Campbell, Miss Zelma Weiss, and Mr. S. M. Nagy for the analyses given in this paper, also to Drs. Henry Rapoport and John N. Ingraham for assistance in some of the early experiments, and to Miss Therese M. Harrington for assisting in the ozonolysis experiments. This article is a part of a research program on the synthesis of vitamins A and D, support of which was derived in part through contributions from Abbott Laboratories, Eli Lilly and Company, Merck and Company, Inc., Parke, Davis and Company, The Upjohn Company, and the United Drug Company, such contributions being made through the Research Corporation of New York.

Summary

1. The application of the Darzens synthesis to β-ionone gives 1-[2′,6′,6′-trimethylcyclohexen-1′-yl]-3-methylbuten-1-al-4 as the main decarboxylation product.

2. Ozonolysis of the main decarboxylation product and other products derived from it yielded geronic acid, showing the presence of the β-ionone ring and a double bond in conjugation with this ring.

3. 1-[2′,6′,6′-Trimethylcyclohexen-1′-yl]-3-methylhexen-1-ol-4, its perhydro derivative and their corresponding ketones have been synthesized from the main decarboxylation product.

4. 1-[2′,6′,6′-Trimethylcyclohexen-1′-yl]-3-methyl-4-hydroxyhexen-1-yne-5, its perhydro derivative and 1-[2′,6′,6′-trimethylcyclohexen-1′-yl]-3-methylhexadien-1,3-yne-5 were also synthesized.

5. The absorption spectra of all the products synthesized were determined and correlated with their structure.

CAMBRIDGE, MASSACHUSETTS RECEIVED JULY 12, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Synthesis of Products Related to Vitamin A. V. The Synthesis of [1-(2′,6′,6-Trimethylcyclohexen-1′-yl)-3,7-dimethyldeca-1,3,5,7-tetraenyl]-10-ethyl Ether[1]

BY NICHOLAS A. MILAS, S. WARREN LEE,[1a] CONRAD SCHUERCH, JR., RICHARD O. EDGERTON,[2] JOHN T. PLATI,[3] FRANK X. GROSSI,[4] ZELMA WEISS[5] AND MARGARET A. CAMPBELL[6]

The synthesis of [1-(2′,6′,6′-trimethylcyclohexen-1′-yl)-3,7-dimethyldeca-1,3,5,7-tetraenyl]-10 ethyl ether[7] or simply homovitamin A ethyl ether (I) and [1-(2′,6′,6′-trimethylcyclohexen-1′-yl)-3,7-dimethyldeca-1,3,5-trien-5-ynyl]-10-ethyl ether or simply 5-dehydrohomovitamin A ethyl ether (II) was undertaken in the early days of our investigation in this field to provide model studies for the corresponding derivatives of the vitamin A itself.

(1) Since this and other work related to the synthesis of vitamin A was under confidential classification during the War, we wish to point out for purposes of priority the existence of two documents deposited in the Office of the Committee on Medical Research of the O. S. R. D. and describing the synthesis of biologically active vitamin A products using the Darzens aldehyde made from β-ionone as the key intermediate. These documents were dated March 6, 1942.

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(7) Milas, U. S. Patent 2,369,159, Feb. 13, 1945.

In the first step of this synthesis, 5-ethoxypentanone-2 was prepared from acetoacetic ester by a modification of the procedure of Clarke and Gurin,[8] and was then converted, in liquid ammonia with sodium acetylide or in *t*-butyl alcohol with potassium acetylide, to 3-methyl-6-ethoxyhexa-1-yn-3-ol (III) which was dehydrated over hot aluminum phosphate to 3-methyl-6-ethoxyhexa-3-en-yne-1 (IV).

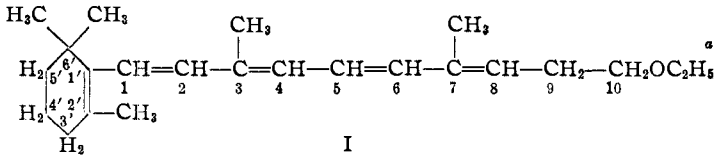
For the synthesis of 5-dehydrohomovitamin A ethyl ether, the acetylene carbinol (III) and the vinylacetylene (IV) were allowed to react via their Grignard reagents[9] with 1-[2′,6′,6′-trimethylcyclohexen-1′-yl]-3 methylbuten-1-al-4 (V)[10] to produce, in the first case, the glycol (VI) and, in the second case, the carbinol (VIII). Both of these compounds were successfully dehydrated, with small amounts of *p*-toluenesulfonic acid in toluene, to 5-dehydrohomovitamin A ethyl ether.

The acetylene glycol (VI) had an absorption maximum at 2200–2230 Å. characteristic for a

(8) Clarke and Gurin, THIS JOURNAL, **57**, 1876 (1935).

