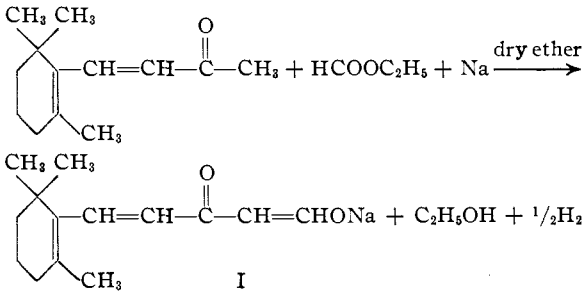
[CONTRIBUTION NO. 87 FROM THE LABORATORIES OF DISTILLATION PRODUCTS, INC.]

Synthesis of Compounds Related to Vitamin A from Hydroxymethylene β-Ionone[1]

BY EDGAR M. SHANTZ

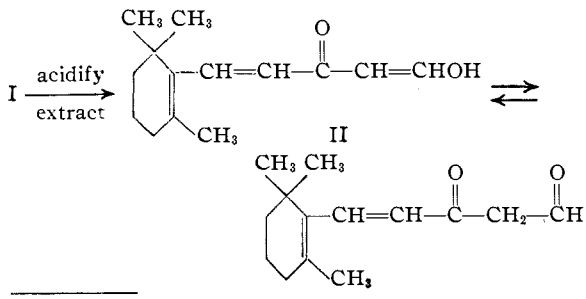
In an endeavor to find a new route to that valuable but most elusive compound, β-ionylideneacetaldehyde, the reduction of hydroxymethylene β-ionone with methylmagnesium iodide was considered. If the Grignard reagent could be condensed with the carbonyl group of hydroxymethylene β-ionone, the resulting compound, after hydrolysis and removal of a molecule of water, should be β-ionylidene acetaldehyde. All attempts to do this failed, but during the course of this investigation several new compounds were synthesized which are closely related to vitamin A and are therefore of interest.

The hydroxymethylene β-ionone was prepared readily from β-ionone in fairly good yields by the following reaction, using the method employed by Claisen[2] for the preparation of the hydroxymethylene compound from acetone.



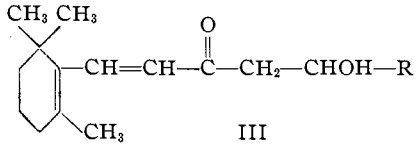
The product (I) came out of solution as the white sodium salt which was filtered off, washed with ether and dried. This compound, which slowly deliquesced to a dark orange-red oil upon exposure to air, appeared to be quite stable when stored under vacuum. The reaction could also be carried out using sodium methoxide in place of the free metal, but the results were not as consistent.

The free hydroxymethylene compound (II) was prepared by acidification and ether extraction, followed by molecular distillation in a cyclic, falling-film still. This substance was very unstable unless kept at −50° and yields of the purified product were low. A large portion of the material formed a viscous, undistillable condensation product during the process of acidification and distillation.



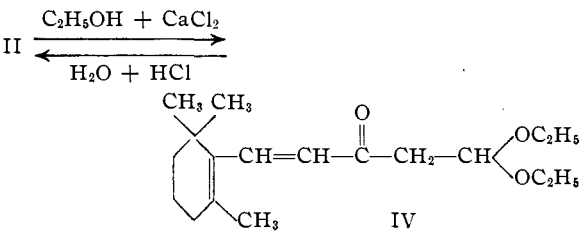
It was found, however, that Grignard reagents reacted readily with the finely ground sodium salt (I) when suspended in ether, so that this compound was used in most of the experiments.

