E corresponds to 0.001 in $pK_1 + pK_2$. Hence, the uncertainty in pK caused by experimental errors is twice that of the conventional method where a single dissociation step is involved.

Summary

The use of electromotive-force measurements of hydrogen–silver chloride cells without liquid junction in resolving the constants for the overlapping dissociation steps of weak dibasic and tribasic acids is discussed. When one constant of an overlapping pair is known, the second can be derived from studies of solutions of the appropriate primary or secondary acid salt with added alkali chloride. The equations for the five possible cases of overlapping have been developed. A simple means of estimating the molalities needed in the computation is described. The method has been applied to a determination of the product of the constants of phthalic acid at 25°. The result is consistent with earlier determinations of the two constants.

WASHINGTON, D. C. RECEIVED OCTOBER 31, 1947

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

Synthesis of Products Related to Vitamin A. IV. The Application of the Darzens Reaction to β-Ionone[1a]

BY NICHOLAS A. MILAS, S. WARREN LEE,[2] EMILE SAKAL,[3] HERBERT C. WOHLERS,[4] NORMAN S. MACDONALD,[5] FRANK X. GROSSI[6] AND HERBERT F. WRIGHT[7]

One of the key intermediates in the synthesis of several biologically active vitamin A products[8] was produced by the application of the Darzens synthesis to β-ionone.[9] The structure of this product presented a special problem in view of the anomalous results obtained in the early stages of our investigation. When β-ionone was condensed with ethyl chloroacetate at low temperatures (−30 to −60°) in anhydrous ether or toluene using alcohol-free sodium ethoxide or methoxide as the condensing agents, the glycidic ester I was produced which upon hydrolysis presumably gave a glycidic acid of similar structure. When the crude glycidic ester was hydrolyzed and the crude glycidic acid decarboxylated in the presence or absence of powdered glass or by passing it under a reduced pressure downwards through a hot tube (140–160°) packed with freshly reduced copper powder on pumice, the decarboxylation product had slightly different properties from that obtained by the decarboxylation of the pyridine salt of the same glycidic acid. Furthermore, decarboxylation under similar conditions of the two glycidic acids, one crystalline and the other highly viscous liquid both derived from pure glycidic ester, yielded products still different in physical and chemical properties. Table I shows the main fractions of decarboxylation products obtained by various methods from crude as well as from crystalline glycidic acids. Upon careful fractionation of a large sample of the decarboxylation product obtained from the crude glycidic acid using a four-foot packed fractionation column, three fractions were obtained: a small low-boiling fraction with a high index of refraction; a large fraction with an intermediate b. p. and an index of refraction ranging from 1.5133 (20°) to 1.5155 (25°); and a small high-boiling fraction with a high index of refraction. It may be seen from the table that the low-boiling fraction resembles in properties the main product obtained from the decarboxylation of the crystalline glycidic acid. The high-boiling fraction, on the other hand, has several properties in common with the main product resulting from the crude glycidic acid, except that it exhibits a secondary absorption maximum at 3000 Å.

The results shown in Table I raise the question whether the purified glycidic ester and the glycidic acids derived from it have the same structure as the corresponding crude compounds. The purified glycidic ester was found to have one active hydrogen (Zer.), while the crystalline glycidic acid showed the presence of two active hydrogens. Both the ester and the acid gave a strong ferric chloride reaction, and upon catalytic hydrogenation showed the presence of approximately three double bonds. Furthermore, the ultraviolet spec-

(1) (a) 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; (b) Paper No. 3, *Science*, **103**, 581 (1946). For paper No. 2, THIS JOURNAL, **63**, 752 (1941). First presented in part before the North Jersey Section of the A. C. S., April 9, 1945.

(2) Research Associate, 1939–1940. Present address: American Cyanamid Co., Bound Brook, N. J.

(3) Research Associate, 1941–1943. Present address: Warner Institute for Therapeutic Research, New York, N. Y.

(4) Research Assistant, 1941–1942. Present address: Michigan Chemical Company, St. Louis, Michigan.

(5) Research Associate, 1942–1943. Present address: Occidental College, Los Angeles, California.

(6) Research Assistant, 1942–1945. Present address: Royal Bond, Inc., St. Louis 2, Missouri.

(7) Research Associate, 1945–1946. Present address: Tufts College, Medford, Massachusetts.

(8) Milas, U. S. Patents 2,369,156–2,369,168, inclusive, excepting 2,369,158, Feb. 13 (1945); 2,382,085–086, Aug. 14 (1945).

(9) (a) Ishikawa and Matsuura, *Sci. Rep. Tokyo Bunrika Daigaku*, **3A**, 173 (1937); (b) Heilbron, Johnson, Jones and Spinks, *J. Chem. Soc.*, 727 (1942); Cymerman, Heilbron, Jones and Lacey, *ibid.*, 500 (1946).

TABLE I

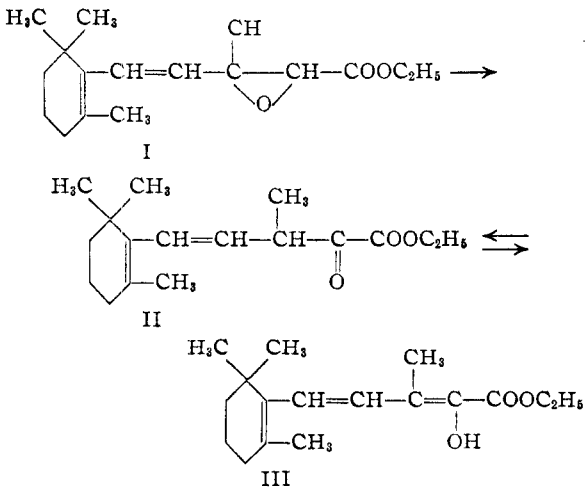
COMPARISON OF PROPERTIES OF FRACTIONS OBTAINED IN THE DECARBOXYLATION OF "β-GLYCIDIC ACIDS"

