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

Synthesis of Products Related to Vitamin A. VI. The Synthesis of Biologically Active Vitamin A Ethers[1]

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Following a scheme originally suggested by Milas and McAlevy,[10] Kipping and Wild[11] were the first to claim the synthesis of vitamin A methyl ether. Since no experimental details, analyses or biological results were given, it is difficult to evaluate this synthesis. Soon after the original announcement of the synthesis of various biologically active vitamin A products[12] developed in this Laboratory during the war, Oroshnik,[13] claimed in a note the synthesis of vitamin A methyl ether, but experimental details as well as biological activity of the final product are lacking.

The present paper describes the synthesis of four biologically active vitamin A ethers. Only two, the methyl and the ethyl and their corresponding 5-dehydrovitamin A derivatives were obtained in relatively pure form, while the isopropyl and the *t*-butyl ethers were obtained in much less pure state.

One of the important intermediates in the synthesis of vitamin A ethers is 4-alkoxybutanone-2 (I). Attempts to prepare this alkoxybutanone, in which R represents methyl or ethyl groups, by the direct alkylation of 4-hydroxybutanone-2 with dimethyl or diethyl sulfates were entirely unsuccessful. Rivers[14] prepared 4-ethoxybutanone-2 from β-ethoxypropionyl chloride and cadmium dimethyl[15] but the yields were low and the method could not be adapted easily for the preparation of the various alkyl ethers of 4-hydroxybutanone-2. Killian, Hennion and Nieuwland[16] prepared 4-methoxybutanone-2 from anhydrous methanol and methyl vinyl ketone in the presence of boron trifluoride-etherate. This method was found satisfactory in the preparation of 4-methoxy, 4-ethoxy, 4-isopropoxy and 4-*t*-butoxybutanone-2's. 4-Alkoxybutanone-2 (R = methyl or ethyl) was then condensed in liquid ammonia with lithium acetylide to give 3-methyl-5-alkoxy-pentyn-1-ol-3 (II) which was dehydrated at 250–280° over aluminum phosphate to 3-methyl-5-alkoxy-3-pentenyne-1 (III).

These three intermediates were used in the study of three different routes for the synthesis of vitamin A ethers (see flow sheet). In the first route the aldehyde (IV)[17] was condensed in liquid ammonia with lithium acetylide to give the acetylene carbinol (V) which was then condensed via the Grignard reaction with 4-alkoxybutanone-2 to give the acetylene glycol (VI) in yields of 70–80%. This glycol was also obtained in somewhat higher yields by the condensation of the Grignard of the acetylene (II) with the aldehyde (IV). This glycol has been obtained in two forms; a crystalline and a highly viscous liquid form. Since the double bond between carbon atoms one and two can exist only in the *trans* form,[18] the difference between the crystalline and the liquid glycols may be one of racemic and *meso* forms.[19] The partial hydrogenation of the acetylene glycol (VI) to give the glycol (VII) was found to be selective when 1% palladium deposited on calcium carbonate was used as the catalyst.

Several methods were employed in the conversion of the glycol ether (VII) (R = methyl) into the vitamin A methyl ether (XI). Using phosphorus tribromide in the presence or absence of pyridine, the glycol was converted into the dibromide which was dehydrobrominated with alcoholic potash. The reaction was also studied with phosphorus trichloride, phosphorus triiodide and thionyl chloride. With thionyl chloride partial dehydrochlorination occurred as was indicated by the appearance in the spectrum of the dichloride of a broad band between 3000 and 3300 Å. Of all the halogenating agents, phosphorus tribromide and thionyl chloride gave the best results. In all

(1) (a) First presented in part before the North Jersey Section of the American Chemical Society, April 9, 1945. (b) 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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(9) Research Associate 1945–1946. Present address, Tufts College, Medford, Massachusetts.

(10) Milas and McAlvy, THIS JOURNAL, **57**, 580 (1935).

(11) Kipping and Wild, *Chemistry and Industry*, 802 (1939).

(12) Milas, U. S. Patents 2,369,157, Feb. 13, 1945; 2,382,086, Aug. 14, 1945; *Science*, **103**, 581 (1945).

(13) Oroshnik, THIS JOURNAL, **67**, 1627 (1945).

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

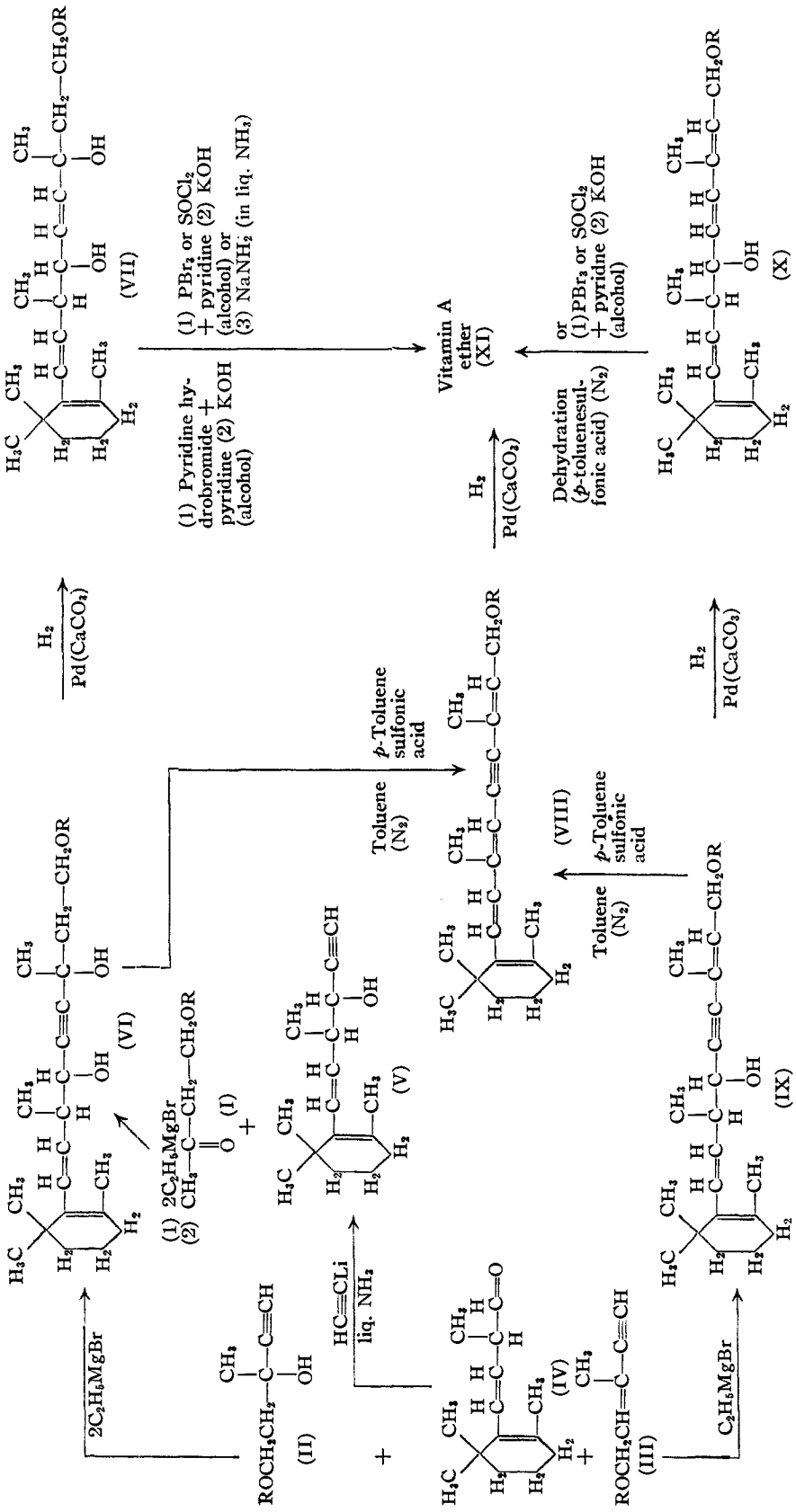
(15) Gilman and Nelson, *Rec. trav. chim.*, **55**, 158 (1936).

(16) Killian, Hennion and Nieuwland, THIS JOURNAL, **58**, 893 (1936).

(17) Milas, *et al.*, *ibid.*, **70**, 1584 (1948).

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

(19) Dupont, *Compt. rend.*, **149**, 1381 (1909); **150**, 1121 (1910); **158**, 714 (1914); *Ann. chim.*, **30**, 500 (1913); Johnson, "Acetylenic Compounds," Edward Arnold, London, 1946, p. 150.

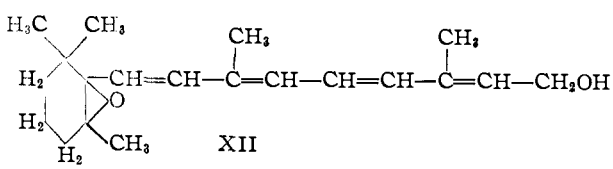


of the cases, however, the product obtained (a pale yellow oil) after a single high vacuum distillation, was found to have two bands in the ultraviolet; one with a maximum at 3250 Å. and the other at 2850–2900 Å. With antimony trichloride in chloroform, it gave a blue color which also showed two bands (Fig. 1, curves with broken lines); one with a maximum at 5800 Å. and another at 6180–6200 Å. Repeated distillation from a shallow vessel at 10^{-5} mm. was detrimental to the chromogen responsible for the absorption band at 3250 Å., which disappeared after five successive distillations.