As might be expected, all Grignard reagents were found to add 1,4 to compound I, giving secondary alcohols of the general type

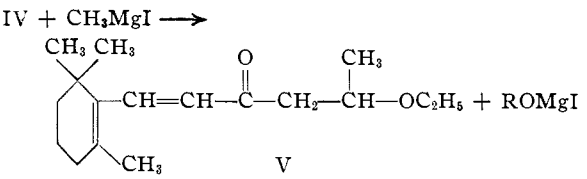


R being dependent upon the Grignard used. This was also found to be the case when methyl lithium and dimethyl cadmium were used.

The acetal (IV) of the aldehyde form of II appeared to be formed by the action of hydrogen chloride or calcium chloride in absolute ethanol.



This could be hydrolyzed back to the original compound with aqueous acid. When compound IV reacted with methylmagnesium iodide, the Grignard probably reacted with the acetal linkage in preference to the carbonyl group to give a compound which apparently had the structure V.

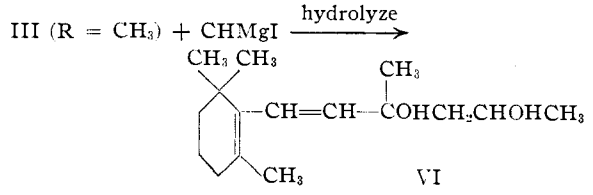


Immediate hopes of preparing β-ionylideneacetaldehyde from compound I were now abandoned, but further investigation indicated that Grignard reagents would now add in the normal manner to the carbonyl group of both compound III and to the product given by dehydration of compound III (such as compound X below). In all cases, water appeared to be removed from compound III to give a double bond in the β,γ-position to the carbonyl goup.

(1) Presented before the Division of Organic Chemistry at the Atlantic City meeting of the American Chemical Society, April, 1946.

(2) L. Claisen and P. Roosen, *Ann.*, **278**, 274 (1894).

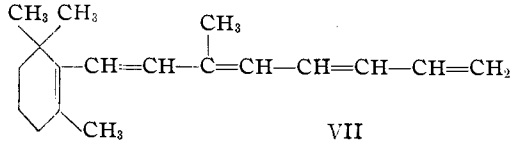
Another synthesis that seemed to have possibilities was the attempted preparation of β-ionylideneacetone in the following manner. Methylmagnesium iodide was condensed with compound I to give compound III (with R = methyl) upon hydrolysis. Methylmagnesium iodide was then added to yield the 1,3 glycol, VI.



VI

It was believed that the secondary hydroxyl group of VI could be oxidized to a carbonyl by the Oppenauer method,[3] leaving the tertiary hydroxyl unaffected. Several efforts to produce a ketone using both aluminum tertiary butoxide and aluminum *i*-propoxide failed.

In order to build up a longer polyene chain and synthesize a compound more closely related to vitamin A, allylmagnesium bromide was condensed with the sodium salt of hydroxymethylene β-ionone to give the compound III with R = (—CH_2—CH=CH_2). After splitting out a molecule of water by azeotropic distillation with toluene containing *p*-toluenesulfonic acid, the resulting compound was treated with methylmagnesium iodide. After hydrolysis and removal of the tertiary hydroxyl group, compound VII was obtained. It can be seen that this compound lacks the terminal carbinol group and a side chain



VII

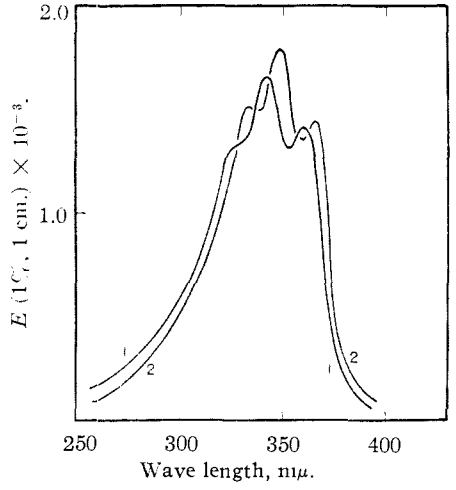
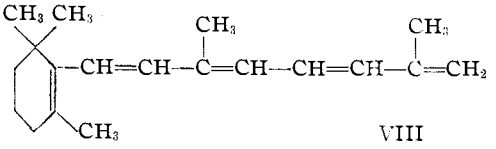


Fig. 1.—Ultraviolet absorption spectrum in ethanol of compound VII (Curve I) and of compound VIII (Curve 2).