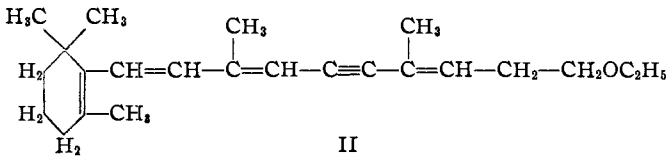
(9) Nesty and Marvel, *ibid.*, **59**, 2662 (1937); Marvel, Mozingo and Kirkpatrick, *ibid.*, **61**, 2003 (1939); Alderson, Ph.D. Thesis, M. I. T., 1939.

(10) Milas, *et al.*, THIS JOURNAL, **70**, 1584 (1948).



I

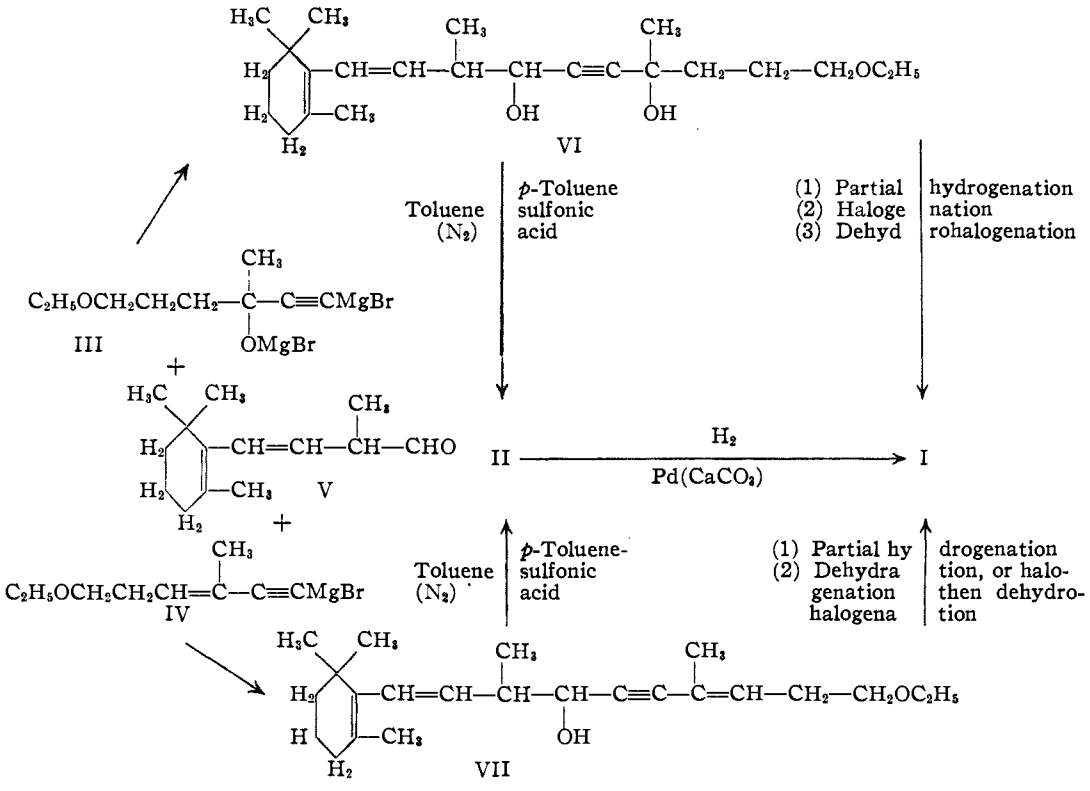
[a] The nomenclature and numbering adopted in this and all subsequent papers of this series is so chosen as to indicate the increase in the carbon side chain and to keep the same numbers present in this chain, irrespective of the increase in the number of carbon atoms, thus facilitating the naming of the intermediate compounds in this field.



II

conjugated system of two double bonds. The existence in the carbinol (VII) of two conjugated systems separated by saturated groups does not seem to have any appreciable effect on the position of the absorption band[11] which appears at 2330 Å.

acid. The crude product obtained from both the glycol VI and carbinol VII, upon a single distillation at pressures $10^{-4}-10^{-5}$ mm., exhibits two bands; one at 3160–3200 Å. and another at 2850–2900 Å. If distillation as a method of purification was repeated several times, the final distillate showed only the 2850–2900 Å. band, and each distillation produced considerable resinification. Other methods were therefore resorted to for the purification of the final products. After a single distillation, the dehydrated product from the carbinol VII was first partitioned between petroleum ether and 90% methanol followed by chromatographic adsorption of the petroleum ether soluble portion on activated alumina. The unadsorbed portion showed a single band at 3210 Å. (Fig. 1, curve A) and gave a blue color with antimony trichloride with absorption maxima at 6220 and 5800 Å. A sample of 5-dehydrohomovitamin



The absorption spectrum of 5-dehydrohomovitamin A ethyl ether (Fig. 1, curves A and C) bears a strong resemblance to that of vitamin A except that it is displaced toward the ultraviolet by about 40 Å., if we take 3250 Å. as the value for the maximum band of natural vitamin A. Both of these substances have been made by dehydration in toluene using catalytic amounts of *p*-toluenesulfonic

(11) Lewis and Calvin, *Chem. Rev.*, **25**, 273 (1939).