During the early part of our work we made several preparations through the halogenation of the glycol (VII) (R = methyl, isopropyl, or *t*-butyl) and the dehydrohalogenation of the resulting dihalide. Many of these were assayed biologically on vitamin A deficient rats and a summary of the results is presented in Table I. The glycol (VII) was also tested biologically in order to find out whether the animal organism would cause dehydration, but the results were negative even when very large doses were fed. Preparation (6) was also tested by several other laboratories and all reported appreciable vitamin A activity but not as high as that shown in Table I. Spectroscopically, this sample showed two bands; one at 3250 Å., $E^{1\%}_{1\,cm.}$ 535, the other at 2850 Å., $E^{1\%}_{1\,cm.}$ 655

with feeble indications at 3450 and 3710 Å., respectively. With antimony trichloride in chloroform, it gave a blue color which exhibited two bands at 5800 and 6170 Å., respectively, with the former being the more intense. The product is a light yellow oil boiling at 90–95° (10^{-5} mm.) having negligible active hydrogen (Zer.) and an unsaturation equivalent to 5.08 double bonds. The ultimate analysis, however, gave percentages of carbon varying from 1.5 to 2.0% low. Attempts to purify this product by fractionation at low temperatures were unsuccessful, although the $E^{1\%}_{1\ cm.}$ (3250 Å.) of other samples was raised to 1090 by this method.

The high intensity of the 5800 Å. band (Fig. 1, broken line) suggests the possibility that the vitamin A methyl ether as prepared through the above dehydrohalogenation method is a mixture of the methyl ether and its epoxide. This reasoning finds some support in the recent work of Karrer and Jucker,[20] who found that the chromogen responsible for the 5800 Å. band of the Carr–Price reaction is the epoxide of vitamin A (XII) and not vitamin A, which is responsible only for the 6200 Å. band. From their findings, Karrer and Jucker advanced the hypothesis that in fishliver oils as well as in animal-liver oils, the vitamin A epoxide coexists with vitamin A, and is formed by the auto-oxidation of the latter.[21] The epoxide of vitamin A has also been obtained by treating vitamin A with phthalic acid peracid[22] in a manner similar to that used for the preparation of α- and β-carotene epoxides.[23]



XII

That auto-oxidation of vitamin A is responsible for the 2850–2900 Å. chromogen was shown recently in this Laboratory when an auto-oxidized sample of pure vitamin A was examined spectroscopically. It was found to have a single band at 2850 Å. This is in close agreement with the spectrum of the epoxide of the synthetic methyl ether, the structure of which has not yet been definitely established. Furthermore, both resemble the 5800 Å. chromogen of van Eekelen[24] and the sub-vitamin A of Embree and Shantz[25] and of Hawkins and Hunter.[26]

Identical results were obtained when the carbinol (X) was treated with phosphorus tribromide and the bromide formed dehydrobrominated with

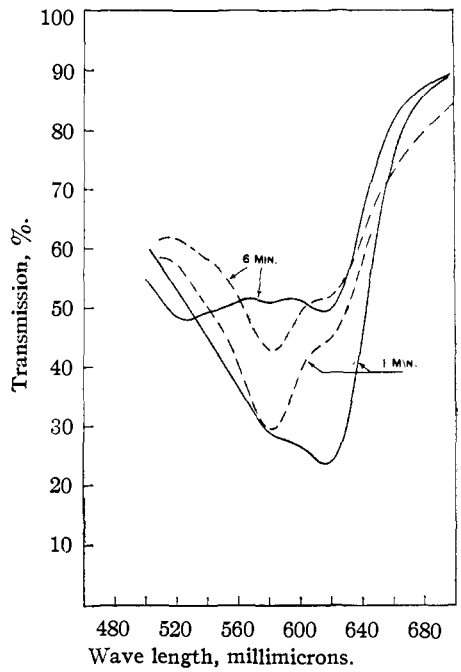


Fig. 1.—Transmission spectra of the antimony trichloride color reaction in chloroform of: (broken line) distilled dehydrobrominated glycol methyl ether (VII), concn., 0.000394%; (solid line) selectively hydrogenated 5-dehydrovitamin A methyl ether (VIII), concn., 0.000192%, taken by the Hardy color analyzer.

alcoholic potash. Since our original publication,[12] Isler, *et al.*,[27] used a similar procedure for the synthesis of vitamin A methyl ether from the carbinol (X) except that the dehydrobromination was carried out with potassium carbonate in acetone. In a more complete publication[28] the same authors used iodine as a catalyst in toluene or ligroin at 95–100° to effect the dehydration of the carbinol (X). The spectroscopic properties of the crude product were similar to those reported by us in the present and earlier publications. The Swiss workers obtained a yellow oil b. p. 90–95° (10^{-5} mm.) having a single band at 3250–3280 Å.; $E^{1\%}_{1\ cm.}$ 1415. When fed to vitamin A deficient rats in doses of 0.8γ and 1.6γ, it was found to be equivalent to 1.1γ and 1.8γ of β-carotene, respectively. Judging from these results, this preparation was not 100% pure vitamin A methyl ether, since the latter has been prepared recently from natural vitamin A by Hanze, *et al.*,[29] who reported a m. p. for this ether of 33–34°, an $E^{1\%}_{1\ cm.}$ (3260 Å.) value of 1660 and a biological potency of about 3,000,000 U.S.P. XXII units per gram.

Sample (10) shown in Table I was prepared by the dehydration in toluene of the methyl ether glycol (VII) using catalytic amounts of *p*-toluene-

(20) Karrer and Jucker, *Helv. Chim. Acta*, **28**, 717 (1945).
(21) Karrer and Jucker, *ibid.*, **28**, 427 (1945).
(22) von Euler, Karrer and Zubris, *ibid.*, **17**, 24 (1934).
(23) (a) Karrer and Rutschmann, *ibid.*, **27**, 1684 (1944); (b) Karrer and Jucker, *ibid.*, **28**, 300, 427, 471 (1945).
(24) van Eekelen, Emmerie, Julius and Wolff, *Nature*, **132**, 171 (1933).
(25) Embree and Shantz, THIS JOURNAL, **65**, 906 (1943).
(26) Hawkins and Hunter, *Biochem. J.*, **38**, 34 (1944).
(27) Isler, Kofler, Huber and Ronco, *Experientia*, **2**, 31 (1946).
(28) Isler, Huber, Ronco and Kofler, Jubilee Volume of Emil C. Barrell, Hoffman–LaRoche and Co., Basle, 1946, p. 31.
(29) Hanze, Conger, Wise and Weisblat, THIS JOURNAL, **68**, 1389 (1946).

TABLE I

SUMMARY OF BIOLOGICAL ASSAYS[a]

MEVA = Methyl ether of vitamin A. iso-PEVA = Isopropyl ether of vitamin A. *t*-BEVA = *t*-butyl ether of vitamin A. DHMEA = 5-Dehydromethyl ether of vitamin A.

	Vitamin preparation	Dose fed per day, *r*	Average gain in wt. per rat per 28 days, g.	Remarks[d]
1	MEVA (crude) via dehydrochlorination (PCl_3) of (VII)	331.0[b]	92.0	
2	MEVA (crude) via dehydrobromination (PBr_3) of (VII)	232.0[b]	95.0	
3	Repeat of (2) after standing at 0° in olive oil for one month	531.0[b]	40.0	
4	Repeat of (2), new preparation	176.0[b]	25.0	
5	Repeat of (4), simultaneously	190.0[b]	35.0	
6	Same as (2) distilled three times	3.0[b]	14.0	
7	Repeat of (6) after standing at 0° in olive oil for one month	6.0[b]	−1.5	All rats survived the test
8	Same as (2) distilled four times	3.0[c]	1.6	One out of eight rats died
9	Repeat of (8)	1.5[c]	7.0	Three out of seven rats died on 6th day of test
10	MEVA (distilled) via dehydration of (VII) with *p*-toluenesulfonic acid as catalyst	189.0[b]	45.0	
11	iso-PEVA (distilled) via dehydrobromination (PBr_3)	183.0[b]	57.0	
12	Same as (11) distilled twice	3.0[c]	11.0	One out of six rats died on 10th day of test
13	*t*-BEVA (distilled) via dehydrobromination (PBr_3)	7.4[b]	4.0	Six out of ten rats died during test
14	DHMEA (distilled)	111.0[c]	17.0	
15	Same as (14) distilled twice	6.0[b]	19.0	Only two rats were used for this test

[a] These results were reported to one of us (N. A. M.) during 1941–1942 by Professor Robert S. Harris (M. I. T.). [b] These samples were prepared in olive oil in which the air was replaced by pure nitrogen. To each sample was also added 0.1% of hydroquinone based on the vitamin concentration. [c] These samples were prepared in corn oil in which the air was replaced by pure nitrogen. To each sample was added 0.05% of hydroquinone and 0.05% of lecithin based on the vitamin concentration. [d] All positive control rats were fed 3 U. S. P. units of Reference Cod Liver Oil per day, and showed an average weight increase of 33–44 g. per rat per 28 days. All negative control rats were fed doses of olive or corn oil containing only the antioxidants, and died in the first period of the test.

sulfonic acid. When distilled from a shallow vessel at 10^{-5} mm., the distillate exhibited both the 3250 and the 2850 Å. bands, and gave a blue color with antimony trichloride in chloroform. Hydrogenation showed the presence of 4.98 double bonds and a Zerewitinoff determination showed negligible active hydrogen.