Decarboxylation product	B. p., °C.	Mm.	n_D	°C.	$\lambda_{max.}$, Å.	$E^{1\%}_{1\ cm.}$	Fuchsin-aldehyde test	M. p. of 2,4-dinitrophenylhydrazone, °C.
Main fraction from crystalline glycidic acid[a]	91–98	2–3	1.5450	25	2380 3150	978 856	Faint (2–3 hr.)	Fails to form
Main fraction from liquid glycidic acid[a]	98–105 49–53	2–3 10^{-4}	1.5320	25	2350	741	Fair (1–2 hr.)	.....
Main fraction from crystalline glycidic acid[b]	106–120	3–4	1.5486	25	2380 3150[d]	661 221	Faint (2–3 hr.)	Fails to form
Main fraction from crude glycidic acid[c]	96–101	2	1.5134	20	2320	996	Strong (0.25–1 hr.)	169–170
Low boiling fraction from crude glycidic acid[c]	79–82	2	1.5450	26	2380 3150	923 645	Faint (2–3 hr.)	Fails to form
High boiling fraction from crude glycidic acid[c]	55–60	10^{-4}–10^{-5}	1.5202	25	2310 3000	737 402	Fair (1–2 hr.)[d]	160.5–162

[a] From purified glycidic ester. Decarboxylation was accomplished via the pyridine salt. [b] Same as in (*a*) except that decarboxylation was accomplished in the presence of copper chips. [c] From crude glycidic acid derived from the condensation without first isolating the pure glycidic ester. [d] Inflection.

trum of both the ester and the acid ($\lambda_{max.}$, 2860 Å.) indicates the presence of three double bonds in conjugation with the ester or carboxyl groups.[10] That spectroscopically the epoxide group is not equivalent to a double bond as Heilbron, *et al.*,[9b] assumed is shown by the spectra of several epoxides (*cf.* structure V)[11] which exhibit maxima in the neighborhood of 2300 Å. In view of these facts we feel that the crude reaction product should be represented by structures I, II and III. The crude glycidic ester and the acids derived from it may be represented mainly by structures I and II while that of the pure glycidic ester and its acids may be represented by structure III. Structure III accounts for all the observed facts for the "crystalline glycidic acid" as well as the large amount of resin produced during its decarboxylation.

These views are in accord with the original assumption of Darzens[12] who found that under certain conditions even the simple glycidic esters rearrange into the α-ketoesters.



The only product used in the synthesis of biologically active vitamin A substances[13] was that represented by the main fraction from a fractionation of the decarboxylation product of the crude glycidic acid, as it was felt that this, being the largest portion, represented the main product of the reaction. It was therefore essential that the structure of this key intermediate be established with some degree of certainty in order to assign structures to products synthesized in the subsequent steps. The structure of this substance is not very easy to establish since it can be represented by four possible isomeric structures (IVa, IVb, IVc and IVd). Of these, structures IVd can be eliminated since a substance represented by this structure should absorb in the region of 2600–2900 Å.,[14] and no maximum was observed in this region. The fact that our substance responds slowly to the fuchsin aldehyde test and forms phenylhydrazones should place it in the aldehyde class, although isomeric compounds having structures similar to IVa or even isobutylene oxide were found to respond similarly to these reactions. Even the spectrum of IVa, IVb and IVc might conceivably be similar, although that of IVc should have, in addition to a band in the region of 2300 Å., a second or even a third band of higher wave lengths and of lower intensity as observed in the spectra of the known α,β-unsaturated aldehydes.[15] No such a band was found in the purified decarboxylation product which was used in our synthetic experiments, although a small high boiling fraction with an abnormally high index of refraction was found to have an additional band

(10) For an analogous structure of ethyl β-ionylidene acetate, see Young and Linden, THIS JOURNAL, **69**, 2042 (1947).

(11) Milas, MacDonald and Black, THIS JOURNAL, **70**, in press (1948).

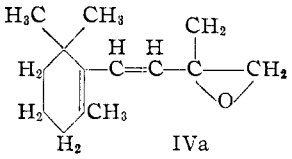
(12) Darzens, *Compt. rend.*, **152**, 443 (1911).

(13) See THIS JOURNAL, **70**, 1591, 1597 (1948).

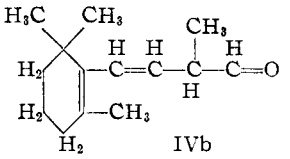
(14) Braude, *Ann. Reports*, **42**, 115 (1945), gives 2630 Å. for sorbaldehyde, which is closely related to structure IVd.

(15) Henri, "International Critical Tables," Vol. V, 1929, p. 372.

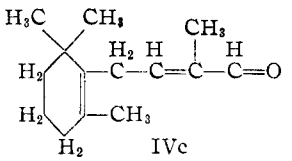
at 3000 Å. It is this fraction which may have structure IVc.



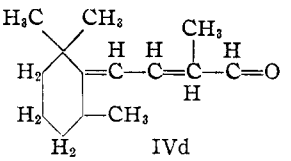
IVa



IVb



IVc



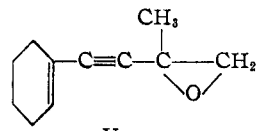
IVd

If our decarboxylation product had structure IVc, as proposed by Heilbron, *et al.*,[9b] it should yield on ozonization 3,3-dimethyloctanedione-2,7, or if the reaction of Böeseken and Jacobs[16] operates in this case, 2,2-dimethyl 6-heptanol-1, both of which are neutral products. No such products were found, but instead, geronic acid was obtained in a yield of about 40%. Since the intermediate product formed upon hydrolysis of the ozonization product should theoretically be a derivative of acetoacetic acid which may oxidize[17] under the conditions of our hydrolytic reaction using small amounts of 30% hydrogen peroxide, we determined the stability of both acetoacetic ester and ethanol under these conditions by measuring the hydrogen peroxide consumed. We have found that the amount of hydrogen peroxide consumed is very small to account for the production of geronic acid from the theoretically possible acetoacetic acid derivative. Furthermore, alcohols are not oxidized rapidly with hydrogen peroxide in the absence of catalysts, and even in the presence of catalysts, glycols have been isolated in good yields.[18] Therefore, if we assume that ozonolysis is a reliable method for determining the structure of organic compounds, we are forced to the conclusion that our main decarboxylation product must have either structure IVa or IVb.

