centration is reduced. Again the extinction coefficients decrease with increase in concentration.

1,3,7-Octatrien-5-yne.—The spectrum of this compound is reminiscent of that of D.V.A. but the peaks have been shifted to longer wave lengths. The extinction coefficients decrease with increase in concentration but the deviations from ideal constancy are considerably less than for M.V.A. or D.V.A.

Unlike the spectrum for D.V.A., however, it is not obvious what vibrational intervals make up the progression of bands. The difference between the two main peaks is about 1900 cm.$^{-1}$ suggesting that part of the spectrum, at least, finds its origin in a perturbed triple bond.

7-yne Tetramer.—It was evident from the original spectrum that inadvertent contamination of the tetramer with Apiezon "N" grease had occurred. By subtracting from this spectrum the absorption due to approximately the same concentration of grease as in the sample, a "difference curve" was obtained which gave an indication of the positions of the tetramer bands.[34]

The approximate wave lengths of the major bands of 1,3,5-octatrien-7-yne may be deduced from a consideration of the spectra published for the analogous alcohols by Heilbron, Jones and McCombie[14,37] as well as from data given previously in this paper.

TABLE III

Compound	Main band $\lambda_{max.}$, mμ	Subsidiary bands $\lambda_{max.}$, mμ	
CH_3=CH—CH=CH—C≡CH (B.D.A.)	252	240sh	265sh
$CH_3CH(OH)CH$=CHCH=CHC≡CH[14,37] (III)	260	247sh	273sh
$CH_3CH(OH)CH$=CHCH=CHCH=CHC≡CH[14,37] (IV)	292	279	305

In comparing B.D.A. with the corresponding alcohol III, an 8-mμ shift in the position of the main band is noted. If the same shift is assumed between 1,3,5-octatrien-7-yne and IV, the peaks for the former would be expected at 271, 284 and 297 mμ.

Another approach can be made through a consideration of the effect of the addition of conjugated ethylenic chromophores.

TABLE IV

Compound	Main band $\lambda_{max.}$ mμ	Shift, mμ
CH_2=CH—C≡CH (M.V.A.)	224 (mean)	
		28
CH_3=CH—CH=CH—C≡CH (B.D.A.)	252	
CH_2=CH—C≡C—CH=CH_2 (D.V.A.)	253	
		30
CH_3=CH—CH=CH—C≡C—CH=CH_2 (I)	283	
$CH_3CH(OH)CH$=CHCH=CHC≡CH (III)	260	
$CH_3CH(OH)CH$=CHCH=CHCH=CHC≡CH		32
(IV)	292	

From the above data it would seem reasonable to expect that the main bands of 1,3,5-octatrien-7-yne would appear at wave lengths about 30 mμ longer than those for B.D.A. This would give values of 270, 282 and 295 mμ. The actual spectrum observed is in good agreement with these predictions. Without knowledge of the extinction coefficients, the identification of the 7-yne tetramer cannot be considered certain from the ultraviolet data alone. However, since no other constitution appears consistent with all of the chemical and spectral evidence, it seems very probable that the compound which has been prepared is 1,3,5-octatrien-7-yne.

Mass Spectra.—The mass spectra of all the acetylene polymers prepared were obtained and appeared to be at least qualitatively consistent with their accepted constitutions. They are not included here. It was noted that very large peaks of mass 78 were obtained with the tetramers. In 1,3,-7-octatrien-5-yne this would appear to require the loss of a CH_2=C= fragment after the migration of a hydrogen from a CH_2=CH– group to an adjacent carbon. Analogous large peaks of mass 52 were obtained with both trimers.

Acknowledgment.—The authors wish to express their thanks to Messrs. A. Dupré, A. Nadeau, E. Blais and Mrs. Y. Richard for their assistance, to Drs. F. P. Lossing and J. L. Kerwin for obtaining and interpreting the mass spectra, and to Dr. R. N. Jones for his helpful comments.