(3) R. V. Oppenauer, *Rec. trav. chim.*, **56**, 137 (1937).

methyl group of the vitamin A molecule. Its ultraviolet absorption spectrum (Curve 1, Fig. 1) showed three bands typical of an unsaturated aliphatic hydrocarbon with maxima at 323, *342*, and 361 mμ. This is similar in appearance to the absorption spectrum of anhydro vitamin A which has been shown by Shantz, *et al.*,[4] to be a hydrocarbon with six conjugated double bonds. The 30 mμ difference in wave length is just about that predicted for a similar compound with one less double bond and two less carbon atoms.

In an analogous manner, the compound VIII was synthesized by substituting β-methallyl



VIII

Grignard for allyl Grignard in the above series of reactions. This compound lacks only the terminal carbinol group of vitamin A. Its ultraviolet absorption spectrum (Curve 2, Fig. 1) is similar to that of VII, with absorption bands at 330, *348* and 367 mμ. The slight shift toward the visible region is probably due to the extra side chain methyl group. Both VII and VIII gave blue products with antimony chloride in chloroform which had absorption maxima at 580 mμ. Neither of these compounds exhibited the slightest degree of biological activity when fed to vitamin A-deficient rats in doses up to 2.0 mg. per day.

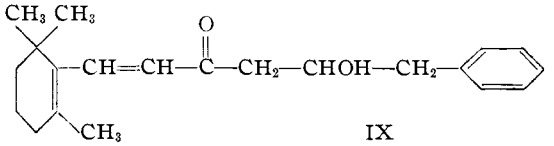
In order to synthesize a compound still more closely related to vitamin A, an effort was made to condense 1-bromo-4-methoxy-2-butene with compound I. If successful, the final product, after subsequent reduction with methyl Grignard and removal of water, should be the methyl ether of vitamin A lacking only the last side chain methyl group. The unsaturated bromo-ether was prepared by performing a Williamson synthesis with sodium methoxide on one end of the *trans* isomer of 1,4-dibromo-2-butene, which had been readily prepared by 1,4-addition of bromine to butadiene. The yields of bromo-ether were extremely low and several redistillations were required to obtain a pure product. Although this compound appeared to form a metallo-organic complex with both lithium and magnesium, no condensation could be effected between it and compound I.

In order to confirm the course of the reactions involved in making compounds VII and VIII, the same synthesis was performed using benzylmagnesium chloride in place of the allyl and methallyl bromides. The absorption curve of each intermediate compound was determined on the ultraviolet spectrophotometer, and the resulting series of spectra form a most interesting study of the relationship between absorption spectrum and chemical constitution.

(4) E. M. Shantz, N. D. Embree and J. C. Cawley, THIS JOURNAL, **65**, 901 (1943).

β-Ionone, which has an absorption maximum at 295 mμ (Curve 1, Fig. 2), was condensed with ethyl formate in the presence of sodium to give the sodium salt of hydroxymethylene β-ionone (compound I). The absorption maximum undergoes a large shift toward the visible region to 335 mμ (Curve 2, Fig. 2). This large shift, which is equivalent to about two additional double bonds, must be due to the unusual chromophore present in compound I.

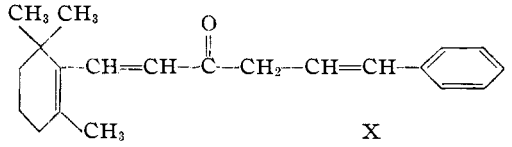
Benzylmagnesium chloride was now added to give, after hydrolysis, compound IX.