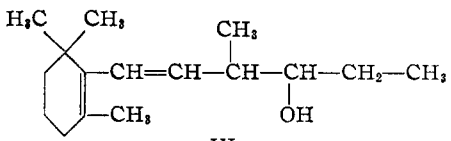
In order to obtain more reliable information concerning the structure of our product, it was necessary to stabilize its functional group by some simple reactions, thereby preventing a possible rearrangement during ozonization. For example, if our product had structure IVc, the addition of lithium acetylide or that of ethylmagnesium bromide should destroy the conjugation, and the ultraviolet absorption spectrum of the resulting carbinols should be that of two isolated double bonds acting individually. Furthermore, both carbinols should yield on ozonolysis 3,3-dimethyloctanedione-2,7 or 2,2-dimethyl-6-heptanol-1 rather than geronic acid. Actually, both carbinols exhibited absorption maxima in the neighborhood of 2260 Å., which indicates the preservation of conjugation. On ozonolysis, both carbinols yielded geronic acid rather than the neutral products mentioned. Again we are forced to the conclusion that the substance from which the carbinols were made must have either structure IVa or IVb.

To decide between structures IVa and IVb, two methods were employed. The synthesis of the epoxide V structurally analogous to IVa was first undertaken.[11] This was found to have similar but not identical properties with those of our key intermediate. It exhibited an absorption maximum at 2320 Å., indicating the presence of a triple and a double bond in conjugation. It responded to the fuchsin-aldehyde test in the same manner but was more reluctant to form a 2,4-dinitrophenylhydrazone than the decarboxylation product. Several attempts to prepare a semicarbazone of the epoxide were entirely unsuccessful. In spite of the fact that some properties of the epoxide resemble those of the decarboxylation product, the evidence is not convincing that the latter has the epoxy structure.

The oxidation of the carbinols derived from the decarboxylation product by the Oppenauer reagent[19] would establish the nature of the hydroxyl group in these carbinols as well as in the vitamin A intermediates.[18] If the carbinols were secondary, ketones would be formed while if they were tertiary no oxidation would be expected to occur. When the unsaturated carbinol VI and its perhydro derivative were actually oxidized with a large excess of aluminum *t*-butoxide, the corresponding ketones were obtained in yields of 79 and 70%, respectively. These results, together with the ozonolysis, seem to establish the structure of the carbinol VI and that of its perhydro derivative.



V



VI

If the decarboxylation product had structure IVb, the acetylene carbinol VII should also be a secondary carbinol and form easily an acid phthalate.[20] Actually, only a small amount could be converted into the acid phthalate, the bulk of the product either remained unchanged or dehydrated into the polyvinylacetylene VIII. Similarly, when 3-nitrophthalic anhydride was used, only a small amount of the acid 3-nitrophthalate was obtained; the remaining product had two bands in

(16) Böeseken and Jacobs, *Rec. trav. chim.*, **55**, 804 (1936).

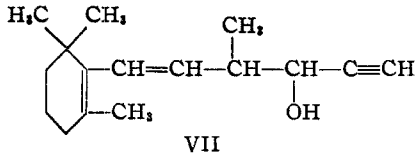
(17) Schaffer and Friedmann [*J. Biol. Chem.*, **61**, 585 (1925)] report that "free acetoacetic acid" resists oxidation with hydrogen peroxide.

(18) Milas and Sussman, THIS JOURNAL, **58**, 1302 (1936); **59**, 2545 (1937); Milas, Sussman and Mason, *ibid.*, **61**, 1844 (1939).

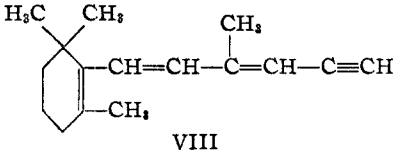
(19) Oppenauer, *Rec. trav. chim.*, **56**, 137 (1937).

(20) McGrew and Adams, THIS JOURNAL, **59**, 1497 (1937).

the ultraviolet, one at 2860 Å. and the other at 2260 Å. Even the crude preparation of the acetylene carbinol showed two bands, the 2260 Å. band attributed to the acetylene itself and a band of low intensity at 2860 Å. with an $E^{1\%}_{1\,cm.}$ value of 18–78 attributed to the polyvinylacetylene. The ease with which the acetylene carbinol dehydrates suggests the possibility of the hydroxyl group being tertiary. However, in accordance with the



VII



VIII

Saytzev rule[21] the same polyvinylacetylene will result by the dehydration of either the acetylene VII or its isomer which is derived from the epoxy IVa. Direct dehydration of the acetylene carbinol using various dehydrating agents produced the polyvinylacetylene mixed with isomeric products which were difficult to remove. Dehydrohalogenation of the acetylene halide using quinoline to remove the hydrogen halide failed to remove all of the halogen, indicating that a small portion of the latter was probably attached to the double bond through an allylic shift to the acetylene bond. The pure polyvinylacetylene was obtained only when the chloroacetylene was treated with alcoholic potash and the acetylene hydrocarbon subsequently purified through its silver derivative. The polyvinylacetylene had an $E^{1\%}_{1\,cm.}$ value at 2860 Å. of 760 and showed normal hydrogenation and other properties.