SHAWINIGAN FALLS, QUEBEC, CANADA

[CONTRIBUTION FROM THE DIVISION OF ORGANIC CHEMISTRY OF THE ORTHO RESEARCH FOUNDATION]

Synthesis of Polyenes. V. α-Vitamin A Methyl Ether

BY WILLIAM OROSHNIK

RECEIVED APRIL 20, 1954

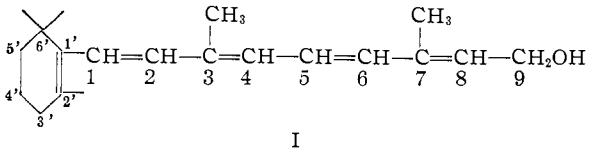
The synthesis and properties of α-vitamin A methyl ether are described.

Several studies attempting to correlate chemical structure with vitamin A activity have been reported during the past several years. Most of these have dealt with the effects of varying the number and position of methyl groups in the ring and side chain of vitamin A (I) and of vitamin A acid (II), as well as in some of their acetylenic analogs.[1] Except for 7-norvitamin A methyl ether, which was found to be 3.3% as active as vitamin A, these variants showed either negligible or no activity. Replacement of the β-ionone ring with a phenyl group in vitamin A,[2] or with a cyclopentenyl or cycloheptenyl group in 1,2-dehydrovitamin A acid,[3] results in complete loss of activity. The only analogs

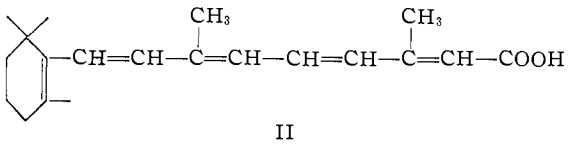
(1) N. A. Milas, *et al.*, THIS JOURNAL, **70**, 1591 (1948); I. Heilbron, E. R. H. Jones and R. W. Richardson, *J. Chem. Soc.*, 287 (1949); I. Heilbron, E. R. H. Jones, D. G. Lewis, R. W. Richardson and B. C. L. Weedon, *ibid.*, 742 (1949); I. Heilbron, E. R. H. Jones, D. G. Lewis and B. C. L. Weedon, *ibid.*, 2023 (1949); G. W. H. Cheeseman, I. Heilbron, E. R. H. Jones and B. C. L. Weedon, *ibid.*, 3120 (1949); J. B. Toogood and B. C. L. Weedon, *ibid.*, 3123 (1949).

(2) B. C. L. Weedon and R. J. Woods, *ibid.*, 2687 (1951).

(3) T. Bruun, I. Heilbron, B. C. L. Weedon and R. J. Woods, *ibid.*, 633 (1950).



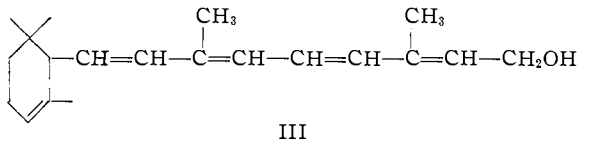
I



II

of vitamin A that have so far been found to show any appreciable activity are vitamin A acid (50%)[4] and 1,2-dehydrovitamin A (40%).[5]

A rather obvious ring variant of vitamin A, which has received surprisingly little attention, involves the replacement of the β-ionone ring with an α-ionone ring. This isomer of vitamin A, which may appropriately be called α-vitamin A (III) has not as yet been synthesized or found in nature. Several



III

related α-ionylidene compounds have been isolated from the oxidation products of α-carotene but none of these have been found to exhibit any biological activity.[6] The hydrocarbon analog of α-vitamin A is also known but apparently has not been tested biologically.[7]