IX

It can be seen that two isolated chromophoric groups are present, that of the original ionone and the phenyl group. The absorption of the phenyl group in the 250 to 260 mμ region, because of its extremely low extinction, is completely masked by that of the ionone portion. The main absorption maximum (Curve 3, Fig. 2) of compound IX has therefore dropped to 300 mμ. The slight difference between the absorption maximum of compound IX and that of the original ionone is caused by the large radical substituted on the α-carbon atom.

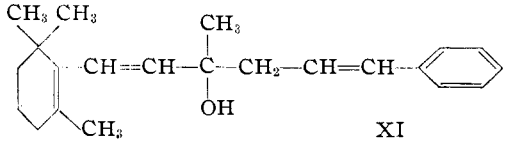
The hydroxyl group of compound IX was split off by refluxing with *p*-toluenesulfonic acid in toluene to give compound X. This substance still has two chromophores isolated from each other by a methylene group, but an aliphatic double bond has been brought into conjugation with the phenyl radical.



X

This does not produce much change in the position of the absorption maxima, but according to Dimroth[5] the extinction should be greatly increased. That this has happened is substantiated by the absorption curve of compound X (Curve 4, Fig. 2.)

Methylmagnesium iodide was now added to compound X, producing the tertiary alcohol XI.



XI

The ionone chromophore has been destroyed leaving two conjugated double bonds which should have absorption maxima at about 230 mμ. The additive effect of this chromophore with the phenylethylene group can be seen in Curve 5 of Fig. 2, where the 300 mμ band has almost completely disappeared.

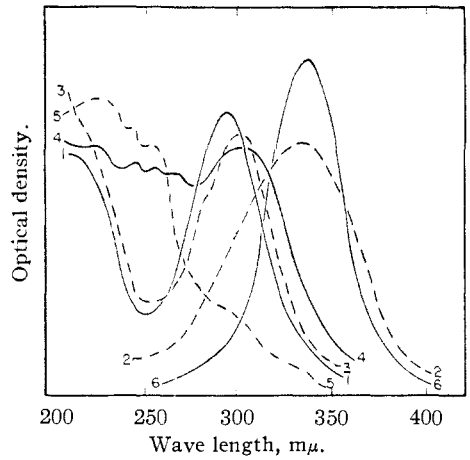
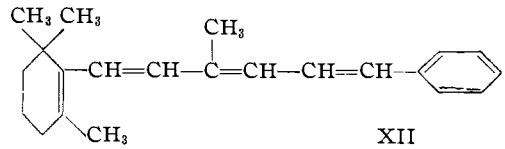


Fig. 2.—Ultraviolet absorption spectra in ethanol of the starting material (Curve 1) and the intermediate compounds (Curves 2, 3, 4, and 5) leading to the synthesis of Compound XII (Curve 6). Although the extinction coefficients of the above compounds varied greatly, their spectra are plotted to approximately equal maximum optical densities to facilitate comparison of the wave lengths of the various maxima.

The hydroxyl group of compound XI was removed by toluenesulfonic acid in benzene, bringing the two chromophores of the molecule into conjugation (compound XII). Since a phenyl group is equivalent to about 1.5 double bonds in



XII

an aliphatic chain, this substance should have an absorption maximum at a slightly longer wave length than that of vitamin A (328 mμ). Its absorption spectrum with a maximum at 338 mμ is shown in Curve 6 of Fig. 2. The fine structure of a hydrocarbon is not evident, but according to Dimroth[5] monophenyl derivatives exhibit only a single absorption band when in conjugation with an unsaturated aliphatic side chain.

Experimental

Purification of β-Ionone.—β-Ionone from the P. R. Dreyer Co., having $E(1\%,1\text{cm.})(294\ m\mu) = 375$, was distilled through a fractionating column 12 mm. in diameter and 800 mm. in length, packed with glass helices. The pressure at the head was maintained at 1 mm. A fore-run, 26.7% by weight, boiled from 55 to 86° and had $E(1\%,1\text{cm.})(294\ m\mu) = 290$. The following 65.1% came over at 86 to 87.5° and had $E(1\%,1\text{cm.})(294\ m\mu) = 452$. This material was used in the syntheses.