Some of the properties of the acetylene carbinol, however, are not consistent with those expected of a secondary carbinol. For example, when its perhydro derivative was treated with acetyl bromide, it was partly converted into a bromide, indicating the presence of a loosely bound hydroxyl group. Although this derivative resembled in physical properties the perhydro carbinol prepared from the carbinol VI, its chemical properties were somewhat different. When it was treated with excess aluminum *t*-butoxide or with chromic acid in acetic acid solution, a product was obtained which failed to form a solid semicarbazone, phenylthiosemicarbazone, or 2,4-dinitrophenylhydrazone. In spite of the fact that the product underwent a change in some of its properties, such as reduction of active hydrogen, increase of unsaturation (with aluminum *t*-butoxide), it was difficult to isolate any pure component from it other than recovering the original product. Therefore, the perhydroacetylene carbinol seems to show properties which cannot be entirely reconciled with the view that the hydroxyl group in this derivative is a secondary hydroxyl, in spite of the fact that the original acetylene carbinol formed a 3-nitrophthalate, which is not usually formed by tertiary carbinols under the conditions employed. At present we cannot explain this anomaly.

Heretofore, the decarboxylation of glycidic acids in general has always led to the production of aldehydes or ketones; the epoxy intermediates which are theoretically possible have never been isolated.[22] Furthermore, authentic epoxides[11] related to structure IVa have been found to have somewhat different properties than those shown by the main decarboxylation product. Therefore, we feel strongly at present that of all the structures considered, structure IVb seems to account best for the properties of our main decarboxylation product, although on standing for long periods of time, it may slowly rearrange to the structure IVc.

Table II summarizes the spectroscopic data of the important substances mentioned in this investigation.

TABLE II

SUMMARY OF ULTRAVIOLET ABSORPTION SPECTRA DATA (IN ALCOHOL)

Compound	$\lambda_{max.}$, Å.	$E^{1\%}_{1\,cm.}$	log $\epsilon_{mol.}$
Hydroxy ester III	2860	793	4.34
Hydroxy acid (crystals) from III	2860	1363	4.53
Main decarboxylation product IV from crude glycidic ester	2320	996	4.31
Semicarbazone of IV	2660	1375	4.56
2,4-Dinitrophenylhydrazone of IV	3800	859	4.52
	2560	550	4.33
Product IV (high boiling fraction)	2310	737	4.18
	3000	402	3.92
2,4-Dinitrophenylhydrazone of high boiling fraction	3800	853	4.52
	2560	506	4.28
Epoxy V	2320	1281	4.32
Carbinol VI	2260	264	3.79
Acetylene carbinol VII	2260	407	3.98
3-Nitroacidphthalate of VII	2260	746	4.50
Ketone from VI	2340	469	4.05
Semicarbazone of ketone from VI	2660	1019	4.40
Polyvinylacetylene VIII	2860	760	4.21
	3050[a]	404	3.94

[a] Inflection.

Experimental

β-Ionone.—Three different methods have been used in this Laboratory for the purification of β-ionone. Although the bisulfite and semicarbazone methods were used for small quantities, fractionation under reduced pressure was resorted to for the purification of larger quantities. The commercial grade (Maywood) of β-ionone ($n^{25}D$ 1.5155–1.5162) was fractionated in quantities

(21) Saytzev, *Ann.*, **179**, 300 (1875); Thoms and Mannich, *Ber.*, **36**, 2544 (1903).

(22) Bodforss, "Sammlung Chemische-technischer Vortrage," Vol. XXVI, 1922, p. 145.

of 1–2 kg. under a constant reduced pressure maintained between 10 and 18 mm. through a four-foot packed fractionating column of about 25 theoretical plates using a reflux ratio of about 5:1. The purity was followed by measuring the index of refraction of every fraction. Those between 1.5168–1.5180 (25°) were collected and refractionated and the fractions boiling 124–126° (10 mm.), or 133–134° (13 mm.), or 135–137° (15 mm.), or 142–143° (18 mm.), collected. These had $n^{25}D$ between 1.15172 and 1.5182 and d^{20}_4 of 0.944 and 0.9442 and $\epsilon_{mol.}$ (2950 Å.) between 10,500–11,000. In the majority of our syntheses, the β-ionone used had an $n^{25}D$ >1.5175. Recently through the courtesy of the du Pont Company we received a generous sample with an $n^{25}D$ 1.5185.[23]

1-[2',6',6'-Trimethylcyclohexen-1'-yl]-3-methyl-4-hydroxypentadien-1,3-oic Ethyl Ester-5 (I, II, III).—This compound was prepared over fifty times under a variety of conditions by several members of our group. A representative procedure embodying our latest modifications follows: A mixture of 184 g. (1.5 moles) of ethyl chloroacetate (b. p. 142–143° at 750 mm.), 96 g. (0.5 mole) of β-ionone and 135 g. of dry thiophene-free toluene was cooled between −50 and −60° in a three-necked flask supplied with a stirrer, a dropping funnel, a thermometer, a nitrogen inlet and a long Gooch tube attached to a flask containing 56.7 g. (1.05 moles) of alcohol-free sodium methoxide.[24] A little over one-half of the sodium methoxide was slowly added with vigorous stirring in the course of one-half hour, then an additional 96 g. (0.5 mole) of β-ionone was added dropwise in the course of one-half hour alternately with the remainder of the sodium methoxide. The mixture was then packed at −50° and allowed to stir gently overnight at the same time warming up slowly to room temperature. The mixture was then heated in nitrogen on the water-bath for four hours, then cooled quickly to −5° and maintained at this temperature while the aqueous solution of 500 cc. of tartaric acid containing 90 g. of the latter was added to it. The toluene layer was separated, washed with water, dried, and the toluene and excess ethyl chloroacetate removed on the water-bath under reduced pressure. The brown residue was fractionated in nitrogen and the fraction (190 g.) boiling at 152–157° (2 mm.) refractionated and the final fraction (178 g.) boiling at 154–156° (2 mm.) collected; $n^{25}D$ 1.5293; $E^{1\%}_{1\ cm.}$ (2860Å.), 793; log $\epsilon_{mol.}$ 4.34.