Vitamin A methyl ether was also synthesized by the selective hydrogenation of 5-dehydrovitamin A methyl ether (VIII) which was prepared by the dehydration of the glycol (VI) (R = methyl) using catalytic amounts of *p*-toluenesulfonic acid. The crude 5-dehydrovitamin A methyl ether was purified by partitioning between petroleum ether and 95% methanol followed by low temperature fractionation from methanol and molecular distillation. The ultraviolet absorption of the purest specimen obtained is shown in Fig. 2, curve A. Although the crude product showed two broad bands, one at 3100–3300 Å. and the other at 2800–2900 Å., the purified product showed a single maximum at 3220 Å.; $E^{1\%}_{1\,cm.}$ 1600, and gave the expected unsaturation. Upon ozonization, it yielded geronic acid, indicating the presence of the β-ionone ring in the molecule. When one mole of hydrogen was added to it in the presence of 1% palladium deposited on calcium carbonate, and the product purified by low temperature fractionation from methanol followed by molecular distillation, a specimen [yellow oil, b. p. 90–95° (10^{-4} mm.)] was obtained which had an ultraviolet spectrum [$E^{1\%}_{1\,cm.}$ (3230 Å.), 1560; Fig. 2, curve B] which was very similar to that of the 5-dehydrovitamin A methyl ether. The spectrum of the antimony trichloride color reaction in chloroform is shown in Fig. 1 (solid line curves) taken one minute and six minutes after mixing, respectively. The one-minute curve shows a principal maximum at 6180 Å.; $E^{1\%}_{1\,cm.}$ 3284. Ozonization of this vitamin A methyl ether gave geronic acid, again indicating the presence of the β-ionone ring.

5-Dehydrovitamin A ethyl ether (VIII) (R = ethyl) was also synthesized by the dehydration of either the glycol (VI) or the carbinol (IX) in the presence of *p*-toluenesulfonic acid. The crude product had similar properties to the corresponding 5-dehydrovitamin A methyl ether and was purified by the same procedure. The purest specimen obtained had an ultraviolet absorption spectrum shown in Fig. 2, curve C. Selective hydrogenation did not change appreciably the shape of the band or the position of the maximum.

Since it is well known[18,30] that selective catalytic hydrogenation of an acetylene leads predominantly to a *cis* olefin, and chemical reduction

(30) Campbell and Campbell, *Chem. Rev.*, **31**, 77 (1942).

usually leads to a *trans* olefin, it was thought advisable to study the chemical reduction of 5-dehydrovitamin A ethyl ether and compare the product formed with that obtained from the catalytic hydrogenation. The following chemical methods of selective reduction have been tested with 5-dehydrovitamin A ethyl ether: (1) zinc–copper couple in alcohol[31]; (2) zinc dust in alcoholic potassium hydroxide[32]; (3) zinc and acetic acid in alcohol; (4) "Devarda's" alloy (aluminum–copper–zinc alloy) in aqueous alcoholic potassium hydroxide; (5) Raney alloy in aqueous alcoholic potassium hydroxide; (6) metallic calcium in 90% ethanol; (7) sodium in liquid ammonia.[33] The ultraviolet absorption spectrum and unsaturation were taken before and after each reduction. No reduction was observed, even after prolonged treatment with methods (3) and (6), while method (7) caused complete polymerization of the 5-dehydrovitamin A ethyl ether. Of all the other methods, zinc dust in aqueous alcoholic potassium hydroxide gave the most satisfactory results. A product was obtained by this method which after purification by low temperature fractionation from methanol had an ultraviolet absorption band shown in Fig. 2, curve D. The product also showed an unsaturation of 4.85–5.2 double bonds as compared with the original of 6.0–6.19 double bonds. Although the intensity of the ultraviolet maximum was increased, an increase which might be due to further purification, the position of the maximum was essentially the same (3230 Å.). Moreover, the shape of the absorption curve is somewhat the same as that obtained from the catalytically hydrogenated 5-dehydrovitamin A methyl ether (curve B).

Partially purified specimens of both the methyl and ethyl ethers of vitamin A made by the selective catalytic hydrogenation of the corresponding 5-dehydroethers of vitamin A (VIII) were found biologically active when tested on vitamin A deficient rats. For example, samples with an $E^{1\%}_{1\,cm.}$ (3200–3230 Å.) of about 400 to 500 gave potencies in the neighborhood of 100,000 U.S.P. units per gram. The final purified products have not yet been assayed biologically.

In an attempt to convert the glycol (VII) (R = ethyl) and the carbinol (X) (R = ethyl) into their corresponding bromides with pyridine hydrobromide in excess pyridine followed by treatment with alcoholic potash, we obtained a product (80–90% yield) which showed a broad band in the ultraviolet of very high intensity between 3000 and 3700 Å. and one of low intensity at 2850–2900 Å. and gave a deep blue color with antimony trichloride in chloroform. When partitioned between equal volumes of 83% ethanol and petroleum ether, most of it went into the petroleum ether layer which was chromatographed on activated alumina. The greater part of the product passed through the alumina unadsorbed. This portion was fractionated through a molecular still of the falling film type at 10^{-5} mm. and the largest fraction (80%), a light yellow oil, was analyzed spectroscopically. It was found to have a fine structure of three bands in the ultraviolet (Fig. 3): one at 3300 Å.; $E^{1\%}_{1\,cm.}$ 1690, a second at 3480 Å.; $E^{1\%}_{1\,cm.}$ 1830, and a third at 3670 Å.; $E^{1\%}_{1\,cm.}$ 1520. The shape and position of these bands are identical with similar bands observed recently by Shantz[34] for a hydrocarbon related to vitamin A and containing five double bonds in conjugation. That our substance was not a hydrocarbon was shown by the fact that it still possessed the ethoxyl group. Furthermore, molecular weight determinations and hydrogenation gave values in remarkable agreement with those expected for the vitamin A ethyl ether, although carbon and hydrogen analyses were slightly lower than the theoretical. On standing under nitrogen at 0° for over six months, it partially crystallized into light yellow crystals which melted at about 28–30°. Upon ozonization it yielded geronic acid (as 2,4-dinitrophenylhydrazone) indicating the presence in the molecule of the β-ionone ring. No biological results are as yet available for this substance.

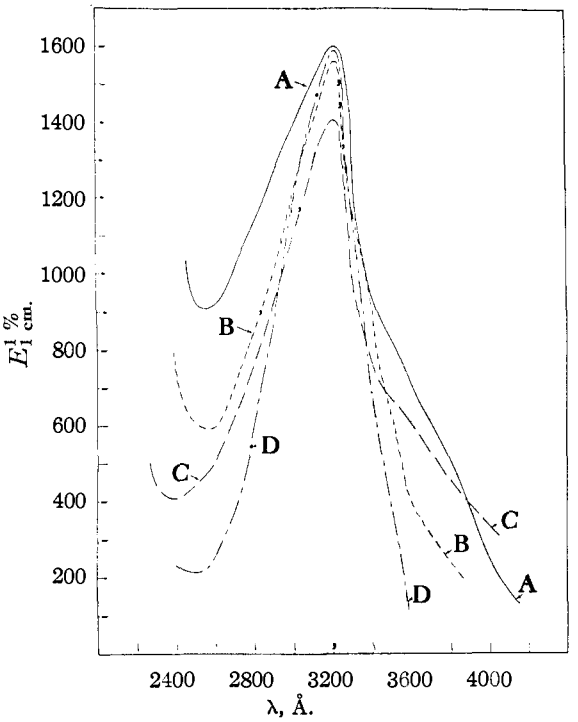


Fig. 2.—Absorption spectra in ethanol of: (A) 5-dehydromethyl ether of vitamin A from (VI); (B) methyl ether of vitamin A via partial hydrogenation of (VIII); (C) 5-dehydrovitamin A ethyl ether via dehydration of either (VI) or (IX); (D) ethyl ether of vitamin A by reduction of (VIII) using zinc dust and alkali.

(31) (a) Straus, *Ann.*, **342**, 190 (1905); (b) Grignard and Teheoufaki, *Compt. rend.*, **188**, 153 (1929); (c) Lebedev, Gulyaeva and Vasil'ev, *J. Gen. Chem.* (U. S. S. R.), **5**, 1421 (1935).

(32) Hurukawa, *J. Electrochem. Assoc. Japan*, **7**, 346 (1939).

(33) Campbell and Edy, THIS JOURNAL, **63**, 216 (1941).

(34) Shantz, *ibid.*, **68**, 2553 (1946).