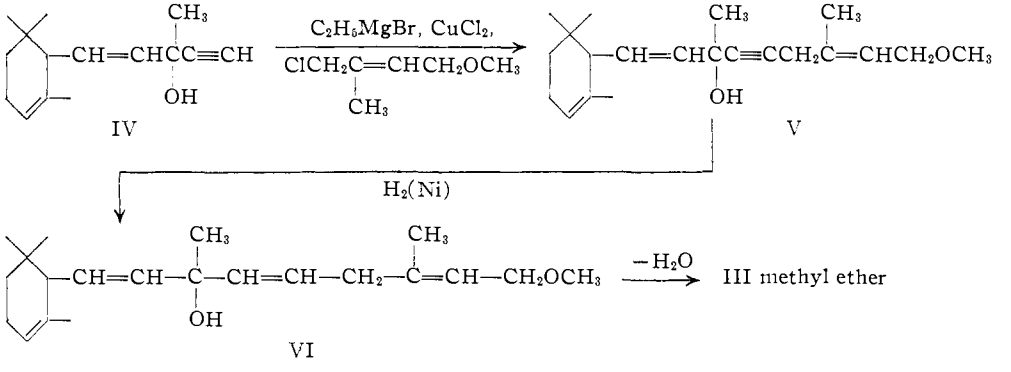
Several years ago the methyl ether of α-vitamin A was synthesized in this Laboratory. On biological assay it showed an activity of 1–3% of that of vitamin A which is of about the same magnitude exhibited by 7-norvitamin A methyl ether, mentioned above. Although of low order, this activity is significant in arising, for the first time, from a conjugated tetraene rather than a pentaene or higher polyene.

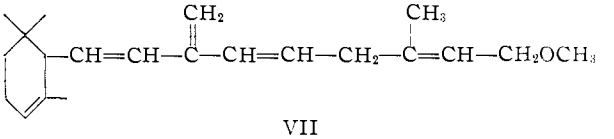
A rather interesting feature exhibited by α-vitamin A methyl ether is its storage in the liver. Extracts of the livers of the assay rats showed an absorption curve identical in all respects with that of the pure α-vitamin A methyl ether fed. The equivalence of the ratio $E_{311\ m\mu}/E_{325\ m\mu}$ of both absorption curves indicated that no vitamin A, $\lambda_{max.}$ 325 mμ, was present. It would thus appear the rat can utilize α-vitamin A methyl ether in the growth-promoting process without prior conversion to vitamin A. In this connection it is of interest that vitamin A acid likewise appears to undergo no conversion to vitamin A in the body.[8] On the other hand, unlike α-vitamin A methyl ether, this compound is not stored in the liver.[8] Liver storage data for the other active congeners of vitamin A have not been reported.

The synthesis of α-vitamin A methyl ether was first carried out by the route shown in Chart I. The coupling of ethynyl-α-ionol (IV) with methoxytiglyl chloride has been described in Part III.[9] Catalytic semihydrogenation of the resulting acetylenic carbinol, V, produced VI in almost quantitative yield. On treatment with catalytic amounts of iodine in refluxing benzene this yielded rearranged carbinol and α-vitamin A methyl ether. The latter, which was present in the crude product to the extent of only 20%, was isolated by alumina chromatography and ultimately purified by distillation under high vacuum. It is a viscous lemon-yellow liquid which showed no inclination to crystallize.

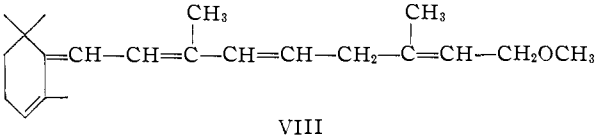
Identification of the dehydration product as α-vitamin A methyl ether is based on its ultraviolet and infrared absorption spectra. Only three isomers are theoretically possible from VI: α-vitamin A methyl ether, the cross-conjugated triene VII, and the conjugated *retro*ionylidene tetraene VIII.