Anal. Calcd. for $C_{17}H_{26}O_3$: C, 73.18; H, 9.39; unsaturation, 3 ⌐¬; active hydrogen (Zer.), 1. Found: C, 73.5, 73.3; H, 8.80, 9.61; unsaturation, 3.19 ⌐¬ (Pt); active hydrogen (Zer.), 1.08.

In alcoholic solution, the ester gives an immediate green color with ferric chloride, indicating the presence of an enol form.

Crystalline Hydroxy Acid from Ester (III).—The pure hydroxy ester (158 g.) was hydrolyzed in the usual manner with alcoholic potash, then the mixture diluted with two volumes of water and extracted several times with petroleum ether to remove non-saponifiable materials. The water layer was then neutralized with dilute phosphoric acid and extracted with ether. Since the ester is strongly enolic, it can be retained by the alkali in the aqueous layer. The ethereal solution was therefore extracted with excess sodium bicarbonate solution, and the hydroxy acid recovered by acidification with dilute phosphoric acid. The crude acid thus obtained was dissolved in the least volume of ether and to the solution was added enough petroleum ether until a cloudiness resulted. The mixture was allowed to stand at 0° for several days, whereby a solid acid separated out. By repeating the process several times and recrystallizing the solid each time from similar solvent mixtures, a total of 44 g. of crystalline acid m. p. 150–150.2° (dec.),[25] and 78 g. (combined total of 86% yield) of liquid acid from which no more crystals could be obtained by any means tried. The crystalline acid is also strongly enolic; it gives a greenish coloration with ferric chloride and has two (1.99, 2.09, 2.15) active hydrogen atoms (Zer.), and an unsaturation of 2.74 double bonds. It also has an $E^{1\%}_{1\ cm.}$ (2850 Å.) value of 1363; log $\epsilon_{mol.}$ 4.53. Calcd. N. Eq. for $C_{15}H_{22}O_3$, 250. Found: 255, 256.

The liquid acid showed similar properties.

Decarboxylation of the Crystalline Acid (Pyridine Method).—In a Claisen flask attached to a 6 inch Vigreux was placed 50 g. of crystalline glycidic acid and to it was added 60 cc. of pure anhydrous pyridine. Some of the excess pyridine was removed by distillation under reduced pressure, then decarboxylation was allowed to proceed in nitrogen and under ordinary pressures at 130–135° for about one to two hours. The mixture was then subjected to a vacuum distillation and the product distilling at 80–125° (2 mm.) collected. A large amount of resin was also formed. The crude distillate was washed in petroleum ether several times with sodium bicarbonate solution, then fractionated under reduced pressure and the fraction boiling at 91–98° (2–3 mm.) collected; $n^{25}D$ 1.5450. This product failed to give the fuchsin-aldehyde test except on long (two to three hours) standing when a faint purplish color developed. It slowly reduced ammoniacal silver nitrate solution, and gave no solid semicarbazones or phenylhydrazones. It gave a negligible (0.12) active hydrogen (Zer.) and showed an unsaturation of 4.1 double bonds. The ultraviolet absorption spectrum showed two bands; one at 2380 Å., $E^{1\%}_{1\ cm.}$ .978, and one at 3150 Å., $E^{1\%}_{1\ cm.}$ 856.

A less pure product was obtained when 10 g. of the crystalline acid was decarboxylated in the presence of clean copper chips. This product had exactly the same properties as the one above except its $E^{1\%}_{1\ cm.}$ value at 2380 Å. was 661 and at 3150 Å., 221.

Decarboxylation of the Liquid Acid.—The liquid acid (124 g.) separated from the crystalline acid was mixed with 150 cc. of pyridine and after removal of the excess pyridine, decarboxylation was effected at 130 to 135°. When decarboxylation was over, the mixture was distilled in nitrogen at 76–135° (2–3 mm.). The crude product was shaken several times with sodium bicarbonate solution, and, after drying, fractionated twice using a 6-inch Vigreux column and a fraction boiling at 98–105° (2–3 mm.) or 49–53° (10^{-4} mm.) collected. This product had the following properties: $n^{25}D$ 1.5320, negligible active hydrogen (0.07) and an unsaturation of 2.32 double bonds. It gave a fair fuchsin-aldehyde test and reduced ammoniacal silver nitrate solution. It showed a band in the ultraviolet at 2350 Å. with an $E^{1\%}_{1\ cm.}$ value of 741.

Decarboxylation without Isolation of the Glycidic Ester (Commonly used in the Various Syntheses).—In the preparation of the glycidic acid, the crude ester prior to its fractionation was dissolved in 10% alcoholic potash and the mixture allowed to stand in nitrogen overnight, then heated on the water-bath for two hours under slightly reduced pressure to remove about one-third of the alcohol. The mixture was then cooled and diluted with three volumes of water and extracted several times either with ether or petroleum ether[26] to remove unsaponifiable matter. The aqueous layer was then acidified with 10% phosphoric acid and extracted several times with ether. The ether extracts were dried and the ether removed under reduced pressure. The crude glycidic acid was then mixed with excess pyridine (2 moles per mole of glycidic acid) and decarboxylated at 130–135°

(23) Determined in our Laboratory.

(24) Best results were obtained when the residual methanol in sodium methoxide was removed under reduced pressure at about 70–80°. Sodium ethoxide treated the same way gives identical results. Sodamide gives much lower yields of the final product.

(25) The decomposition point was determined by the method of Cocker and Lapworth, *J. Chem. Soc.*, 1398 (1931).

(26) β-Ionone dissolves in alkali to give red solutions, but it can be extracted to the extent of 98% with petroleum ether or ethyl ether.

in the usual manner. When decarboxylation was over, the resulting mixture was fractionated under reduced pressure and the fraction boiling up to 135° (2–3 mm.) collected and treated several times with sodium bicarbonate; yield of crude product, 40–60%, a variation of several experiments. The crude product was refractionated twice using a 6-inch Vigreux and the largest fraction with an acceptable index of refraction was used for synthetic purposes. The results of a representative final fractionation are given in Table III.