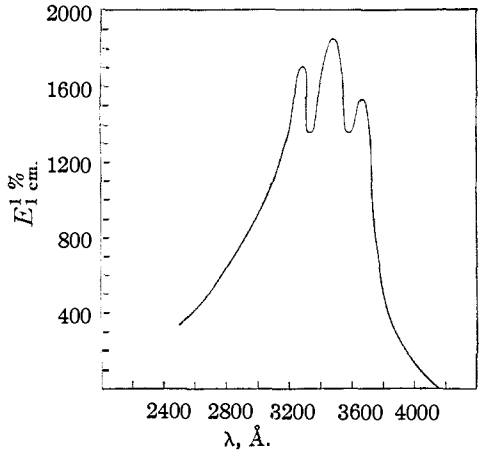


Fig. 3.—Absorption spectrum in ethanol of dehydrobrominated (pyridine hydrobromide) glycol ethyl ether (VII)—"*allo*-vitamin A ethyl ether."

In view of the peculiar nature of its spectrum, one cannot state unequivocally at present that this substance is the normal ethyl ether of vitamin A, in spite of the fact that other evidence seems to point strongly to this conclusion. For this reason, the term "*allo*-vitamin A ethyl ether" is suggested.

A summary of the spectroscopic data of the important compounds discussed in this paper is given in Table II.

TABLE II

SUMMARY OF ULTRAVIOLET ABSORPTION SPECTRA OF ETHERS AND 5-DEHYDROETHERS OF VITAMIN A (IN ALCOHOL)

Vitamin A ether	$\lambda_{max.}$ Å.	$E^{1\%}_{1\ cm.}$	$\epsilon_{mol.}$	log $\epsilon_{mol.}$
DHME (Fig. 2, curve A)[a]	3220	1600	47680	4.68
MEVA (Fig. 2, curve B)[b]	3230	1560	46800	4.67
MEVA[c]	3250	1090	...	..
MEVA[28]	3250–3280	1415	42450	4.63
MEVA (natural)[29]	3260	1660	49800	4.70
DHEE (Fig. 2, curve C)[d]	3220	1410	43992	4.64
EEVA (Fig. 2, curve D)[e]	3230	1590	49926	4.70
EEVA[f]	3250–3270	1500	47100	4.67
EEVA (Fig. 3)[g]	3300	1690	53066	4.70
	3480	1830	57462	4.76
	3670	1520	47728	4.68

[a] 5-Dehydromethyl ether of vitamin A from VI. [b] Methyl ether of vitamin A from VIII. [c] Methyl ether of vitamin A via dehydrobromination of either the dibromide of VII or the bromide of X purified by fractionation at temps. between 0 and −78°. This sample exhibits also the 2850–2900 A. band. [d] 5-Dehydroethyl ether of vitamin A prepared by dehydration of either VI or IX purified via low temperature fractionation and chromatography + molecular distillation. [e] Ethyl ether of vitamin A from VIII via reduction with Zn dust + aqueous alcoholic alkali. [f] Ethyl ether of vitamin A via dehydration of the carbinol X with *p*-toluenesulfonic acid, purified by low temperature fractionation. [g] *allo*-Vitamin A ethyl ether via the dehydrobromination (pyridine hydrobromide) of either VII or X purified by chromatography + molecular distillation.

Experimental

Methyl Vinyl Ketone.—Methyl vinyl ketone was made by the dehydration of β-hydroxyethyl methyl ketone which was prepared by the condensation of acetone with formaldehyde in the presence of small amounts of sodium hydroxide. β-Hydroxyethyl methyl ketone (1150 g.) was best dehydrated by dropping it slowly into hot (160°) *n*-dibutyl phthalate (160 g.) containing 3 g. of iodine and 3 g. of hydroquinone. A yield of 590 g. of crude methyl vinyl ketone was obtained. This was further purified by distilling it from 190 g. of acetic anhydride,[35] followed by fractionation from a six-plate Podbielniak column; b. p. 81°; d^{25}_4 0.842; $n^{22}D$ 1.4095; $n^{15}D$ 1.4120. A yield of 10–15% was obtained based on the formaldehyde used. Pure methyl vinyl ketone is stable for long periods of time over hydroquinone at 0°, but should be freshly distilled as needed.

4-Methoxybutanone-2.—All attempts to make this ketone by the methylation of 4-hydroxybutanone-2 were unsuccessful. It was finally prepared by the method of Killian, Hennion and Nieuwland[16] from methyl vinyl ketone, anhydrous methanol and boron trifluoride-etherate.[36] A yield of 45–51% was obtained based on the amount of methyl vinyl ketone used; b. p. 142–143°; $n^{23}D$ 1.4045. This product had a negligible active hydrogen (Zer.), 0.08.

Anal. Calcd. for $C_5H_{10}O_2$: C, 58.82; H, 9.8. Found: C, 58.73; H, 9.8.

4-Ethoxybutanone-2.—This ketone was made by two independent methods: (1)[14] From β-ethoxypropionyl chloride [b. p. 43–45° (10 mm.)] and cadmium dimethyl.[15] Best results were obtained when the cadmium dimethyl was prepared from methylmagnesium chloride rather than from the corresponding iodide. A yield of 20% of the ketone was obtained; b. p. 43–45° (16 mm.); 2,4-dinitrophenylhydrazone, m. p. 89–90° (from alcohol).

Anal. Calcd. for $C_{18}H_{16}N_4O_8$: N, 18.95; OC_2H_5, 15.23. Found: N, 19.0, 19.0; OC_2H_5, 15.6.

(2) The second procedure was based on the addition of absolute ethanol to methyl vinyl ketone in the presence of boron trifluoride-etherate. This method was employed several times for the preparation of this ketone, and yields were obtained from 52 to 77%; b. p. 149–150° (764 mm.); 74° (50 mm.); 61–62° (23 mm.).

Anal. Calcd. for $C_6H_{12}O_2$: C, 62.04; H, 10.32. Found: C, 62.44, 61.98; H, 10.46, 10.28.

4-Isopropoxybutanone-2.—Using the boron trifluoride-etherate method, this ketone was prepared in 33.5% yield; b. p. 72–75° (37 mm.).

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.63; H, 10.74. Found: C, 64.63, 64.88; H, 9.90, 10.00; active hydrogen (Zer.), 0.1.

4-*t*-Butoxybutanone-2.—This ketone was prepared by the same method as the previous ketone: b. p. 54–57° (15 mm.); $n^{20}D$ 1.4137.

Anal. Calcd. for $C_8H_{16}O_2$: C, 66.7; H, 11.1. Found: C, 66.83, 66.89; H, 12.19, 11.17; active hydrogen (Zer.), 0.14. A semicarbazone was prepared, m. p. 127–129°.

3-Methyl-5-ethoxypentyn-1-ol-3 (II, R = ethyl).—The preparation of this acetylene carbinol from 4-ethoxybutanone-2 and sodium acetylide in liquid ammonia or potassium acetylide in *t*-butyl alcohol resulted in low yields of the desired product and large amounts of resinous products. However, with lithium acetylide in liquid ammonia, yields of 30–40% of the desired product were obtained in accordance with the following procedure. A liter of liquid ammonia was saturated with dry acetylene and while the latter was passing through the solution, 7.6

(35) White and Howard, *J. Chem. Soc.*, 25 (1943).

(36) Hennion, Hinton and Nieuwland, THIS JOURNAL, **55**, 2858 (1933).

g. of lithium was added with stirring in the course of one hour. Stirring was continued until the solution was decolorized. The mixture was then cooled to −70° and 116 g. of 4-ethoxybutanone-2 was added dropwise in the course of one and one-half hours with acetylene passing through the solution. Stirring was continued for two hours longer, then the ammonia was allowed to evaporate and the residual product acidified with concentrated solution of tartaric acid. Finally, the mixture was extracted several times with ether, the ethereal extracts dried and the ether removed. The crude product was fractionated under reduced pressure and the fraction (46–50 g.) boiling at 67° (7 mm.) collected and analyzed; $n^{25}D$ 1.4370; *MR*, 40.41; calcd. *MR*, 40.32; d^{25}_4 0.922.

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.58; H, 9.93; unsaturation, 2.0 ⌐; active hydrogen (Zer.), 2.0. Found: C, 67.59, 67.83; H, 9.44, 9.55; unsaturation, 2.11 ⌐ (Pd); active hydrogen (Zer.), 2.06, 1.95.

Following the same procedure, the corresponding 5-methoxyacetylene carbinol was prepared in 25% yield, b. p. 80–81° (25 mm.).

3-Methyl-5-ethoxy-3-pentenyne-1 (III).—This enyne was prepared by passing upwards through a hot tube (270–280°) charged with a mixture of aluminum phosphate (17 g.) and pumice (37 g.) the acetylene carbinol (II) at the rate of about 0.6 g. per minute and under a nitrogen pressure of 35 mm. A yield of 50% was obtained per pass; b. p. 68–70° (37 mm.); $n^{25}D$ 1.4448; *MR*, 39.4; calcd. 38.33; d^{25}_4 0.839. An absorption spectrum showed a maximum at 2250 Å., log $\epsilon_{mol.}$, 4.095.

Anal. Calcd. for $C_8H_{12}O$: unsaturation, 3.0 ⌐; active hydrogen, 1.0. Found: unsaturation, 3.1 ⌐; active hydrogen (Zer.), 1.01.