CHART I





VII

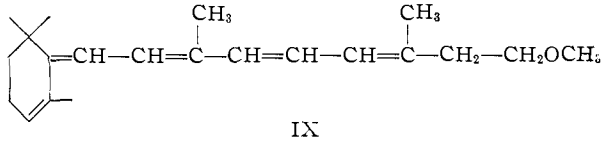


VIII

The absorption maximum of the dehydration product, 311 mμ, corresponds to a conjugated tet-

(4) D. A. Van Dorp and J. F. Arens, *Rec. trav. chim.*, **65**, 338 (1946).
(5) J. Attenburrow, *et al.*, *J. Chem. Soc.*, 1094 (1952).
(6) See the references in "Carotinoide" by P. Karrer and E. Jucker, Verlag Birkhäuser, Basel, 1948.
(7) P. Karrer, K. P. Karanth and J. Benz, *Helv. Chim. Acta*, **32**, 436 (1949).
(8) J. F. Arens and D. A. Van Dorp, *Nature*, **158**, 622 (1946).
(9) W. Oroshnik, A. D. Mebane and G. Karmas, THIS JOURNAL, **75**, 1050 (1953).

raene which automatically rules out the cross-conjugated triene as a possibility. The *retro*ionylidene tetraene VIII is known and shows $\lambda_{max.}$ 317 mμ in 4,5-*trans* form and $\lambda_{max.}$ 296 mμ in the 4,5-*cis* form.[10] While neither of these corresponds to the dehydration product obtained, a mixture of the two products could conceivably duplicate its absorption curve. This presented a real possibility since the 4,5-*cis* double bond in VI would be expected to invert partially even during dehydration toward the ring.[11] In fact, with the β-analog of V, which almost exclusively follows this reaction course, such *cis–trans* mixtures with a $\lambda_{max.}$ falling anywhere between 303 and 315 mμ are the usual product.[10,11] But this possibility definitely was disposed of by the fact that the dehydration product of VI was inert to iodine as well as to alkali treatment. Mixtures of *cis*- and *trans*-VIII invert completely to the *trans* isomer, $\lambda_{max.}$ 317 mμ,[10] on treatment with iodine, and isomerize readily to the conjugated pentaene, *retro*vitamin A methyl ether (IX), in the presence of alkali.[10]



IX

TABLE I

SPECTRAL COMPARISON OF α-VITAMIN A METHYL ETHER WITH SOME TYPICAL CONJUGATED TETRAENES

Compound	Number of substituents	$\lambda_{max.}$ (mμ)[a]	$\epsilon_{max.}$	Estim. $\lambda_{max.}$ for tetrasubstitution[b]
1,3,5,7-Octatetraene[c]	0	291[d]	....	311
2,4,6,8-Decatetraene[e]	2	295[f]	52,000[g]	305
2,4,6,8-Decatetraene-1-ol[h]	2	299	64,000	309
6-Methyl-2,4,6,8-undecatetraene-10-ol[i]	3	302	48,000	307
2,4,6,8-Dodecatetraene-10,11-diol[j]	2	299[k]	64,000	309
4,5-*trans*-VIII[10]	5	317	47,000	312
all-*trans*-X[l]	4	309.5	58,900	309.5
mono-*cis*-X[5]	4	307	58,000	307
α-Vitamin A hydrocarbon[7]	4	308	55,100	308
α-Vitamin A methyl ether	4	311	57,200	311

[a] The solvent used was ethanol unless otherwise noted. [b] To permit a reasonable comparison, the $\lambda_{max.}$ of each compound is "corrected" here for four substituents by assuming a bathochromic effect of 5 mμ for each substituent. It is recognized that this method of "correction" ignores the hyperconjugative effects of allylic hydroxyl groups as well as the effects of differences in the size and position of substituents. It is being used here only as a rough approximation. [c] G. F. Woods and L. H. Schwartzman, THIS JOURNAL, **71**, 1396 (1949). [d] Solvent, cyclohexane. [e] E. R. Blout and M. Fields, THIS JOURNAL, **70**, 189 (1948). [f] Solvent hexane. [g] R. Kuhn, *Angew. Chem.*, **50**, 705 (1937). [h] T. Reichstein and G. Trivelli, *Helv. Chim. Acta*, **15**, 1074 (1932). [i] K. R. Bharucha and B. C. L. Weedon, *J. Chem. Soc.*, 1589 (1953). [j] F. Bohlmann, *Chem. Ber.*, **85**, 386 (1952). [k] Solvent, methanol. [l] Present work.