TABLE III

FINAL FRACTIONATION OF THE DECARBOXYLATION PRODUCT FROM THE CRUDE GLYCIDIC ACID

Wt., g.	B. p. (< 1 mm.) °C.	$n^{24}D$
32	<86	1.5330
74	86–89	1.5144
7	90–137	1.5234

The middle fraction was used for synthetic and analytical purposes. Yields of the pure product varied from 19–30% not including products obtained from refractionations of the low and high boiling fractions. The specific fraction given above had a d^{25}_{25} 0.956, and an $E^{1\%}_{1\ cm.}$ (2320 Å.) value of 967.

Anal. Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75; unsaturation, 2.0 ⌐¬; active hydrogen (Zer.), 0.0. Found: C, 81.90, 81.49; H, 11.2, 10.75; unsaturation, 3.38, 3.01, 3.43 (Pt), 1.91 (Pd) ⌐¬; active hydrogen (Zer.), 0.12, 0.07.

This product gave a strong fuchsin-aldehyde test only after fifteen minutes to one hour of standing, and reduced alcoholic ammoniacal silver nitrate solution. The semicarbazone, m. p., 149.5–150.5° (from 50% alcohol), $E^{1\%}_{1\ cm.}$ (2660 Å.), 1375; the thiosemicarbazone, m. p., 156–159° (from alcohol); and the 2,4-dinitrophenylhydrazone, m. p., 169–170° (from alcohol), $E^{1\%}_{1\ cm.}$ (2560 Å), 550, $E^{1\%}_{1\ cm.}$ (3800 Å.), 859 were prepared from this product. In all cases the production of these derivatives was slow and the yields were low.

When appreciable quantities of the low and high boiling fractions were collected, they were fractionated several times and the main fractions separated. They had the following properties.

Low Boiling Fraction.—B. p., 79–82° (2 mm.); $n^{25}D$ 1.5450; $E^{1\%}_{1\ cm.}$ (2380 Å.), 923, $E^{1\%}_{1\ cm.}$ (3150 Å.), 645. It gave a negative fuchsin-aldehyde test (faint purple color developed after two to three hours). After long standing it reduced alcoholic ammoniacal silver nitrate solution. It failed to form solid semicarbazone and nitrophenylhydrazones. This product was not investigated further.

High Boiling Fraction.—B. p. 113–115° (1.5 mm.), 55–60° (10^{-4}–10^{-5} mm.), $n^{25}D$ 1.5202; $E^{1\%}_{1\ cm.}$ (2310 Å.), 737, $E^{1\%}_{1\ cm.}$ (3000 Å.), 402. It gave a positive fuchsin-aldehyde test (one to two hours) and reduced alcoholic ammoniacal silver nitrate solution. 2,4-Dinitrophenylhydrazone, m. p. 161–162° (from alcohol); mixed m. p. with 2,4-dinitrophenylhydrazone of the main fraction, 160.5–166°. Like the 2,4-dinitrophenylhydrazone of the normal decarboxylation product, this derivative showed two maxima in the ultraviolet with values of $E^{1\%}_{1\ cm.}$ (2560 Å.), 506 and $E^{1\%}_{1\ cm.}$ (3800 Å.) 853, respectively. The parent product gave the following analyses:

Anal. Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75; unsaturation, 2.0 ⌐¬; active hydrogen (Zer.), 0.0. Found: C, 81.2, 81.3; H, 10.4, 10.4; unsaturation, 2.27 ⌐¬; active hydrogen (Zer.), 0.12.

Ozonization of Aldehyde (main product IV).—About 4 g. of aldehyde IV was ozonized following the method of Strain[27] and the 2,4-dinitrophenylhydrazone precipitated. The precipitate was almost completely soluble in sodium bicarbonate solution from which the crude 2,4-dinitrophenylhydrazone of geronic acid was precipitated by the addition of 20% potassium bisulfate. A yield of about 40% calculated as geronic acid was obtained at this stage, having a m. p. of 115–120°. This was recrystallized several times from aqueous acetic acid, from aqueous methanol and finally from cyclohexane; m. p. 131–132.5° (cor.). A mixed m. p. with an authentic sample of the geronic acid derivative gave a m. p. of 132–133.5° (cor.).

1-[2′,6′,6′-Trimethylcyclohexen-1′-yl]-3-methylhexen-1-ol-4 (VI).—A Grignard was prepared from 5.8 g. of ethyl bromide and 1.3 g. of magnesium in about 150 cc. of anhydrous ether. To this was added 10 g. of the normal decarboxylation product ($n^{24}D$ 1.5144). When the Grignard reaction mixture was hydrolyzed and the product fractionated under a reduced pressure using a 6-inch Vigreux, a carbinol (8 g.) was obtained which boiled at 66–68° (10^{-4}–10^{-5} mm.); $n^{25}D$ 1.5020; $E^{1\%}_{1\ cm.}$ (2260 Å.) 264.

Anal. Calcd. for $C_{16}H_{26}O$: C, 81.29; H, 11.94; unsaturation, 2.0 ⌐¬; active hydrogen (Zer.), 1.0. Found: C, 81.00, 81.30; H, 11.80, 12.00; unsaturation, 2.3, 2.4 ⌐¬; active hydrogen (Zer.), 0.90, 0.95, 0.97.

Ozonization of Carbinol VI.—About 2.8 g. of carbinol VI was ozonized as before and the 2,4-dinitrophenylhydrazone precipitated, extracted with sodium bicarbonate and reprecipitated; yield of the crude bicarbonate soluble product, about 35%. This was purified as in the previous case, m. p. 133.5–134.5° (cor.). A mixed m. p. with an authentic sample of the geronic acid derivative showed no significant depression.