A ethyl ether obtained by the dehydration of the carbinol VII and distilled once under high vacuum was tested biologically by Professor Robert S. Harris of the Nutritional Laboratories of this Institute. He reported that when fed to vitamin A deficient rats in doses of 98γ per day, it cured xerophthalmia and caused an average weight increase per rat of 32 g. for the 28-day test period.

Similarly, the dehydrated product from the gly-

col VI, after a single distillation, was partitioned and the petroleum ether soluble portion fractionated at low temperatures using absolute methanol as the solvent. The fraction insoluble in methanol below −30° solidified at about −40° but failed to remain solid at higher temperatures. This product exhibited a single band at 3210 Å. (Fig. 1, curve C), while the methanol soluble portion had both the 2850–2900 and the 3160–3200 Å. bands.

When one mole of hydrogen was added to glycol VI in alcohol using 1% palladium hydroxide on calcium carbonate, the ethylenic glycol VIII was produced. This glycol was treated with pyridine hydrobromide in a large excess of pyridine and the product formed dehydrobrominated with alcoholic potash. The final product was partitioned and the petroleum ether portion chromatographed using activated alumina. The unadsorbed portion was distilled once through a molecular still of the falling film type, and the largest fraction showed an absorption maximum at 3280 Å. (Fig. 1, curve B), and a faint inflection at 3670 Å. From the experimental evidence on hand, it is difficult to decide, at present, whether this product is identical in every respect with the homovitamin A ethyl ether produced by other methods used in this investigation.

Early in our work the glycol VIII was treated in pyridine with either thionyl chloride or phosphorus tribromide and the products formed dehydrohalogenated with alcoholic potash, or, as in one case, with sodamide in liquid ammonia. The crude product from one dehydrobromination experiment was found biologically active in doses of about 0.06 mg. per day, but its stability under feeding experiments was low. The products formed by the dehydrohalogenations when further purified by first partitioning, then by low temperature fractionation in methanol, showed a single absorption band between 3210 and 3220 Å. They also gave a deep blue color with antimony trichloride with bands at about 6220 and 5800 Å.

When one mole of hydrogen was added to carbinol VII in the presence of 1% palladium hydroxide on calcium carbonate, the carbinol IX was produced, and was dehydrated in toluene using catalytic amounts of *p*-toluenesulfonic acid. After molecular distillation, followed by low temperature fractionation in methanol, a product was obtained which showed an absorption maximum at 3210 Å. (Fig. 1, curve D).

The addition of one mole of hydrogen in the presence of palladium to 5-dehydrohomovitamin A ethyl ether did not materially change its ultraviolet absorption spectrum except that the extinction coefficient was slightly lowered, but not appreciably enough to indicate a large percentage of 1,4-addition or some other addition which would radically alter the position of the maximum. It may be of interest to note that in all of the above cases, the 5-double bond formed in the final product may be a *cis*-double bond, although in natural carotenoids and vitamin A, according to Zechmeister,[12] this double bond exists only in the *trans*-form.

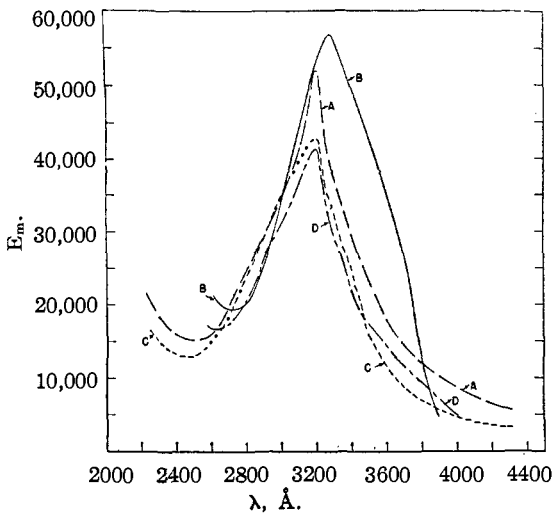


Fig. 1.—Absorption spectra in ethanol of: (A) 5-dehydrohomovitamin A ethyl ether from (VII); (B) homovitamin A ethyl ether via dehydrobromination (pyridine hydrobromide) of partially hydrogenated (VI); (C) 5-dehydrohomovitamin A ethyl ether from (VI); (D) homovitamin A ethyl ether via dehydration of partially hydrogenated (VII).