(10) W. Oroshnik, G. Karmas and A. D. Mebane, THIS JOURNAL, **74**, 295 (1952).

(11) W. Oroshnik, G. Karmas and A. D. Mebane, *ibid.* **74**, 3807 (1952).

The ultraviolet absorption spectrum of the dehydration product is consistent in all respects with that expected for the α-vitamin A chromophore. From the data in Table I, it can be seen to fall into line with other known tetrasubstituted conjugated tetraenes. Because of the break in conjugation between the ring and side chain there is no steric hindrance in α-ionylidene compounds as compared to the β-ionylidene series where interference between one of the *gem*-methyl groups and the 2-hydrogen causes a break in coplanarity. This is reflected not only in the $\lambda_{max.}$ of α-vitamin A methyl ether, but also in the fine structure of its absorption curve and its notably higher extinction than that of vitamin A methyl ether (Fig. 1).

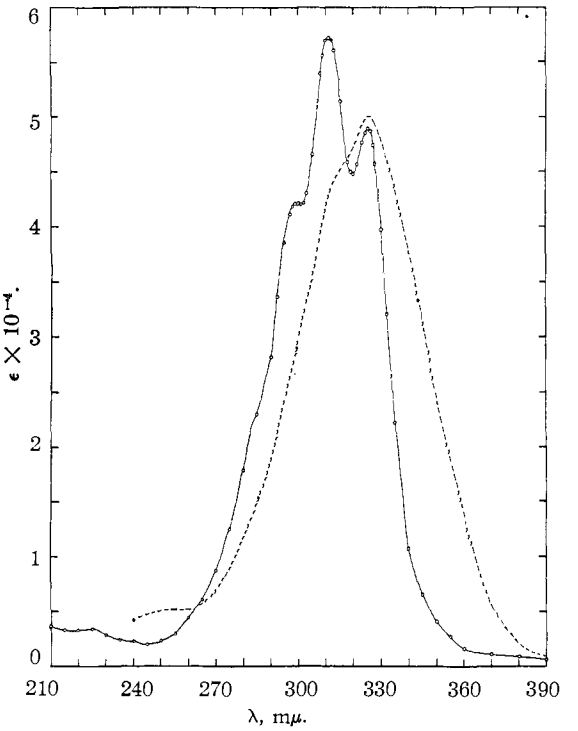
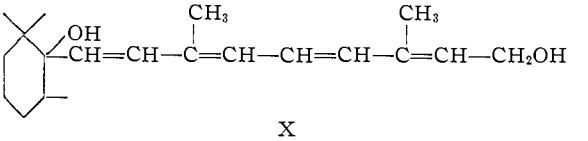


Fig. 1.—Ultraviolet absorption spectra of α-vitamin A methyl ether, —; vitamin A methyl ether ----. The latter curve is taken from A. R. Hanze, T. W. Conger, E. C. Wise and D. I. Weisblat, THIS JOURNAL, **70**, 1253 (1948).

Compound X, which has the same chromophore as α-vitamin A, has been reported to show a $\lambda_{max.}$



X

of only 307 mμ.[5] This apparent inconsistency was found to be due to the presence of a *cis* double bond in X. The product reported was prepared by the lithium aluminum hydride reduction of the corresponding 1,2-acetylene compound, a reaction which can be accompanied, as shown in Part VI,[12] by inversion of the adjacent double bond. This apparently was the case here, for treatment of a specimen of X, prepared in this way, with catalytic quantities

(12) W. Oroshnik and A. D. Mebane, THIS JOURNAL, in press.

of iodine, shifted its $\lambda_{max.}$ to 309.5 mμ. No change in $\lambda_{max.}$ was observed with α-vitamin A methyl ether on iodine catalysis.