1-[2′,6′,6′-Trimethylcyclohexen-1′-yl]-3,7-dimethyl-9-methoxy-1-nonen-yne-5-diol-3,7 (VI, R = methyl).—A Grignard was prepared in 800 cc. of anhydrous ether from 9.8 g. of magnesium and 43.9 g. of freshly distilled ethyl bromide. The mixture was then cooled to 0° in an atmosphere of nitrogen and to it was added, in the course of thirty minutes with rapid stirring, 48.1 g. (active hydrogen, 1.94) of the acetylene carbinol (V) in 50 cc. of anhydrous ether. The mixture was then refluxed gently in nitrogen for five hours, cooled to 0° and to it added, in the course of twenty minutes, 23.3 g. of 4-methoxybutanone-2 in 20 cc. of anhydrous ether. A whitish precipitate separated out immediately. To complete the reaction the mixture was stirred in nitrogen for twenty-four hours, then cooled and hydrolyzed with a mixture of ice (480 g.) and ammonium chloride (48 g.) and the resulting product extracted several times with ether. The combined ether extracts were washed once with 50 cc. of 10% salt solution, dried with anhydrous magnesium sulfate, and the ether removed. The residue was then subjected to a high vacuum (10^{-5} mm.) at 100° for two hours to remove low boiling constituents. A yield of 63.7 g. (88%) of a yellowish highly viscous product was obtained.

Heating the glycol under high vacuum failed to remove entirely the unreacted acetylene carbinol, so further purification was effected by removing the latter as its silver salt. To a solution of 63.7 g. of the crude glycol in 140 cc. of absolute ethanol was added 35.2 g. of silver nitrate in 240 cc. of absolute ethanol and 120 cc. of concentrated ammonia (d = 0.901). The mixture was protected from light and shaken in nitrogen for twenty minutes, then centrifuged to remove the silver salt of the acetylene carbinol. The clear alcoholic layer was then diluted with an equal volume of water and extracted several times with petroleum ether. The combined petroleum ether extracts were washed with water and dried over anhydrous magnesium sulfate. The mixture was then filtered, the petroleum ether removed and the pale yellow residue subjected to a vacuum of 10^{-5} mm. at 50° for one hour. A yield of 49.5 g. of a gummy product was obtained. Attempts to crystallize this glycol were not successful. Analyses are recorded in Table III.

1-[2′,6′,6′-Trimethylcyclohexen-1′-yl]-3,7-dimethyl-9-ethoxy-1-nonen-yne-5-diol-3,7 (VI, R = ethyl; left → right).—This glycol ether was prepared in the same manner as the corresponding glycol methyl ether except that the Grignard of the acetylene glycol (V) was added to an ethereal solution of 4-ethoxybutanone-2 instead of the reverse. A yield of 92% of the crude product was obtained. This was purified by removing the unreacted acetylene carbinol as its silver salt and the glycol ether obtained partitioned between equal volumes of 90% methanol and petroleum ether. The glycol ether was recovered from the methanol layer by adding two volumes of 10% salt solution and extracting with petroleum ether. A yield of 85% of the purified product was obtained as a pale yellow gum. An ultraviolet absorption spectrum of this substance showed a principal band with a maximum at 2260 Å.; long $\epsilon_{mol.}$, 4.044. Analytical data are given in Table III.

When this glycol (31 g.) was dissolved in petroleum ether and the solution allowed to stand under nitrogen at −20° for several weeks, a white crystalline product (9.2 g.) separated out, m. p. 41–42°. Further successive coolings of the mother liquor from −20 to −78° failed to produce any more crystalline product. The solid was recrystallized several times from petroleum ether at −10 to −20° until a constant m. p. of 68–69° was obtained. An ultraviolet absorption spectrum of this product showed a band with a maximum at 2260 Å.; log $\epsilon_{mol.}$, 4.12. Analytical data are given in Table III.

1-[2′,6′,6′-Trimethylcyclohexen-1′-yl]-3,7-dimethyl-9-ethoxy-1-nonen-yne-5-diol-3,7 (VI, R = ethyl; right → left).—A Grignard was prepared from 19.5 g. of magnesium and 87.5 g. of ethyl bromide. The mixture was cooled to 0° in an atmosphere of nitrogen and to it was added dropwise 57 g. (7.5% excess) of the acetylene carbinol (II, R = ethyl) in the course of one hour. The mixture was then allowed to stir in nitrogen for ten hours, then cooled to 0° and to it was added dropwise 77 g. of the aldehyde (IV) in 100 cc. of ether in the course of one and a half hours. Stirring was continued at room temperature for twenty-four hours, then the mixture was hydrolyzed with a saturated solution of ammonium chloride containing 80 g. of the latter. A yield of 120 g. of the crude glycol was obtained which was purified in the same manner as the glycol prepared from left to right. A yield of 112 g. of the purified product was obtained as a pale yellow gum which had an ultraviolet spectrum with a maximum at 2260 Å.; log $\epsilon_{mol.}$, 3.992. Other analytical data are given in Table III.

When 112 g. of this glycol was dissolved in a liter of petroleum ether and the solution allowed to stand under nitrogen at −20° for several weeks, a white solid (60 g.) separated out which had a m. p. of 41–47°. This was recrystallized several times from petroleum ether at −10 to −20° until a constant m. p. of 67–68° was obtained. An ultraviolet absorption spectrum showed a maximum at 2260 A., log $\epsilon_{mol.}$, 4.018. Other analytical data are given in Table III.

5-Dehydroglycol isopropyl and 5-dehydroglycol *t*-butyl ethers were synthesized in the same manner as the 5-dehydroglycol methyl ether from the Grignard of the acetylene carbinol (V) and 4-isopropoxybutanone-2 and 4-*t*-butoxybutanone-2, respectively. The products were purified only to the stage of removing the volatile constituents by heating at 100° (10^{-4} mm.) for one hour.

The high hydrogenation values shown in Table III are due to partial hydrogenolysis of the hydroxyl groups in the presence of a large excess of catalyst usually required for obtaining quick and accurate estimation of unsaturation with an especially designed semicrohydrogenation apparatus[37] which was thoroughly tested with several known unsaturated compounds.

1-[2′,6′,6′-Trimethylcyclohexen-1′-yl]-3,7-dimethyl-9-ethoxy 1,7-nonadien-yne-5-ol-3 (IX).—A Grignard was prepared in 300 cc. of anhydrous ether from 1.4 g. of magnesium and 6.0 g. of ethyl bromide. The Grignard was cooled to 0° in nitrogen and to it was added dropwise 6.8 g. of 3-methyl-5-ethoxy-3-pentyne-1 (III). The

(37) Rivers, Ph.D. Thesis, M. I. T., 1941, p. 48.

TABLE III

ANALYTICAL DATA OF 5-DEHYDROGLYCOL ETHERS

5-Dehydroglycol-ethers	Yield, %	M. p., °C.	Analyses C Calcd.	C Found	H Calcd.	H Found	A. H. (Zer.) Calcd.	A. H. (Zer.) Found	H_2 (Pd, Pt) Calcd.	H_2 (Pd, Pt) Found
										4.1 (Pd)
Methyl (1 → r)[a]				75.42		9.97		1.98		5.9 (Pt)
($C_{21}H_{34}O_3$)	74	Gum	75.44	75.09	10.24	10.01	2.0	1.93	4.0	5.4 (Pt)
										4.67(Pd)
Ethyl (1 → r)				75.97		11.01		2.15		4.89(Pd)
($C_{22}H_{36}O_3$)	80–85	Gum	75.81	75.55	10.41	11.17	2.0	2.12	4.0	5.15(Pt)
				75.79		10.79				4.99(Pt)
Ethyl (1 → r)										5.27(Pt)
solid	30–40	68–69	75.81	75.95	10.41	10.42	2.0	2.2	4.0	5.31(Pd)
Ethyl (r → 1)[b]				75.5		10.3		2.06		5.47(Pt)
($C_{22}H_{36}O_3$)	85–88	Gum	75.81	75.2	10.41	10.5	2.0	2.09	4.0	5.16(Pt)
Ethyl (r → 1)				75.6		10.5		1.93		
solid	40–50	67–68	75.81	75.2	10.41	10.6	2.0	2.10	4.0	4.95(Pt)
Isopropyl (1 → r)										
($C_{23}H_{38}O_3$)	54	Gum	...	...	...	...	2.0	1.80	4.0	5.6 (Pt)
t-Butyl (1 → r)				75.1		10.13		1.97		
($C_{24}H_{40}O_3$)	79	Gum	76.55	74.9	10.58	10.02	2.0	1.91	4.0	4.8 (Pt)

[a] (1 → r) indicates the preparation of the glycol by adding the Grignard of the acetylene carbinol (V) to the corresponding 4-alkoxybutanone-2. [b] (r → 1) indicates the preparation of the glycol by adding the Grignard of the acetylene carbinol (II) to aldehyde (IV).

mixture was allowed to stir overnight at room temperature, then cooled to 0° and to it added dropwise in the course of one hour 10.8 g. of the aldehyde (IV) in equal volume of ether and again allowed to stir in nitrogen at room temperature overnight. Finally, the mixture was hydrolyzed with excess cold concentrated ammonium chloride solution and the product recovered and heated for one hour at 100° (10^{-4} mm.) to remove low boiling products; yield, 13.5 g., (75%). This was further purified by distillation in a molecular still of the falling film type and the fraction (almost all of the product) distilling at 156° (0.005 mm.) collected and analyzed; $n^{25}D$ 1.5169. An ultraviolet absorption spectrum showed a maximum at 2320 Å.; log $\epsilon_{mol.}$, 4.315.