The ultraviolet absorption spectra of the various compounds reported in this investigation are summarized in Table I.

TABLE I

SUMMARY OF SPECTROSCOPIC DATA

Compound	λmax., Å.	ε mol.	log ε mol.
Homovitamin A ethyl ether (I) from VIII via dehydrobromination (pyridine hydrobromide). Curve B	3280	56750	4.75
	3670[a]	30000	4.48
Homovitamin A ethyl ether (I) from IX via dehydration. Curve D	3210	41250	4.62
5-Dehydrohomovitamin A ethyl ether (II) from VII via dehydration. Curve A	3210	52000	4.72
5-Dehydrohomovitamin A ethyl ether (II) from VI via dehydration. Curve C	3210	42500	4.63
Compound VI	2200–2230	4470	3.65
Compound VII	2330	21500	4.33

[a] Faint inflection.

Experimental

β-Ethoxyethyl Bromide.—This product was prepared in 59–65% yields, b. p. 125–127°, by a method[13] essentially

(12) Zechmeister, *Chem. Rev.*, **34**, 267 (1944).

(13) Schuerch, B.S. Thesis, M. I. T., 1940.

the same as that published later by Harrison and Diehl[14] except that olefin-free petroleum ether was used as a solvent.

5-Ethoxypentanone-2.—This ketone was obtained in a yield of 26.4% using the procedure described by one of us elsewhere.[7] It had a b. p. of 170.5–171° (763 mm.); $n^{20}D$ 1.4176.

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.62; H, 10.77. Found: C, 64.60, 64.50; H, 10.80, 10.80.

Semicarbazone of **5-Ethoxypentanone-2.**—This product was recrystallized from ethanol, m. p. 86–87.5°.

Anal. Calcd. for $C_8H_{17}O_2N_3$: N, 22.4. Found: N, 21.7, 22.2.

3-Methyl-6-ethoxyhexa-1-yn-3-ol (Carbinol of III).—This product was also prepared by a procedure described elsewhere[7] and fractionated using a packed column of about 20 theoretical plates; yield, 83%; b. p. 94–95° (15 mm.); $n^{24}D$ 1.4466; $n^{20}D$ 1.4482; MR_D, 44.61; calcd., 44.86; d^{20}_4 0.938.

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.24; H, 10.26; unsaturation, 1 ⫤; active hydrogen, 2.0; —OC_2H_5, 28.8[4] Found: C, 69.23, 69.37; H, 9.77, 9.60; unsaturation, 0.94, 1.06 ⫤; active hydrogen (Zer.), 1.9; —OC_2H_5, 28.2.

With alcoholic silver nitrate solution the acetylene carbinol forms a white precipitate which explodes on the hot plate.

This acetylene carbinol was also prepared in a somewhat lower yield (30%) by an adaptation of the method of Gould and Thompson.[15] It was identical with that obtained in liquid ammonia with sodium acetylide.

3-Methyl-6-ethoxyhexa-3-en-yne-1 (Vinylacetylene of IV).—Twenty grams of 3-methyl-6-ethoxyhexa-1-yn-3-ol was passed upward under a reduced nitrogen pressure (11 mm.) through a tube containing a mixture of aluminum phosphate and pumice and maintained at temperatures between 270 and 290°. The crude dehydrated mixture was then dried and fractionated under a reduced nitrogen pressure and the fraction boiling at 55–55.5° (12 mm.) collected; yield, 36% per pass; $n^{20}D$ 1.4522; d^{20}_4 0.8538; MR_D, 43.74; calcd., 42.95.

Anal. Calcd. for $C_9H_{14}O$: C, 78.26; H, 10.14; unsaturation, 3 ⫤; active hydrogen, 1; —OC_2H_5, 32.6. Found: C, 77.99, 77.71; H, 10.60, 9.86; unsaturation, 3.07 ⫤; active hydrogen (Zer.), 0.93, 0.94; —OC_2H_5, 30.4, 33.4.

[1-(2′,6′,6′-Trimethylcyclohexen-1′-yl)-3,7-dimethyl-4-hydroxydeca-1,7-dien-5-ynyl]-10-ethyl Ether (VII).—A Grignard reagent was prepared in about 300 cc. of anhydrous ether from 3.9 g. of magnesium and 17.5 g. of ethyl bromide freshly distilled from phosphorus pentoxide. The mixture was then cooled to 0° and added to it dropwise with rapid stirring and in a stream of nitrogen, 22.1 g. of 3-methyl-6-ethoxyhexa-3-en-yne-1 in 25 cc. of anhydrous ether in the course of one-half hour. Stirring was continued at room temperature overnight, then the mixture was cooled to 0° and to it was added dropwise with rapid stirring 30 g. of the aldehyde (V) in an equal volume of anhydrous ether. The mixture was finally stirred overnight in nitrogen at room temperature, then hydrolyzed with an ammonium chloride–ice mixture and the ether layer recovered, dried and the ether removed under reduced pressure. The residue was subjected to a high vacuum, 10^{-4}–10^{-5} mm., at 100° to remove low boiling constituents, leaving a light-yellow, highly viscous liquid. Attempts to crystallize it were unsuccessful. An absorption spectrum of the final product showed a band at 2330 Å.; log $\epsilon_{mol.}$ 4.33.