The lower $\lambda_{max.}$ (308 mμ)[7] of α-vitamin A hydrocarbon, on the other hand, is to be expected from the absence of a primary allylic methoxyl (or hydroxyl) group in the molecule.[9] The spectrum of the β-hydrocarbon is similarly displaced from that of its methoxyl and hydroxyl analogs.[9]

The infrared spectrum of α-vitamin A methyl ether is distinguished from that of vitamin A methyl ether by the presence of absorption bands of medium strength at 12.2 and 13.6 μ (Fig. 2). The same relationship exists between the infrared spectra of α- and β-ionone.[13] There can be little doubt, therefore, that these bands characterize the α-ionone ring.

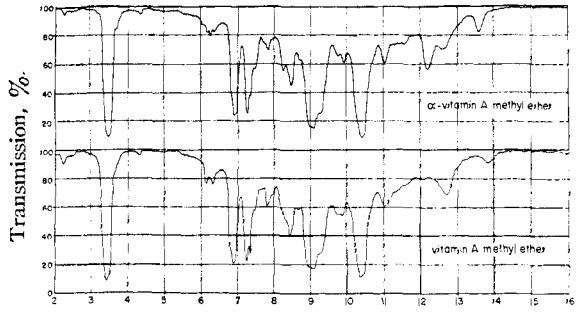
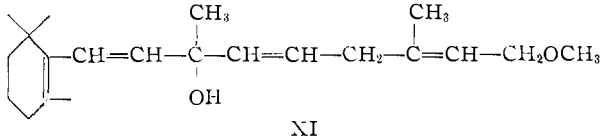
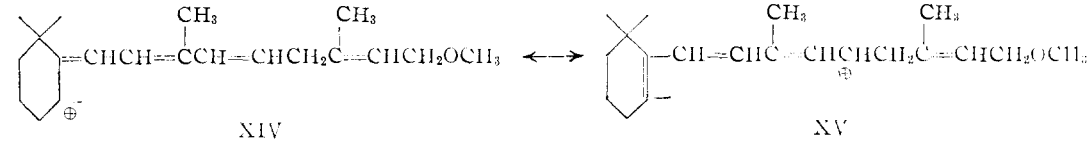


Fig. 2.—The infrared spectra. (The author is indebted to Dr. O. Isler, F. Hoffmann-La Roche and Company, Basel, Switzerland, for the infrared absorption curve of vitamin A methyl ether.)

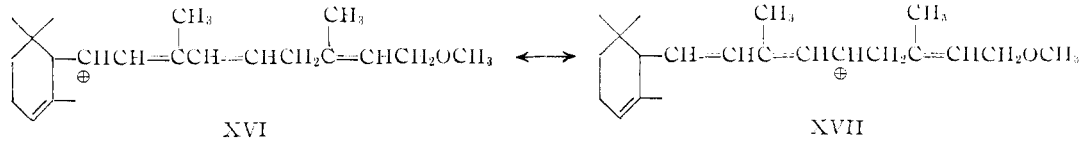
It is of interest at this point to note the difference in behavior between VI and its β-analog XI on



XI

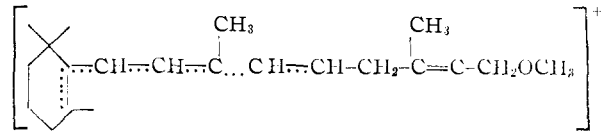


XIV XV

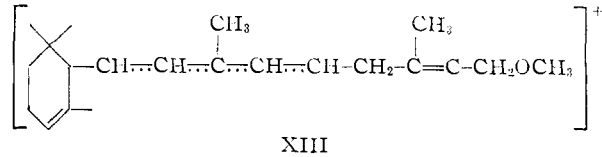


XVI XVII

dehydration. The latter rearranges and dehydrates quickly and completely, even on mild acid catalysis, as compared to the rather slow rearrangement and only partial dehydration of the α-compound under relatively more forceful conditions. The greater acid-sensitivity of XI stems from the fact that the mesomeric ion XII, formed in the rate-determining step, is derived from a longer conjugated system than is XIII, the ionic intermediate