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.94; H, 10.36; unsaturation, 5 ⌐¬; active hydrogen (Zer.), 1.0. Found: C, 79.67, 79.80; H, 10.2, 10.16; unsaturation, 5.31 ⌐¬ (Pt), 5.20 (Pd) ⌐¬; active hydrogen, (Zer.), 1.15, 1.1.

Selective Hydrogenation of 5-Glycol Ethers.—Attempts to add two hydrogen atoms to the acetylene bond of the 5-dehydroglycol ethers chemically were not successful. For example, the solid 5-dehydroglycol ethyl ether, m. p. 68–69°, was treated in methanol or in liquid ammonia with sodium or lithium, or with a large excess of calcium in 90% ethanol and in every case the product was recovered unchanged; *e. g.*, melting point, hydrogenation and active hydrogen determinations were identical with the original; even mixed melting point with the original showed no depression. Catalytic hydrogenation in alcohol, however, using 1% palladium deposited on calcium carbonate showed a high degree of selectivity, so that all of our preparations, including that of 1-[2′,6′,6′-trimethylcyclohexen-1′-yl]-3,7-dimethyl-9-ethoxy-1,7-nonadien-yne-5-ol-3 (IX) were partially hydrogenated by adding one mole equivalent of hydrogen to each. In most of the cases the products recovered were checked by hydrogenation and active hydrogen estimations.

Conversion of the Glycol Ethers (VII) into the Dihalides.—Phosphorus trichloride, tribromide and triiodide were first tried as halogenating agents both in the presence and absence of pyridine. Phosphorus tribromide was found to give the best results. To 100 cc. of dry benzene was added 25 g. of freshly distilled phosphorus tribromide and dry purified nitrogen was allowed to bubble through the solution for five to ten minutes to displace any free hydrogen bromide present. The mixture was then cooled to 0° and, while nitrogen was bubbling through it, 15.3 g. of the glycol (VII, left → right) in 100 cc. of benzene and 22 cc. of dry pyridine was added dropwise in the course of fifteen minutes. The mixture was allowed to stand at 0° for one-half hour, then heated to 60–80° for one hour. The mixture was then cooled, diluted with water and the layers separated. The organic layer was extracted several times with a 5% solution of phosphoric acid, dried and the solvent removed under reduced pressure. The residue was subjected to a high vacuum (10^{-4} mm.) at 50° for one hour; yield of a highly viscous brownish residue, 13 g.

Anal. Calcd. for $C_{21}H_{34}OBr_2$: Br, 34.57. Found: Br, 31.61, 31.60.

The low bromine was due to a partial hydrolysis of the tertiary bromine and to a slight dehydrobromination, since the dibromide showed a small amount of active hydrogen and bands of low intensity at 2850 and 3250 Å.

Dehydrobromination of the Dibromides.—Ordinarily the dehydrobromination was accomplished without isolating the dibromide. Following the above experiment as a typical example, the benzene and other volatile products were removed at the end of the reaction under reduced pressure and to the residue was added 400 cc. of hot 95% alcohol containing 40 g. of potassium hydroxide. Heating was continued in nitrogen at 60–80° under a slightly reduced pressure for one hour, then most of the alcohol was removed and the residue cooled, diluted with six volumes of water and extracted with 4 × 100 cc. of olefin-free petroleum ether. The extract was shaken several times with 5% phosphoric acid solution, then with 10% salt solution, and dried with magnesium sulfate. When the petroleum ether was removed, a yield of 10.9 g. (82%) of the crude product was obtained. This was distilled under a highly reduced pressure and the pale yellow fraction (8 g.) boiling at 90–95° (10^{-4}–10^{-5} mm.) was collected and analyzed. Spectroscopically, this sample had two prominent bands in the ultraviolet, one at 3250 Å.; $E^{1\%}_{1\,cm.}$ 535, the other at 2850 Å.; $E^{1\%}_{1\,cm.}$ 655, and two feeble indications at 3450 and 3710 Å., respectively. With antimony trichloride in chloroform, it gave a deep blue color with maxima at 5800 and at 6180–6200 Å., respectively (Fig. 1, curves with broken lines). Biological results of products prepared by this method are given in Table I, assays 1–9.

Anal. Calcd. for $C_{21}H_{32}O$: C, 83.93; H, 10.73; OCH_3, 10.33; unsaturation, 5 ⌐¬; active hydrogen, 0.0. Found: C, 81.88, 82.09; H, 10.95, 11.12; OCH_3, 11.2; unsaturation, 4.96 (Pd), 5.11, 5.17 (Pt) ⌐¬; active hydrogen (Zer.), negligible.

Repeated distillation of a sample having an $E^{1\%}_{1\text{ cm.}}$ (3250 Å.) value of 1000 at 10^{-5} mm. from a shallow vessel caused considerable decomposition of the vitamin ether. In fact, after five consecutive distillations the band at 3250 Å. had vanished completely. Another sample from a single distillation was fractionated in absolute methanol at temperatures between 0 and −78° and the product (pale yellow solid) insoluble below −40° separated and analyzed spectroscopically. It was found to have a prominent band at 3250 Å.; $E^{1\%}_{1\text{ cm.}}$ 1090.

Dehydrochlorination of the Glycol Methyl Ether (VII, left → right) via Thionyl Chloride and Alcoholic Potash.—A solution of 5.96 g. of freshly distilled thionyl chloride in 10 cc. of ether was added dropwise in the course of fifteen minutes to a well-stirred mixture of 8.5 g. of the glycol methyl ether (VII), 3.96 g. of anhydrous pyridine and 20 cc. of ether, maintained at 0° with nitrogen passing through the solution. The mixture was allowed to come to room temperature, then heated on the water-bath to 60–80° for three hours. During this time all the ether had evaporated, and the residue was cooled and extracted with petroleum ether, the latter removed and the residue (7 g.) analyzed. It gave a deep blue color with antimony trichloride in chloroform and a broad band in the ultraviolet between 3000 and 3300 Å. with an $E^{1\%}_{1\text{ cm.}}$ (3250 Å.) value of 350, showing definite spontaneous dehydrochlorination.

To completely dehydrochlorinate the above product, it was mixed with 60 cc. of methanol containing 3 g. of potassium hydroxide and the mixture heated on the water-bath in an atmosphere of nitrogen for two hours, then cooled, diluted with three volumes of water and extracted with petroleum ether, the extract washed with 10% tartaric acid solution and dried over magnesium sulfate. The final product was free from chlorine, and was purified further by fractionation at low temperatures from a 50–50 mixture of absolute methanol and petroleum ether. A small amount of brown solid separated at −70° which had an ultraviolet spectrum in the region of 3100–3300 Å. and gave a deep blue color with antimony trichloride in chloroform, but was discarded because it was found to contain sulfur. The filtrate yielded a product free from sulfur and chlorine and was found to exhibit two maxima in the ultraviolet; one at 2830 Å.; $E^{1\%}_{1\text{ cm.}}$ 650; the other at 3250–3280 Å.; $E^{1\%}_{1\text{ cm.}}$ 502. When fed to vitamin A deficient rats, it was found biologically active in doses of 10 to 28 γ. Other analytical data of this product were no different from those obtained by the dehydrobromination method using phosphorus tribromide. Similar results were obtained by the dehydrochlorination of the glycol ethyl ether (right → left) using thionyl chloride and alcoholic potash.

The dehydrobromination of the glycol isopropyl (VII, R = isopropyl) and the glycol *t*-butyl (VII, R = *t*-butyl) ethers (left → right) was effected in the same manner as that of the corresponding glycol methyl ether using the phosphorus tribromide method. Yields of about 50–60% were obtained. After preliminary purification from methanol at low temperatures, the isopropyl ether was distilled from a shallow vessel and the product, a yellow viscous liquid, boiling at 87–90° (10^{-5} mm.) was collected and tested spectroscopically and biologically. Table I (assays 11 and 12) gives the biological results of this ether. Spectroscopically it exhibited the usual two broad bands; one at 2800–2900 Å. and the other at 3100–3300 Å. The spectrum of the antimony trichloride color also showed two maxima; one at 5800 Å.; $E^{1\%}_{1\text{ cm.}}$ 506, and the other at 6180 Å.; $E^{1\%}_{1\text{ cm.}}$ 367.