Anal. Calcd. for $C_{23}H_{36}O_2$: C, 80.18; H, 10.54; unsaturation, 5 ⫤; active hydrogen, 1. Found: C, 80.0, 79.9; H, 10.3, 10.5; unsaturation, 5.68, 5.15 ⫤ (Pt), 5.28 ⫤ (Pd); active hydrogen (Zer.) 1.00, 1.23.

(14) Harrison and Diehl, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., 1943, Vol. XXIII, p. 32.

(15) Gould and Thompson, THIS JOURNAL, **57**, 340 (1935).

Since all of the semimicrohydrogenations were done in aldehyde-free glacial acetic acid, the high values are probably due to a slow hydrogenolysis of the hydroxyl groups.

[1-(2′,6′,6′-Trimethylcyclohexen-1′-yl)-3,7-dimethyl-4,7-dihydroxydeca-1-en-5-ynyl]-10-ethyl Ether (VI).—A Grignard reagent was prepared from 2.1 g. of magnesium and 9.5 g. of ethyl bromide in about 200 cc. of anhydrous ether. The mixture was then cooled to 0° and added to it dropwise with rapid stirring and in a stream of nitrogen, 8 g. of 3-methyl-6-ethoxyhexa-1-yn-3-ol in 40 cc. of dry ether in the course of one-half hour. A thick finely divided semi-solid separated out. The mixture was refluxed gently for about six hours then cooled to 0° and added to it dropwise 8 g. of the aldehyde (V) in 20 cc. of dry ether. To complete the reaction, the mixture was refluxed overnight in an atmosphere of nitrogen, then cooled and hydrolyzed with an ammonium chloride–ice mixture. The ether extract was dried and the ether removed under reduced pressure. To remove the low boiling constituents, the residue was subjected to a high vacuum 10^{-4}–10^{-5} mm. at 100°. A highly viscous amber-colored liquid remained; yield 13 g. (93%). A semimicrohydrogenation (Pt) of this product showed the presence of 5.6 ⫤. Spectroscopically it had a prominent band at 2230 Å. and indications at 2400–2500, 2700–2800 and 3200–3300 Å., respectively. Further purification of this glycol was effected by partitioning it between equal volumes of petroleum ether and 90% methanol. The glycol went predominantly into the methanol layer from which it was recovered by diluting with water and extracting with petroleum ether. The final product had a single band at 2200–2230 Å.; log $\epsilon_{mol.}$ 3.65. Semimicrohydrogenation, 4.24 ⫤.

When this glycol was dissolved in dry petroleum ether and the solution allowed to stand at −20° for several weeks, a small amount of white solid separated out. Successive fractionations of the non-crystallizable product from −20 to −78° yielded only a small additional amount of the white solid. After several crystallizations from hot petroleum ether, the white solid had a m. p. of 74.5–75°, a semimicrohydrogenation of 5.53 ⫤ and a band at about 2200 Å., log $\epsilon_{mol.}$ 3.575. The non-crystallizable highly viscous liquid analyzed as follows:

Anal. Calcd. for $C_{23}H_{28}O_2$: C, 76.19; H, 10.56; unsaturation, 4 ⫤; active hydrogen, 2. Found: C, 76.5, 76.3; H, 10.8, 10.7; unsaturation, 4.22, 4.46 ⫤ (Pt); active hydrogen (Zer.), 1.96. Found (crystalline): C, 75.95; H, 10.42.