Preparation of Hydroxymethylene β-Ionone Sodium Salt (I).—A typical preparation of hydroxymethylene β-ionone was done as follows: 24 g. (1 atom) of sodium wire cut into pieces about 1 cm. long were placed under 2 liters of dry ether in a three-neck, three-liter flask equipped with a condenser, dropping funnel and stirrer. A powerful

(5) K. Dimroth, *Angew. Chem.*, **52**, 545 (1939).

stirrer with large blades or paddles is required, as the precipitate of the product becomes quite heavy and voluminous toward the end of the reaction.

One hundred and ninety-two grams (1 mole) of β-ionone and 74 g. (1 mole) of redistilled ethyl formate (Eastman Kodak Co., White Label) were mixed and added slowly through the dropping funnel over a period of two hours at such a rate that the ether was kept refluxing gently. The reaction started in a few minutes, accompanied by a gradual darkening of the mixture to an orange-red color. After about half an hour, the first precipitate of the white sodium salt appeared. After all the ketone and ester had been added, the mixture was stirred for four more hours. At the end of this time, the reaction appeared to be complete and stirring became very difficult. The mixture was poured into a large Buchner funnel and the ether filtered off. The product was washed with ether until it was white and the filtrate coming through was colorless. The solid was then transferred to an evaporating dish and dried over night in a desiccator under water-pump vacuum. The following morning the large lumps of dried product were ground in a mortar and passed through a 40-mesh screen. This removed a few small pieces of unreacted sodium. The powdered material was again dried over night in the desiccator under mechanical pump vacuum. The final yield of powdered, sifted and dried product was 203 g. (83.8%). *Anal.* Calcd. for $C_{14}H_{19}O_2Na$: C, 69.39; H, 7.90. Found: C, 69.21; H, 7.81.

Preparation of Free Hydroxymethylene β-Ionone (II).—Sixty-five grams of compound I was dissolved in 400 ml. of water and 200 ml. of ether added; 1 *N* hydrochloric acid was added slowly with shaking until the aqueous layer was acid to litmus. About 250 ml. of acid were required. The ether layer was removed, and the aqueous layer was extracted twice more with 200 ml. portions of ether. The ether extracts were washed, dried over sodium sulfate, and the ether removed under nitrogen. The residue, a dark red viscous oil, was dissolved in 50 ml. of corn oil as a carrier, placed in a cyclic molecular still, and passed several times over the column at a temperature of 100° and a pressure of 0.1 mm. The distillate was a pale yellow oil weighing 29 g. (49% yield). This product had an absorption maximum in the ultraviolet at 334 mμ (the same as the sodium salt) with $E(1\%,1cm.)$ = 625. *Anal.* Calcd. for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.8; H, 9.19.

Formation of Hydroxymethylene β-Ionone Diethyl Acetal (IV).—Forty-four grams (0.2 mole) of hydroxymethylene β-ionone (compound II) was dissolved in 200 ml. of absolute ethyl alcohol and shaken with 16 g. of anhydrous calcium chloride. This solution was allowed to stand for twenty hours at 5° over the undissolved calcium chloride. The alcoholic solution was then decanted and most of the solvent removed under nitrogen. After adding 200 ml. of ether, the solution was washed twice with 0.5 *N* potassium hydroxide and twice with water. The ether was removed and the residue distilled in the cyclic still at 0.1 mm. pressure. A fraction weighing 12.6 g. (21.5% yield) was removed at a column temperature of 140°. This was a light yellow oil which had an absorption maximum in the ultraviolet at 300 mμ. Upon hydrolysis by shaking with aqueous hydrochloric acid, the ultraviolet absorption maximum shifted back to that of the hydroxymethylene compound at 334 mμ. *Anal.* Calcd. for $C_{18}H_{30}O_3$: C, 73.44; H, 10.27. Found: C, 73.29; H, 10.12.