XII



XIII

from VI, and therefore has a lower energy of activation for its formation.[14] The preference of XII for losing a proton to complete dehydration, as compared to the partial recombination of XIII with an anion, is due in part also to its longer conjugated system. But an equally important factor, contributing both to its ease of formation and to its complete dehydration, is the fact that one of the resonance forms of XII is a tertiary carbonium ion, XIV, as compared to only secondary carbonium ion forms, XVI and XVII, possible for XIII.[15]

The difference in orientation of dehydration shown by the two carbinols is indeed surprising. The β-compound dehydrates almost entirely toward the ring giving over 90% of *retro*ionylidene tetraene (VIII) and only a very small amount of vitamin A methyl ether.[10] The very minor contribution from the secondary carbonium ion XV has been pointed out in Part II[11] as due to the steric hindrance inherent in β-ionylidene structures and to the normally greater stability of a tertiary carbonium ion XIV.

The α-compound, on the other hand, dehydrates exclusively in the opposite direction to α-vitamin A methyl ether. This would hardly have been predicted on the basis of one of the two resonance forms involved, XVI and XVII, being more stable than the other, for both appear to have equivalent stability characteristics. Furthermore, because of the break in conjugation at the ring-side-chain junction in α-ionylidene compounds, steric hind-

(13) K. Seitz, Hs. H. Günthard and O. Jeger, *Helv. Chim. Acta*, **33**, 2196 (1950).

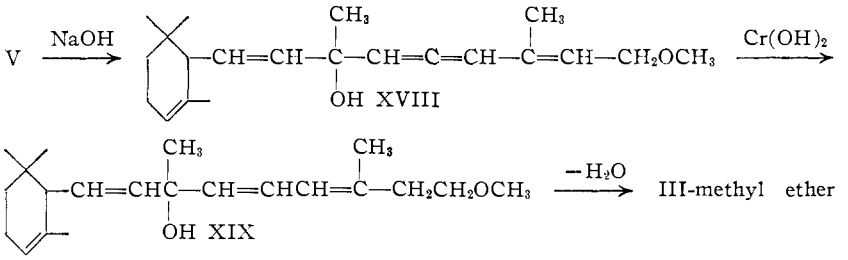
(14) The effect of increased conjugation in the intermediate mesomeric ion is well illustrated by the ability of α-vinylethynyl crotyl alcohol to rearrange sixty times faster than α-ethynyl crotyl alcohol (E. A. Braude and E. R. H. Jones, *J. Chem. Soc.*, 122 (1946)).

(15) The contribution of resonance forms of the type —CH=CH—$\overset{+}{\underset{|}{C}}$—CH=CH— was considered as negligible because of the tendency toward conjugation.

rance is not a factor here as it is in the β-series. The reason for the unidirectional dehydration of VI is at present obscure, but may be related in some way to the unusual stability that appears to be inherent in the 1′-hydrogen of α-ionylidene compounds. This was evidenced by the difficulty encountered in dehydrating IV and V, in which the acetylenic group necessitates dehydration toward the ring, and by the inability to effect a prototropic shift in the α-ionylidene group of III-methyl ether, VI or XIX, as described below.

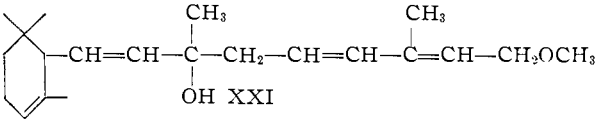
α-Vitamin A methyl ether also was synthesized by a variation of the first route which gave considerably better yields. This is shown in Chart II.

CHART II



The isomerization of V to the vinylallenol XVIII has been described in Part III.[9] Reduction of XVIII with chromous hydroxide followed the course previously demonstrated for the analogous compound in the β-series,[9] giving 4,5-*trans*-XIX. The *trans* configuration was verified by comparison with an authentic specimen of 4,5-*trans*-XIX prepared by the method shown in Chart III.