[1-(2′,6′,6′-Trimethylcyclohexen-1′-yl)-3,7-dimethyl-deca-1,3,5-trien-5-ynyl]-10-ethyl Ether (II) via Dehydration of Carbinol (VII).—About 0.3 g. of *p*-toluenesulfonic acid monohydrate was dehydrated in 300 cc. of toluene (thiophene-free) by distilling 75 cc. of the latter. The mixture was then cooled in nitrogen and 10 g. of [1-(2′,6′,6′-trimethylcyclohexen-1′-yl)-3,7-dimethyl-4-hydroxydeca-1,7-dien-5-ynyl]-10-ethyl ether in 200 cc. of toluene was added to it and distillation resumed in a stream of nitrogen until about 200 cc. of toluene was distilled over in the course of twenty minutes. The residual liquid which had turned deeply reddish-brown was cooled to room temperature and shaken in nitrogen with 2 × 50 cc. of 10% sodium hydroxide solution, washed with water, dried and the toluene removed under reduced pressure. The greenish viscous residue (8 g.) was dissolved in absolute methanol and the solution treated with about 1 g. of solid potassium hydroxide which caused the green color to disappear and the solution assumed a yellowish-orange tinge. Enough water was then added to make the methanol 95% and the mixture extracted with two volumes of olefin-free petroleum ether. The solution was washed with water, dried and the solvent removed. The crude light-brown viscous residue was subjected to a vacuum of about 0.01 mm. at 40–50° for about one hour to remove low boiling constituents. This product gave a deep blue color in chloroform with antimony trichloride;

it showed a negligible active hydrogen (Zerewitinoff) and had an unsaturation equivalent to 5.88 double bonds. When 0.0000956 g. was fed to a group of vitamin A deficient rats per day, a weight increase of 32 g. in twenty-eight days resulted, as compared with an increase of 44 g. in a positive control group fed 3 U. S. P. units of Reference Cod Liver Oil per day. All negative controls died.

The crude product was then fractionated once from a specially designed shallow flask sealed on to it a thermometer well and proper receivers to take cuts, and the largest fraction (light orange oil) boiling at 94–106° (10^{-4}–10^{-5} mm.) collected and examined spectroscopically. It showed two bands; one at 2850–2900 Å. and the other at 3160–3200 Å. Repeated fractionations caused considerable decomposition of the chromogen having the 3160–3200 Å. band.

In subsequent preparations, the crude product was fractionated once at 10^{-4}–10^{-5} mm. and the main fraction partitioned between equal volumes of petroleum ether and 90% methanol. Most of the product went into the petroleum ether layer. This fraction was chromatographed in nitrogen through a column 110 cm. long and 10 mm. bore, packed with 40–60-mesh activated alumina, and washed with about 2 liters of petroleum ether. A small yellowish-brown band 2 cm. long developed on the top of the column while the rest of the column was light orange-yellow. The unadsorbed product in petroleum ether was light orange, and when the petroleum ether was removed and the residue fractionated once, the main fraction (light orange oil) boiled at 100–104° (10^{-5} mm.). This had a single band at 3210 Å. and an $\epsilon_{mol.}$ value of 52,000. It also gave a blue color with antimony trichloride.

Anal. Calcd. for $C_{28}H_{34}O$: C, 84.60; H, 10.49; unsaturation, 6 ⌐⌐. Found: C, 83.99, 84.06; H, 10.46, 10.25; unsaturation, 5.98 ⌐⌐.

The adsorbed material was eluted with absolute alcohol and a small amount of a product recovered in petroleum ether. This was found to have a strong band at 2850–2900 Å. and a weaker one at 3160–3200 Å. All operations in this and subsequent experiments were carried out in a stream of purified nitrogen.

Partial Hydrogenation of Compound VII to Compound IX.—To 16.6 g. of the carbinol VII in 300 cc. of absolute alcohol and an equal weight of 1% palladium hydroxide deposited on calcium carbonate was added the calculated amount of hydrogen to convert the acetylene bond into an olefin bond taking also into consideration the amount of hydrogen necessary to reduce the palladium hydroxide into palladium black. The product was recovered from this solution and used in the dehydration experiment.

Dehydration of Compound IX.—The product from the previous experiment was dehydrated in 300 cc. of toluene containing about 0.4 g. of *p*-toluenesulfonic acid. The dehydrated product was recovered as in the previous case and treated in absolute methanol with solid potassium hydroxide (2 g.); the methanol diluted with water to 95% and extracted with two volumes of petroleum ether, the latter washed with water, dried, and the petroleum ether removed; yield of the crude product, 11 g. The highly viscous reddish-brown residue was dissolved in about 100 cc. absolute methanol and fractionated in nitrogen at successively lower temperatures, using 10° intervals from 0 to −78°. After a number of such fractionations, the entire product was obtained in three fractions: (1) a very small amorphous resinous fraction insoluble in methanol at 0°; (2) a methanol soluble fraction at −40°; (3) a methanol insoluble fraction at −40° or below which exists as a light orange solid below −50°. Fraction (2) was found to have an absorption band with two maxima; one at 2850–2900 Å., $E^{1\%}_{1\ cm.}$ 994, and the other at 3220 Å., $E^{1\%}_{1\ cm.}$ 710. Fraction (3) had only one maximum at 3210 Å., $\epsilon_{mol.}$. 41,250. The last fraction was also analyzed.

Anal. Calcd. for $C_{23}H_{36}O$: C, 84.08; H, 11.05; unsaturation, 5 ⌐⌐. Found: C, 83.22; H, 10.78; unsaturation, 4.88 ⌐⌐.