Preparation of the 1,3-Glycol (VI).—One hundred and thirty grams (0.55 mole) of compound I was added to a solution of the Grignard reagent from 85 g. (0.6 mole) of methyl iodide and 14.6 g. (0.6 atom) of magnesium in 1 liter of ether. After stirring for fifteen hours, the product was decomposed by pouring onto crushed ice and ammonium chloride. The ether solution was washed and dried over sodium sulfate. Removal of the ether under nitrogen left 118 g. of dark red oil.

This was distilled in a modified Claisen flask with a Vigreux sidearm 20 cm. long at a pressure of 1 mm. The distillate was a light yellow oil weighing 85.6 g. which distilled over a range of 126 to 139°. This product was presumed to have the structure of compound III with R = methyl. Eighty-five grams (0.35 mole) of the distillate was added to a solution of 0.75 mole of methylmagnesium iodide in 1 liter of ether (2 equivalents of Grignard must now be used since the compound contains a free hydroxyl group). After stirring for four hours, it was broken up in crushed ice and ammonium chloride. After washing, drying, and removal of the ether, 85 g. of yellow oil remained. This product, which should have a single absorption band at about 235 mμ in the ultraviolet, actually showed two bands—one at 232 mμ with $E(1\%,1cm.)$ = 210, and one at 300 mμ with $E(1\%,1cm.\mu)$ = 150.

Since the desired product with two hydroxyl groups should be quite strongly adsorbed, this material was passed through a chromatographic column containing 800 g. of aluminum oxide (Merck, according to Brockmann). The column was washed with petroleum ether until no more material came through. The eluted fraction consisted of 15.5 g. of yellow oil with a single absorption band at 300 mμ with $E(1\%,1cm.)$ = 310.

The adsorbed portion was removed by washing with ethyl ether containing 10% ethanol. Fifty-four grams of a pale yellow viscous oil was obtained which had a single absorption maximum at 232 mμ with $E(1\%,1cm.)$ = 225.

This fraction was dissolved in 100 g. of corn oil and distilled in the cyclic molecular still. After removing a forerun (16.3 g.) of a pale yellow, mobile oil at 70 to 80° and 1 mm. pressure, the pressure was decreased to 0.01 mm. and the temperature raised to 100°. The bulk of the product distilled under these conditions; 27.2 g. of a very viscous and a very pale yellow oil were obtained. This represents an over-all yield from compound I of 24.5%. This product had an absorption maximum in the ultraviolet at 231 mμ with $E(1\%,1cm.)$ = 265. *Anal.* Calcd. for $C_{16}H_{28}O_2$: C, 76.17; H, 11.17; active hydrogen (Zerewitinoff[6]), 2.0. Found: C, 76.58; H, 10.88; active hydrogen, 1.84. Attempts to oxidize this material to a β-hydroxy ketone by the Oppenauer method were unsuccessful.

Synthesis of Compound VII.—24.2 g. (0.1 mole) of compound I was added slowly to the Grignard reagent formed from 24.2 g. (0.2 mole) of allyl bromide and 4.8 g. (0.2 atom) of magnesium. After stirring for four hours, the addition product was broken up by pouring into crushed ice and ammonium chloride. The ether solution was washed, dried, and the solvent removed under nitrogen. The residue was taken up in 100 ml. of toluene containing 0.5 g. of *p*-toluenesulfonic acid and refluxed in a moisture determination apparatus until no more water could be observed splitting out. About 0.95 ml. (0.052 mole) of water was removed. The toluene solution was washed with 5% sodium bicarbonate, twice with water, and dried over sodium sulfate. Upon removal of the solvent under nitrogen *in vacuo*, 20.6 g. of a dark red oil was obtained.