The *t*-butyl ether could not be distilled without appreciable decomposition, so it was fractionated at low temperatures from methanol and the fraction which separated out below −30° was tested biologically and spectroscopically. Assay 13 of Table I gives the biological test on rats of this crude sample of vitamin A *t*-butyl ether. Spectroscopically it also gave the two usual broad bands in the ultraviolet. The spectrum of the antimony trichloride color gave the usual two maxima: one at 5800 Å.; $E^{1\%}_{1\text{ cm.}}$ 388 and the other at 6180–6200 Å.; $E^{1\%}_{1\text{ cm.}}$ 200. This work was done during the early part of the war and no further attempt was made to purify these ethers. However, an attempt was made to convert both of these ethers by the method of Rigby[38] into the corresponding palmitic and acetic esters of vitamin A by treating them with palmityl or acetyl chloride in the presence of traces of anhydrous zinc chloride. Partial conversion was actually accomplished, as it was indicated by the saponification number of the esters produced. With acetyl chloride, the acetate produced had a saponification number between 270 and 300, as against the theoretical of 328. In view of the difficulty encountered in the purification of these esters no further work was done along these lines.

Direct Dehydration of Glycol Methyl Ether (VII, left → right).—Preliminary investigation on the direct dehydration of 1,4-glycol model compounds of the type of the glycol (VII) led to the production of dihydrofurans. However, when 5.7 g. of the glycol methyl ether (VII) was dehydrated in toluene (190 cc.) in the presence of 0.3 g. of *p*-toluenesulfonic acid, by distilling in nitrogen 60 cc. of toluene, a product was obtained which behaved like that obtained by the dehydrobromination process. When distilled from a shallow vessel, a yellow oil (2 g.) was obtained boiling at 90–95° (10^{-4}–10^{-5} mm.). It gave a deep blue color with antimony trichloride in chloroform and exhibited the usual dual maxima in the ultraviolet. Upon hydrogenation it absorbed 4.98 moles of hydrogen as against the theoretical of 5 for the methyl ether of vitamin A. A Zerewitinoff determination showed less than 0.1 active hydrogen, indicating the absence of hydroxyl groups. The preliminary assay 10, Table I, shows the biological activity of this product.

Dehydrobromination of Glycol Ethyl Ether (VII, right → left) via Pyridine Hydrobromide and Alcoholic Potash.—To 40 g. of dry pyridine was added 4.5 g. of dry gaseous hydrogen bromide. The partly solid-partly liquid mixture was cooled in nitrogen and to it was added 8.5 g. of solid glycol ethyl ether (VII) in 50 cc. of anhydrous benzene and heated on the water-bath for three hours while nitrogen was slowly bubbling through it. Most of the solvent was then removed under reduced pressure and to the residue was added 100 cc. of 10% hot alcoholic potash, and the mixture again heated on the water-bath for one-half hour. It was then cooled in nitrogen, diluted with three volumes of water and extracted with petroleum ether. The petroleum ether extract was shaken with 5% phosphoric acid solution, then with water and dried over magnesium sulfate. From the final solution was obtained a yellowish-brown viscous liquid (6.5 g.) which gave a deep blue color with antimony trichloride in chloroform, and exhibited two bands in the ultraviolet: one of very high intensity at 3000–3700 Å. and the other of very low intensity at 2850–2900 Å. For further purification, it was partitioned between equal volumes (100 cc.) of 83% ethanol and petroleum ether, the latter was washed with water, dried and passed through a column 4′ × 1″ filled with 40–60 mesh activated alumina (ALORCO). The column was further washed with a total of 1500 cc. of petroleum ether and the latter removed from the washings; a yellow residue (4.5 g.) remained. This was distilled in a molecular still of the falling film type and the largest fraction (3.5 g.), a clear yellow highly viscous liquid, boiling at 95–98° (10^{-4}–10^{-5} mm.) (bath temperature 145–150°), collected and analyzed. This gave a deep blue color with antimony trichloride and a fine structure

(38) Rigby, Ph.D. Thesis, M. I. T., 1930.

in the ultraviolet of three bands (Fig. 3): one at 3300 A.; $E^{1\%}_{1\ cm.}$ 1690; a second at 3480 Å.; $E^{1\%}_{1\ cm.}$ 1830; and a third at 3670 Å.; $E^{1\%}_{1\ cm.}$ 1520. No distinct bands developed on the alumina, and the product eluted from it with hot ethyl alcohol exhibited the usual two bands in the ultraviolet, but with lower intensity.

Anal. Calcd. for $C_{22}H_{34}O$: C, 84.00; H, 10.89; OC_2H_5, 14.03; unsaturation, 5.0 ⌐; mol. wt., 314.5. Found: C, 82.78, 83.32; H, 10.50, 10.90; OC_2H_5, 13.26; unsaturation, 4.94, 5.06 ⌐ (Pt); mol. wt. (in benzene), 313.7, 310.3, 310.2.

After standing at 0° in nitrogen for over six months, it partially crystallized into pale yellow needles which had a m. p. of 28–30°.

The dehydrobromination of the glycol ethyl ether (left → right) by the above method gave similar results, except much lower yields of the desired product. Similarly, the dehydrobromination of the carbinol (X) by the same procedure yielded a product which in its crude form showed two bands in the ultraviolet; one with a low intensity at 2800–2900 Å., and another with a high intensity at 3000–3700 Å.

Dehydration of the Carbinol (X).—To 150 cc. of thiophene-free toluene was added 0.09 g. of *p*-toluenesulfonic acid and 25–30 cc. of toluene distilled to remove traces of water present in the mixture. The toluene solution was then cooled in nitrogen and to it was added 4.5 g. of the carbinol (X) in 60 cc. of toluene. Enough toluene (50–60 cc.) was then distilled in nitrogen until the distillate was completely free from cloudiness. The contents (reddish-brown) of the flask was cooled and treated with 50 cc. of methanol containing 2.5 g. of potassium hydroxide. Enough water was then added to separate the layers, the organic layer removed, washed with water, and dried over magnesium sulfate. When the toluene was completely removed, a reddish-brown viscous liquid (3.8 g.) remained. This gave a blue color with antimony trichloride in chloroform and exhibited two broad bands in the ultraviolet; one at 2800-2900 Å. and the other at 3000–3400 Å., the latter being more intense. To further purify this product, it was partitioned between 100 cc. of petroleum ether and 100 cc. of 90% methanol. Most of the product went into the petroleum ether which was washed with water, dried, and the solvent removed under reduced pressure. The residue was taken up in absolute methanol and fractionated at temperatures between −10 and −78°, the product (a yellow semi-solid) which separated out in various fractions below −40° recovered in methanol and extracted from it with petroleum ether by adding 5% salt solution. From the petroleum ether a product was obtained which gave a deep blue color with antimony trichloride in chloroform and exhibited a single band in the ultraviolet with a well-defined maximum at 3250–3270 Å.; $E^{1\%}_{1\ cm.}$ 1500 and log $\epsilon_{mol.}$ 4.67 (see Table II).

Dehydration of 5-Dehydroglycol Methyl Ether (VI left → right) to 5-Dehydrovitamin A Methyl Ether (VIII).—The 5-dehydroglycol methyl ether (31.5 g.) was dehydrated in toluene (400 cc.) using *p*-toluenesulfonic acid (0.7 g.) in the usual manner. The dehydrated product was first treated with 5% methyl alcoholic potash followed by partitioning between equal volumes of petroleum ether and 90% methanol. The petroleum ether layer was washed with water, dried and the solvent removed; yield, 24 g. This product gave a purplish-blue color with antimony trichloride in chloroform and two broad bands in the ultraviolet: one with a high intensity at 3000–3300 Å., the other with a low intensity at 2800–2900 Å. When distilled under a high vacuum from a shallow vessel, a clear light orange liquid came over at 85–95° (10^{-4}–10^{-5} mm.). This was tested biologically and the results are given in Table I, assay 14. Hydrogenation of this sample showed the presence of 6.35 double bonds and showed negligible active hydrogen (Zer.). Although the hydrogen analysis was close to the theoretical value the carbon was about 2% low. Further purification was effected by alternate distillation and low temperature fractionation from absolute methanol. The results are given in Table IV. The product from the second distillation was again tested biologically (Table I, assay 15).

The final product (see Table IV) was a light orange viscous oil, having the following analytical data:

Anal. Calcd. for $C_{21}H_{31}O$: C, 84.50; H, 10.13; OCH_3, 10.39; unsaturation, 6.0 ⌐. Found: C, 83.87, 83.60; H, 10.34, 9.92; OCH_3, 11.25; unsaturation, 6.3, 6.08, 6.1 ⌐ (Pt).

A freshly distilled sample of 5-dehydrovitamin A methyl ether (7.8 g.) with an $E^{1\%}_{1\ cm.}$ (3200 Å.) value of 1000 was selectively hydrogenated in absolute ethanol by adding to it one mole-equivalent of hydrogen in the presence of 1% palladium deposited on calcium carbonate (using one-half the weight of the sample). The crude product was recovered and analyzed spectroscopically. It was found to have a peak at 3220–3230 Å.; $E^{1\%}_{1\ cm.}$ 886. This was further purified by low temperature fractionation from absolute methanol and the fraction insoluble below −30° recovered and distilled under high vacuum. A product (yellow oil) boiling at 90–95° (10^{-4} mm.) was collected and analyzed. It gave a blue color with antimony trichloride in chloroform, the transmission spectrum of which is shown in Fig. 1 (solid line curves). In this case the 6180 Å. maximum is much more intense than that of the 5800 Å. with an $E^{1\%}_{1\ cm.}$ value of 3284. The ultraviolet absorption spectrum showed a single well-defined band with a maximum at 3230 Å.; $E^{1\%}_{1\ cm.}$ 1560 (Fig. 2, curve B). Hydrogenation showed the presence of 5.15 (Pt) double bonds.