Dehydrochlorination of Compound IX.—A small sample of the carbinol IX (1.1 g.) was treated at 0°, in a mixture of 10 cc. petroleum ether, 10 cc. ethyl ether and 0.25 g. anhydrous pyridine, with 0.4 g. of thionyl chloride for fifteen minutes. It was then allowed to warm to room temperature for one-half hour, then heated in nitrogen under reflux for an additional one-half hour. The mixture was then cooled and filtered off the solid pyridine hydrochloride. Finally the solvent was removed under reduced pressure and the residue taken up in 20 cc. hot 95% ethanol containing 1 g. of potassium hydroxide. To complete dehydrochlorination, the mixture was heated in nitrogen for one-half hour at 60–80°, then cooled, diluted with three volumes of water and extracted with petroleum ether. The petroleum ether extract was once partitioned with an equal amount of 95% methanol, washed with water, dried and examined spectroscopically. It showed two bands; one at 2820–2900 Å., $E^{1\%}_{1\ cm.}$ 406, and the other at 3220–3230 Å., $E^{1\%}_{1\ cm.}$ 313.

[1-(2′,6′,6′-Trimethylcyclohexen-1′-yl)-3,7-dimethyldeca-1,3,5-trien-5-ynyl]-10-ethyl Ether via Dehydration of Glycol VI.—About 150 cc. of anhydrous toluene was mixed with 0.03 g. of *p*-toluenesulfonic acid monohydrate, and a little over 50 cc. of toluene was distilled to cause the dehydration of *p*-toluenesulfonic acid. The mixture was then cooled and to it was added about 1 g. of the glycol VI in 25 cc. of toluene. About 50 cc. of toluene was then distilled in nitrogen and the mixture (deep orange) was cooled, the product recovered as in the previous dehydrations and treated with methyl alcoholic potash. It was recovered from this mixture with petroleum ether and distilled (temperature of boiling cyclohexanone) once, using a molecular still of the falling film type. In addition to a small amount of residue, a dark orange-brown viscous liquid (about 0.6 g.) was obtained which had an absorption band at 3200–3210 Å., $E^{1\%}_{1\ cm.}$ 723. This was further purified by fractionation from absolute methanol at temperatures between 0 and −78°. The fraction insoluble in methanol below −40° was recovered and examined spectroscopically. It was found to have a band with a maximum at 3210 Å., $\epsilon_{mol.}$ 42,500. A semimicrohydrogenation showed the presence of 5.93 double bonds.

Partial Hydrogenation of Glycol VI to Glycol VIII.—To 10.8 g. of glycol VI in 200 cc. of absolute alcohol and 11 g. of 1% palladium hydroxide deposited on calcium carbonate was added the calculated amount of hydrogen necessary to convert the acetylene bond into an olefin bond, and the product recovered and used in the dehydrohalogenation experiments.

Dehydrohalogenation of Glycol VIII. (a) Via Phosphorus Tribromide.—A mixture of 6.9 g. of freshly distilled tribromide, 25 cc. of dry benzene and a few drops of pyridine was cooled to −5°. A solution of 4.62 g. of the glycol VIII, 25 cc. of dry benzene and 6.5 g. of pyridine was then added dropwise with shaking in the course of one-half hour. The mixture was then allowed to stand at room temperature in nitrogen for two hours, heated to 70° for twenty minutes, then cooled and poured on cracked ice and immediately extracted with ether. The ether extract was shaken with two 50-cc. portions of cold phosphoric acid, then once with cold water and dried over anhydrous magnesium sulfate. After filtration, the solvent was removed and to the residue was added 80 cc. of hot methyl alcoholic potash containing 10 g. of potassium hydroxide. The mixture was further heated in nitrogen for one-half hour at 70° then cooled, diluted with two volumes of water and extracted with petroleum ether. This crude product was found biologically active in doses of 0.06 mg. per day, but the activity was not maintained until the end of the test, showing considerable instability. This product was further purified by partitioning between equal volumes of petroleum ether and 90% methanol and the product in the petroleum ether layer analyzed spectroscopically. A yield of about 2 g. was obtained at this stage. It showed two maxima in the ultraviolet; one at

2800–2900 Å. and the other at 3210–3230 A. With antimony trichloride in chloroform, it gave two bands; one at 6220 Å. and the other at 5800 Å., the latter being more prominent.