This oil was dissolved in 50 ml. of ether and added to the Grignard reagent obtained from 28.4 g. (0.2 mole) of methyl iodide and 4.8 g. (0.2 atom) of magnesium. After refluxing for one hour, the product was treated as above; 18.1 g. of a dark, red-brown oil remained after removal of the solvent. This was dissolved in 100 ml. of benzene and refluxed in a moisture determination apparatus with 0.5 g. of *p*-toluenesulfonic acid; 0.35 ml. of water was removed. After washing, the benzene was removed under nitrogen *in vacuo*.

The residue, weighing 17.6 g., was dissolved in corn oil and distilled in the molecular still at a pressure of 10 μ. The distillate consisted of 9.8 g. of a light orange oil which came over at 95 to 120°.

This oil was dissolved in Skellysolve F and chromatographed on a column containing 100 g. of aluminum oxide (Merck, according to Brockmann). The least strongly adsorbed material, washed through a column with Skelly-

(6) The Zerewitinoff determination and all elementary microanalyses were done by Mr. Donald Ketchum of the Eastman Kodak Research Laboratories.

solve, was 1.3 g. of a thin brown oil which had an ultraviolet absorption maximum at 320 mμ. This was not further investigated. The next fraction, eluted from the column with benzene, contained the desired product; 3.15 g. of a pale orange oil was obtained upon removal of the solvent. Over-all yield from compound I was 13%. The material remaining adsorbed on the column was removed by washing with ether containing 10% methanol. This gave 4.1 g. of a deep yellow oil which showed general absorption in the 260 to 300 mμ region of the ultraviolet.

Fraction 2 had an ultraviolet absorption curve with maxima at 323, *342*, and 361 mμ (Curve 1, Fig. 1); $E(1\%,1\text{ cm.})$ at 342 mμ = 1650. *Anal.* Calcd. for $C_{18}H_{26}$: C, 89.23; H, 10.77. Found: C, 89.30; H, 10.69.

Preparation of Compounds VIII and XII.—These two compounds were prepared in a manner exactly analogous to that used for compound VII above with the substitution of methallyl bromide and benzyl chloride, respectively, in the initial Grignard condensation with compound I.

Compound VIII.—The over-all yield of chromatographically purified final product from 90 g. of compound I was 4.78 g. (5.1% yield) of a pale orange oil. The ultraviolet absorption curve (Curve 2, Fig. 1) showed three maxima at 332, *348* and 367 mμ with $E(1\%,1\text{ cm.})$ (348 mμ) = 1800. *Anal.* Calcd. for $C_{19}H_{28}$: C, 89.0; H, 11.0. Found: C, 88.67; H, 10.75.

Compound XII.—From 50 g. of compound I, the purified final product was 5.0 g. (8.3% over-all yield) of a light yellow oil. Its ultraviolet absorption spectrum showed a single maximum at 338 mμ (Curve 6, Fig. 2) with $E(1\%,1\text{ cm.})$ = 1875. *Anal.* Calcd. for $C_{22}H_{28}$: C, 90.43; H, 9.57. Found: C, 90.24; H, 9.44.

Preparation of 1-Bromo-4-methoxy-2-butene.—Butadiene (Matheson Co., E. Rutherford, New Jersey) was passed from a cylinder into 1 liter of chloroform at −30° until 162 g. (3.0 moles) had been dissolved. Bromine (480 g., 3.0 moles) was added dropwise with stirring over a period of three hours, maintaining the temperature at −30° with a Dry Ice–acetone-bath. When the bromine addition was complete, the chloroform was removed by distillation, the last traces under diminished pressure. The pressure was lowered to 12 mm. and the bulk of the reaction product distilled over at 80 to 110°. A small amount of the tetrabromide remained in the undistilled residue. The distillate was dissolved in 750 ml. of methanol and chilled slowly with frequent shaking to −50°. The white crystals of *trans*-1,4-dibromo-2-butene were filtered off and recrystallized twice more. This material was dried for sixteen hours in a vacuum desiccator at room temperature, giving 256 g. (40% yield) of crystalline dibromide which melted sharply at 52.5°. *Anal.* Calcd. for $C_4H_6Br_2$: C, 22.43; H, 2.80; Br, 74.77. Found: C, 22.48; H, 2.88; Br, 74.65.