TABLE IV

THE EFFECT OF ALTERNATE HIGH VACUUM DISTILLATION AND LOW TEMPERATURE FRACTIONATION ON 5-DEHYDROVITAMIN A METHYL ETHER

No. of distillations (10^{-4}–10^{-5} mm.) and low temp. fractionations	$\lambda_{max.}$, Å	$E^{1\%}_{1\ cm.}$ max.
Second distillation	3180	1300
Third distillation	3180	1200
Fourth distillation	3200	844
First fractionation (methanol) of distilled product (4th time)	3190	1090
Second fractionation	3200	1120
Third fractionation	3200	1140
Distillation of final fractionated sample	3220	1600 (Curve A, Fig. 2)

Ozonization of Vitamin A Methyl Ether (XI).—A sample (1.81 g.) of the vitamin A methyl ether prepared by the foregoing method and kept under nitrogen at −20° for over two years was ozonized by the method of Strain.[39] It yielded about 0.5 g. (26%) of crude sodium bicarbonate soluble geronic acid 2,4-dinitrophenylhydrazone. This was recrystallized several times from aqueous acetic acid and from aqueous methanol; m. p. 133.5–134.5° (cor.). Mixed m. p. with an authentic sample of geronic acid 2,4-dinitrophenylhydrazone showed no depression; 134–134.5° (cor.).

Dehydration of 5-Dehydroglycol Ethyl Ether (VI, left → right).—The 5-dehydroglycol ethyl ether (22 g.) was dehydrated in toluene (550 cc.) in the presence of 0.45 g. of *p*-toluenesulfonic acid using the general procedure adopted in this paper. The crude product was treated with 5% methyl alcoholic potash, then partitioned between equal volumes (200 cc.) of petroleum ether and 90% methanol. The fraction taken by the petroleum ether was recovered (15.5 g.) and fractionated several times in

(39) Strain, *J. Biol. Chem.*, **102**, 137 (1933).

absolute methanol between 0 and −78° and the fractions insoluble below −30° (orange-yellow solid) were combined and distilled from a shallow vessel under a high vacuum. A light orange oil boiling at 95–98° (10^{-4}–10^{-5} mm.) was collected and analyzed. The ultraviolet spectrum showed a single, well-defined band with a maximum at 3210–3220 Å.; $E^{1\%}_{1\,cm.}$ 1400.

Anal. Calcd. for $C_{22}H_{32}O$: C, 84.55; H, 10.33; unsaturation, 6.0 ⌐═; active hydrogen, 0.0. Found: C, 84.58, 85.22; H, 10.90, 11.00; unsaturation, 6.1, 6.2 ⌐═ (Pt), 6.05 ⌐═ (Pd); active hydrogen (Zer.), 0.05 (within experimental error).

Dehydration of 5-Dehydroglycol Ethyl Ether (VI, right → left).—This glycol ethyl ether (20 g.) was dehydrated in the same manner as the previous sample in 500 cc. of toluene and in presence of 0.4 g. of *p*-toluenesulfonic acid. After washing with 5% methyl alcoholic potash and partitioning between petroleum ether and 90% methanol, a product (14 g.) was obtained which had an $E^{1\%}_{1\,cm.}$ (3210 Å.) value of 1320. Further purification was effected by dissolving the product in petroleum ether and passing it with nitrogen through a 4′ × 1″ column packed with 40–60 mesh of activated alumina (ALORCO). The column was then washed with 1.5 liters of petroleum ether and the unadsorbed portion (11–12 g.) was recovered from the petroleum ether and fractionated once at low temperatures from absolute methanol. The fractions insoluble below −30° were collected and distilled under a high vacuum. An orange-yellow oil boiling at 95–100° (10^{-4}–10^{-5} mm.) was collected and analyzed. It had a single, well-defined band with a maximum at 3220 Å.; $E^{1\%}_{1\,cm.}$ 1410 (Fig. 2, curve C). Upon catalytic hydrogenation (Pt) it absorbed 6.1 moles of hydrogen. Molecular weight determinations in benzene by the freezing point method gave the following values: Calcd. for $C_{22}H_{32}O$: 312.5. Found: 310.7, 308.3, 313.

Dehydration of 5-Dehydrocarbinol Ethyl Ether (IX).—About 10 g. of 5-dehydrocarbinol ethyl ether (IX) was dehydrated in 400 cc. of toluene in the presence of 0.2 g. of *p*-toluenesulfonic acid. The resulting mixture was treated with 5% methyl alcoholic potash and the product recovered from it partitioned between petroleum ether and 90% methanol. The fraction (7.5 g.) taken up by the petroleum ether was recovered and fractionated at low temperatures from absolute methanol. The fractions insoluble below −30° were combined and distilled under high vacuum. An orange-yellow oil was obtained boiling at 95–98° (10^{-4}–10^{-5} mm.). This had a single band with a maximum at 3210–3220 Å.; $E^{1\%}_{1\,cm.}$ 1350.

Anal. Calcd. for $C_{22}H_{32}O$: C, 84.55; H, 10.33; unsaturation, 6.0 ⌐═; active hydrogen, 0.0. Found: C, 83.67, 83.38; H, 10.54, 10.31; unsaturation, 6.10, 6.28 ⌐═ (Pt); active hydrogen (Zer.), 0.03 (negligible).

Ozonization of 5-Dehydrovitamin A Ethyl Ether (VIII).—About 1.5 g. of 5-dehydrovitamin A ethyl ether prepared by the dehydration of 5-dehydroglycol ethyl ether (right → left) was ozonized in the usual manner and the 2,4-dinitrophenylhydrazone precipitated. The bicarbonate soluble portion was recrystallized once from aqueous methanol; m. p. 126.5–127.5° (cor.); yield, 0.3 g. (20%). This was again recrystallized from aqueous methanol three times, and a final m. p. of 134–134.5° (cor.) was obtained. Mixed m. p. with an authentic sample of geronic acid 2,4-dinitrophenylhydrazone gave no depression.

Selective Chemical Reduction of 5-Dehydrovitamin A Ethyl Ether.—The selective chemical reduction of the acetylene bond in 5-dehydrovitamin A ethyl ether was studied using the estimation of unsaturation and the extinction coefficient in the ultraviolet as guides in estimating the degree of reduction. No appreciable reduction was observed when zinc dust and acetic acid in ethanol or calcium in 90% ethanol were used as reducing agents. Sodium in liquid ammonia brought about complete destruction of the molecule. Partial reduction was observed with zinc–copper couple in absolute ethanol and with "Devarda's" (Baker) and Raney alloys in 2% of aqueous (1:9) alcoholic potassium hydroxide. The most successful results were obtained with zinc dust in aqueous alcoholic potassium hydroxide. The following is a representative experiment: 5-Dehydrovitamin A ethyl ether (2.03 g.; unsaturation 6.19 ⌐═ (Pt); $E^{1\%}_{1\,cm.}$ 1350) was dissolved in 90 g. of absolute ethanol and to the solution added, with cooling and purified nitrogen slowly bubbling through it, 10 cc. of water, 6 g. of solid potassium hydroxide and 0.6 g. of zinc dust. Nitrogen was allowed to bubble slowly through the mixture for twenty hours, then 20 cc. of water was added and the reaction allowed to proceed five hours longer. Finally, the mixture was diluted with 20 cc. of water and extracted with petroleum ether, the extract washed with water, dried, and the solvent removed under vacuum. The residue (2 g.) was fractionated at low temperatures from 20 cc. of absolute methanol and the fractions (1.5 g., pale yellow solid) separating below −30° combined and analyzed. An ultraviolet absorption spectrum showed a well-defined band with a maximum at 3230 Å.; $E^{1\%}_{1\,cm.}$ 1590 (Fig. 2, curve D). Hydrogenation (Pt) showed the presence of 4.85–5.2 double bonds. The combined filtrates from the above purification exhibited a band at 3220–3230 Å.; $E^{1\%}_{1\,cm.}$ 1215. This experiment was repeated several times, in some cases with a large excess of zinc dust, and the results were identical.

Acknowledgment.—The authors are indebted to Mrs. Alice R. Lowry, Mrs. Silvia P. Solar, and Mr. S. M. Nagy for most of the analyses; to Mrs. Ruth B. Pitt for assistance in some of the tedious purification experiments; to Miss Therese M. Harrington for assistance in the ozonization and other experiments; and to Professor Robert S. Harris for the biological assays. 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 synthesis of biologically active vitamin A ethers has been achieved via several routes, using 1-[2′,6′,6′-trimethylcyclohexen-1′-yl]-3-methylbuten-1-al-4 as the key intermediate.

2. Synthetic methyl and ethyl ethers of vitamin A have been obtained in relatively pure form. The isopropyl and *t*-butyl ethers have been obtained in less pure form.

3. Several new intermediates used in the various syntheses are described with complete analytical data for the first time.

CAMBRIDGE, MASSACHUSETTS RECEIVED JULY 12, 1947