(b) **Via Pyridine Hydrobromide.**—To 30 g. of dry pyridine was added 1.5 g. of dry hydrogen bromide (Dow Chemical Co.) and the mixture cooled to room temperature while nitrogen was allowed to bubble through it. A solution of 2.5 g. of the glycol VIII in 50 cc. of dry benzene was then added to the above mixture and heated on the water-bath in nitrogen for two hours. All of the benzene and most of the pyridine were then removed under reduced pressure, and to the residue, with nitrogen still flowing through the system, was added 100 cc. of hot 95% alcohol containing 10 g. of potassium hydroxide. The mixture was then heated on the water-bath for one-half hour, then cooled, diluted with two volumes of water and extracted with petroleum ether. About 1.8 g. of a yellowish-brown viscous liquid was recovered which, unlike any other crude dehydrohalogenation product, had a single broad absorption band in the ultraviolet between 3200 and 3400 Å. It also gave a deep blue color with antimony trichloride in chloroform. To purify this product further, it was partitioned between equal volumes of petroleum ether and 90% methanol and the petroleum ether portion chromatographed in nitrogen through a column 110 cm. × 1 cm. packed with activated alumina. The column was then washed with 1.5 liters of petroleum ether and the unadsorbed portion (light yellow) was removed from petroleum ether and fractionally purified at 0 to −78° from absolute methanol. A yellow, highly viscous product (*ca.* 1 g.) was finally obtained and to free it completely from methanol, it was dissolved in petroleum ether and the solution extracted with water, dried and examined spectroscopically. It showed an absorption band at 3280 Å., $\epsilon_{mol.}$ 56,750 and a possible inflection at 3670 Å., $\epsilon_{mol.}$ 30,000. Semimicrohydrogenation showed the presence of 4.85 double bonds.

Anal. Calcd. for $C_{23}H_{36}O$: C, 84.08; H, 11.05. Found: C, 82.32; H, 10.90.

This product was highly unstable and easily autoxidizable and in spite of the precautions taken to obtain pure samples for combustions, the carbon analyses were always from 1.5 to 2% low. This difficulty was also encountered in the early stages of the natural vitamin A purifications.

The adsorbed portion was eluted from alumina with absolute alcohol and, after diluting with water, extracted with petroleum ether. It was found to have two bands in the ultraviolet; one at 3440 Å., $E^{1\%}_{1\,cm.}$ 250, the other at 3670 Å., $E^{1\%}_{1\,cm.}$ 188. The amount of this product was too small for further investigation.

Partial Hydrogenation of 5-Dehydrohomovitamin A Ethyl Ether.—A sample of 0.1271 g. of 5-dehydrohomovitamin A ethyl ether having an $E^{1\%}_{1\,cm.}$ (3210 Å.) value of 1250 was placed in a wafer glass capsule sealed flat on one end and, after weighing, drawn into an open capillary on the other end. The sample was placed into a glass key attached to a rod revolving around a ground glass stopper and sealed on to a specially designed vessel of a semimicro-hydrogenation apparatus.[16] The vessel contained an alcoholic suspension of 0.254 g. of 1% palladium hydroxide on calcium carbonate. After the palladium hydroxide was reduced with hydrogen and equilibrium was established in the system, the capsule was crushed and exactly one mole equivalent of hydrogen was allowed to be absorbed. Hydrogenation was discontinued and the hydrogen in the apparatus was quickly replaced with pure nitrogen. The product was then recovered in the usual manner and analyzed spectroscopically. It was found to have an absorption band at 3200–3210 Å., $E^{1\%}_{1\,cm.}$ 1000 with a faint inflection at 2900 Å. (?).

These results seem to indicate that the addition of hydrogen on the en-yne system had taken place mainly on the acetylene bond, since 1,4-addition would have produced an allene which should be optically equivalent to 5.5 double bonds[17] and its absorption maximum should have been in the region of about 3400 Å. However, the possibility of a rearrangement of the allene into an en-yne with one less double bond should not be excluded. Such an en-yne should have a prominent absorption band in the region of 2900 Å. The fact that a faint inflection was found in this region indicates that some of the hydrogen had actually added 1,4 with a subsequent rearrangement of the allene formed.

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Summary

1. The synthesis of [1-(2′,6′,6′-trimethylcyclohexen - 1′ - yl) - 3,7 - dimethyldeca - 1,3,5,7 - tetraenyl]-10 ethyl ether, or homovitamin A ethyl ether, and [1-(2′,6′,6′-trimethylcyclohexen-1′ - yl) - 3,7 - dimethyldeca - 1,3,5 - trien - 5 - ynyl]-10-ethyl ether, or 5-dehydrohomovitamin A ethyl ether, and that of several new intermediates has been described. Crude preparations of both homovitamin A and 5-dehydrohomovitamin A ethyl ethers have been found to possess antixerophthalmic (vitamin A) activity.

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(16) Rivers, Ph.D. Thesis, M. I. T., Dec., 1941.

(17) Kuhn and Wallfels, *Ber.*, **71B**, 783 (1938); see also Shantz, Cawley and Embree, THIS JOURNAL, **65**, 904 (1943).