Two hundred and thirty-four grams (1 mole) of the dibromide was dissolved in 200 ml. of methanol. Twenty-three grams (1 mole) of metallic sodium was added to another 100-ml. portion of methanol. The resulting solution of sodium methoxide was added slowly to the dibromide solution and the mixture was refluxed gently for four hours. Five hundred ml. of ether was added to help precipitate the sodium bromide, and the salt was removed by filtration.

The 132 g. of yellow liquid obtained upon removal of the solvent was distilled at 36 mm. pressure in a modified Claisen flask with a 16″ Vigreux sidearm. Eight fractions were collected over a temperature range of 33 to 73°. Analysis showed the lower boiling fractions to contain the dimethyl ether, while the high boiling fractions contained some of the unchanged dibromide. The two main fractions (55–60°, and 60–66°) were combined and refractionated. The main portion (36 g.) distilled at 58 to 65° at 36 mm. This was refractionated at the same pressure once more. The main fraction (27 g.) distilled at 60–63°, representing an over-all yield of purified material from butadiene equal to 5.4%. The product was a clear, water-white, extremely lachrymatory liquid. *Anal.* Calcd. for C_5H_9OBr: C, 36.36; H, 5.45; Br, 48.48. Found: C, 37.12; H, 5.71; Br, 48.90.

Several attempts to condense this material with compound I employing magnesium and lithium failed completely.

Summary

β-Ionone has been condensed with ethyl formate to give hydroxymethylene β-ionone. This compound, its sodium salt, and its diethyl acetal have been involved in a series of reactions with various metallo-organic compounds. Attempts to form β-ionylideneacetaldehyde by normal addition to the carbonyl group were unsuccessful. By 1,4-addition of various unsaturated Grignard complexes, several compounds related to vitamin A have been synthesized. None of these compounds is biologically active. The relationship between ultraviolet absorption spectrum and structure has been emphasized.

ROCHESTER, NEW YORK RECEIVED AUGUST 29, 1946

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

Streptomyces Antibiotics. XII. The Degradation of Streptomycin and Dihydrostreptomycin with Methanol

BY NORMAN G. BRINK, FREDERICK A. KUEHL, JR., EDWIN H. FLYNN AND KARL FOLKERS

Streptomycin hydrochloride was cleaved by the action of anhydrous methanol containing hydrogen chloride into streptidine and methyl streptobiosaminide dimethyl acetal hydrochloride, which upon acetylation gave crystalline methyl tetraacetylstreptobiosaminide dimethyl acetal. It was further demonstrated that the streptobiosamine moiety of streptomycin possessed a methylamino group and also a free or potential carbonyl group, as was shown by the preparation of the oxime and semicarbazone of streptomycin hydrochloride.[1] Details of these investigations and new data on the degradation products and the analogous degradation of dihydrostreptomycin[2] are described in the present publication. Other investigators[3] have studied the reaction of streptomycin and hydrogen chloride in methanol solution and obtained an amorphous, optically active hydrochloride of a base with properties which agreed with

(1) Brink, Kuehl and Folkers, *Science*, **102**, 506 (1945).

(2) Peck, Hoffhine and Folkers, THIS JOURNAL, **68**, 1390 (1946).

(3) Carter, Clark, Dickman, Loo, Meek, Shell, Strong, Alberi, Bartz, Binkley, Crooks, Hooper and Rebstock, *Science*, **103**, 53 (1946).