Oxidation of Carbinol VI with Aluminum *t*-Butoxide.—The carbinol (2.8 g.) was oxidized in a mixture of 70 cc. of anhydrous, thiophene-free benzene and 40 cc. of pure, freshly distilled acetone with 4 g. (large excess) aluminum *t*-butoxide[16] by refluxing the mixture on the water-bath in an atmosphere of nitrogen for fourteen hours. The crude product was isolated in the usual manner and distilled at a pressure of 10^{-4} mm. in a molecular still of the falling film type using a heating liquid (mixture of ethanol and carbon tetrachloride) which boiled at 65.2°. The largest fraction (79%) obtained had the properties: $n^{25}D$ 1.5033; $E^{1\%}_{1\ cm.}$ (2340 Å.), 469; active hydrogen (Zer.), 0.19, 0.22. A semicarbazone was prepared from it, m. p. 167.5–169° (from 50% alcohol); $E^{1\%}_{1\ cm.}$ (2660 Å.), 1019.

Anal. Calcd. for $C_{17}H_{29}ON_3$: C, 70.06; H, 10.03. Found: C, 70.11; H, 10.05.

Reduction of Carbinol VI to the Perhydrocarbinol.—To avoid hydrogenolysis with platinum oxide as catalyst, the carbinol (8 g.) was first reduced in alcohol using Raney nickel (0.16 g.) for sixteen hours under a hydrogen pressure of 7–12 pounds. Complete hydrogenation was effected in the same solvent (minimum hydrogenolysis is known to occur in alcohol) for several days using platinum oxide as catalyst. The product was finally recovered and fractionated using a 6-inch Vigreux and the fraction boiling at 58–59° (10^{-4}–10^{-5} mm.) collected; $n^{25}D$ 1.4838; active hydrogen (Zer.), 0.96.

Oxidation of the Perhydrocarbinol with Aluminum *t*-Butoxide.—When this carbinol was oxidized with excess aluminum *t*-butoxide using the same procedure as above, a product was obtained boiling at 44–50° (10^{-4}–10^{-5} mm.); $n^{25}D$ 1.4855; active hydrogen (Zer.), 0.25; semicarbazone, m. p. 165–166° (from 75% ethanol, 25% water); 2,4-dinitrophenylhydrazone, m. p. 111–114° (from alcohol).

1-[2′,6′,6′-Trimethylcyclohexen-1′-yl]-3-methyl-4-hydroxyhexen-1-yne-5 (VII).—After a number of trials using calcium and sodium acetylide in liquid ammonia, and sodamide in ether, it was found that lithium acetylide gave the best yields of the acetylene carbinol VII. Into a 3-necked, round-bottomed flask provided with a stirrer, a dropping funnel and an inlet tube and externally cooled

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

to −60°, was condensed 1.5 liters of ammonia. The liquid ammonia was then saturated with dry acetylene and, while stirring and the latter passing through the solution, 3.1 g. of small pieces of metallic lithium was added in the course of two hours. When the color of the mixture turned gray, the latter was cooled to −70° and to it was added dropwise in the course of one hour 80 g. of the aldehyde IV in 80 cc. of dry ether while acetylene was still passing through the solution. Stirring and cooling to −70° was continued overnight then the cold-bath was removed, the ammonia slowly expelled and the mixture allowed to warm up to 0°. At this temperature 500 cc. of dry ether was added and the mixture acidified with 80 g. of tartaric acid in 120 cc. of water. The ether layer was then separated, washed with a 10% salt solution, dried and the ether removed. The residue was fractionated twice under reduced pressure using a 3-inch Vigreux and the fraction (67 g., 83.8% yield) boiling at 69–72° (10^{-4} mm.) collected; $n^{25}D$ 1.5122; d^{25}_{25} 0.9538; M_D (calcd.), 72.48; found, 73.02; $E^{1\%}_{1\text{ cm.}}$ (2260 Å.), 407. Crude samples of the acetylene carbinol had an additional band of low intensity with a maximum at 2860 Å.; $E^{1\%}_{1\text{ cm.}}$, 18–78.

Anal. Calcd. for $C_{16}H_{24}O$: C, 82.70; H, 10.41; unsaturation, 4.0 ⌐¬; active hydrogen (Zer.), 2.0. Found: C, 82.28; H, 10.30; unsaturation, 4.01, 4.07, 4.39 ⌐¬ (Pt), 3.83, 3.95 ⌐¬ (Pd); active hydrogen (Zer.), 2.01, 2.06, 1.91, 1.99.

The acetylene carbinol formed a silver derivative which exploded on rubbing and on the hot plate. This derivative was purified from benzene by precipitation with methanol.

Anal. Calcd. for $C_{16}H_{23}OAg$: Ag, 31.8. Found: Ag, 31.5.

The acetylene carbinol also formed a solid acid 3-nitrophthalate[17] in low yields (7–10%); m. p. 149.5–150° (methanol); $E^{1\%}_{1\text{ cm.}}$ (2260 Å.), 746.

Anal. Calcd. for $C_{24}H_{27}O_6N$: C, 67.76; H, 6.40; unsaturation (including benzene ring and nitro group), 9.0 ⌐¬. Found: C, 68.14; H, 6.61; unsaturation, 9.24 ⌐¬ (Pt).

The recovered product from this reaction had a spectrum with maxima at 2260 Å., $E^{1\%}_{1\text{ cm.}}$ 254, and at 2860 Å., $E^{1\%}_{1\text{ cm.}}$ 141.

With phosphorus tribromide in pyridine at 0° the acetylene carbinol formed a bromide which retained its acetylene properties; b. p. 53–56° (10^{-4}–10^{-5} mm.); $n^{25}D$ 1.5413; d^{25}_{25} 1.076.

Anal. Calcd. for $C_{16}H_{23}Br$: Br, 27.12. Found: Br, 27.0.

The acetylene carbinol also formed a chloride with thionyl chloride in pyridine at 0°. This reaction, however, caused a slight dehydrochlorination since the percentage of chlorine was found to be slightly lower than the theoretical and the product gave, in addition to the 2260 Å band, the 2860 Å. band which is characteristic of the polyvinyl acetylene.

Anal. Calcd. for $C_{16}H_{23}Cl$: Cl, 14.13; active hydrogen (Zer.), 1.0. Found: Cl, 12.64, 12.57; active hydrogen (Zer.), 0.74.

Ozonization of Acetylene Carbinol VII.—About 4.97 g. of acetylene carbinol was ozonized as in the previous cases and the 2,4-dinitrophenylhydrazone precipitated. The precipitate was extracted with sodium bicarbonate and reprecipitated with 20% potassium acid sulfate solution. A yield of about 41% of the crude product calculated as geronic acid was obtained, m. p. 118–123°. This was recrystallized as before, using aqueous acetic acid, aqueous methanol and cyclohexane; m. p. 133–134° (cor.). A mixed m. p. with an authentic derivative of geronic acid showed no depression.

Perhydroacetylenecarbinol.—Acetylene carbinol (10 g.) was hydrogenated in 200 cc. of absolute ethanol in the presence of Raney nickel (0.2 g.) with shaking and under a 15-lb. hydrogen pressure for two days. The product was recovered and found to be still unsaturated, so it was further hydrogenated for several days in alcohol with shaking using platinum oxide (0.12 g.) as catalyst. Finally, the completely saturated carbinol was recovered and fractionated and the fraction (8.5 g.) boiling at 62–66° (10^{-4} mm.) collected and analyzed; $n^{25}D$ 1.4830.

Anal. Calcd. for $C_{16}H_{32}O$: C, 79.93; H, 13.40; active hydrogen (Zer.), 1.0. Found: C, 79.50; H, 13.03; active hydrogen (Zer.), 0.91, 0.81, 0.94.

Oxidation of Perhydroacetylenecarbinol with Aluminum *t*-Butoxide.—A solution of perhydroacetylenecarbinol (0.8 g.) in 25 cc. of anhydrous acetone and 30 cc. pure benzene was heated to 85° then a solution of 2.5 g. of aluminum *t*-butoxide in 25 cc. of benzene was quickly added and the mixture refluxed for eighteen hours. The product was then recovered in the usual manner and distilled under a reduced pressure, b. p. 38–42° (10^{-5} mm.); $n^{25}D$ 1.4848; active hydrogen (Zer.), 0.48; unsaturation, 1.53 ⌐¬. This product failed to give a solid semicarbazone, phenylsemicarbazone or 2,4-dinitrophenylhydrazone.

Oxidation of Perhydroacetylenecarbinol with Chromic Acid.—About 3 g. of the perhydroacetylenecarbinol was oxidized with chromic acid (1.1 g.) in glacial acetic acid (60 cc.) and 7 cc. of water at 35–40°. The product was recovered and fractionated and the fraction (2.5 g.) boiling at 37–43° (10^{-5} mm.) collected. This had an active hydrogen of 0.21 and an unsaturation of 1.64 ⌐¬. This product failed to yield a solid semicarbazone, phenylsemicarbazone, or 2,4-dinitrophenylhydrazone. These results seem to indicate that this perhydroacetylenecarbinol is not identical with the perhydrocarbinol obtained from the carbinol VI.

1-[2′,6′,6′-Trimethylcyclohexen-1′-yl]-3-methylhexadien-1,3-yne-5.—Attempts to make this polyvinylacetylene by the direct dehydration of the acetylene carbinol VII using aluminum phosphate at 250–300° or distilling it from small amounts of *p*-toluenesulfonic acid or mixtures of this acid with various anhydrides (acetic, succinic, etc.), or with *p*-toluenesulfonic acid in toluene at 110°, gave very poor yields and much polymerization. Even when the salt-Grignard of the acetylene carbinol was treated with one mole of anhydrous *t*-butyl alcohol and the resulting product distilled under a highly reduced pressure, the yields of the polyvinylacetylene were poor.

Dehydrobromination of the acetylene bromide with quinoline under various conditions failed to remove all of the bromine from the molecule. Even when the acetylene bromide was refluxed with quinoline for long periods of time, the product formed, when fractionated, contained from 6 to 7% bromine. The bromine could easily be removed by refluxing with alcoholic potash, but the product formed had rather low active hydrogen (Zer.).

Dehydrochlorination of the acetylene chloride with alcoholic potash was much more successful. Into 200 cc. of 95% alcohol containing 23 g. of potassium hydroxide under a gentle reflux in an atmosphere of nitrogen was added in the course of fifteen minutes 51.5 g. of acetylene chloride in an equal volume of alcohol. Gentle refluxing was continued for one and one-half hours longer, then about one-third of the alcohol was removed under reduced pressure and the mixture cooled and diluted with two volumes of water. It was then extracted with 3 × 100 cc. of olefin-free petroleum ether and the extract dried and the solvent removed. The residue was distilled under a highly reduced pressure and a product (33 g.) was obtained boiling at 53–56° (10^{-4}–10^{-5} mm.). This was free from chlorine and had an active hydrogen (Zer.) of 0.7 and a hydrogenation number of 4.34 ⌐¬. Further purification was effected by preparing its silver derivative in alcoholic ammoniacal silver nitrate solution. The silver derivative of the polyvinylacetylene precipitates rapidly while that of the acetylene carbinol comes down very slowly, and this difference in the precipitation rate made the separation of the two possible. The polyvinylacetylene was recovered from its silver derivative by sus-

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.

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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.

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[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.

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

(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.

(1a) Research Associate, 1939–1940. Present address, American Cyanamid Co., Bound Brook, N. J.

(2) Research Associate, 1940–1941. Present address, Eastman Kodak Co., Rochester, N. Y.

(3) Research Associate, 1940–1942. Present address, Hoffman-LaRoche, Nutley, N. J.

(4) Research Assistant, 1942–1945. Present address, Royal Bond, Inc., St. Louis, Mo.

(5) Research Assistant, 1943–1945.

(6) Research Assistant, 1945–1946. Present address, Arthur D. Little, Inc.

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