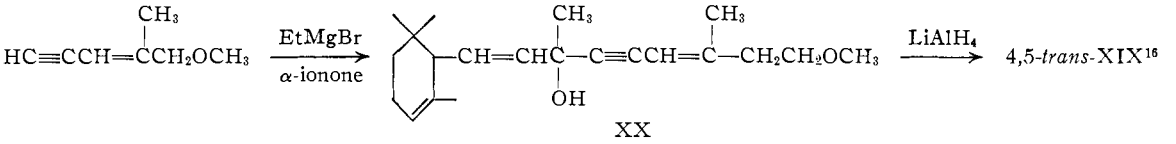
kali. Fractional distillation of the product on the basis of refractive index increments yielded 4,5-*trans*-XIX, comparable spectrally and in refractive index to that obtained by chromous hydroxide reduction of XVIII. The distillation tails however showed a drop in $\lambda_{max.}$ from 241 to 238 mμ. This



may perhaps be indicative of the presence of some of the isomeric compound XXI which would result from the prototropic shift of the 4,5-double bond, and which would be expected to show $\lambda_{max.}$ *ca.* 235 mμ.[18]

The lower prototropic mobility of the 4,5-double bond as compared to the 7,8 has also been observed in the analogous β-compound. This may possibly be due to the fact that the 4,5-double bond in each case is part of a divinylcarbinol system, wherein there appears to exist some partial conjugation between the double bonds adjacent to the hydroxyl group. Evidence for such conjugation was presented in Part IV[19] where it was shown that an unsaturated group in the 4,5-position of a β-ionol or a ψ-ionol exerts a bathochromic effect on the spectrum. This is most readily explained by the fact that both double bonds in such a system

CHART III



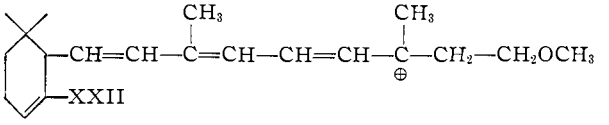
XX

The two specimens showed almost identical ultraviolet spectra, $\lambda_{max.}$ 241 mμ, except for a somewhat lower extinction in the chromous hydroxide product. Its refractive index was also lower.[17] Since both specimens were analytically identical, it seems most likely that the non-absorbing impurity in the chromous hydroxide reduction product is the unconjugated compound VI which would arise from a 5,6-addition to hydrogen to the allene group. Removal of this impurity was only partially accomplished by alumina chromatography.

Compound XIX also was obtained by the prototropic rearrangement of VI. Although VI has two potential prototropically mobile systems, the unconjugated ring-side-chain diene and the unconjugated diene substituent of the α-ionol group, only the latter was affected on refluxing in alcoholic al-

are hyperconjugated with a common hydroxyl group and hence must be partially conjugated with each other.

The dehydration of XIX proceeded much more readily and in better yields than that of VI. This is to be expected from its longer conjugated system and the fact that a tertiary carbonium ion XXII is



now possible among the resonance forms of the ionic intermediate. The product consisted of about equal parts of undehydrated carbinol and α-vitamin A methyl ether. The latter, after chromatographic isolation and distillation, proved to be identical with the specimen obtained by dehydration of

(16) The lithium aluminum hydride reduction of the acetylenic bond in conjugated enynols gives, as a rule, the corresponding *trans*-olefin only [see examples in Parts II[11] and VI,[12] and R. A. Raphael and F. Sondheimer, *J. Chem. Soc.*, 3185 (1950)]. While an accompanying inversion of the adjacent ethylenic bond may be expected with the use of this reagent,[12] there was no evidence that this occurred with XX or its β-analog.[11]

(17) The same relationship has been found between specimens of the β-analog of 4,5-*trans*-XIX prepared by these two methods.[9]

(18) The corresponding 5,6-*trans* compound in the β-series shows $\lambda_{max.}$ 235 mμ.[12] Since the contribution from the β-ionol chromophore is only very slight (ε 6500) it can be expected that the α-isomer would show the same $\lambda_{max.}$ Both the α- and β-isomers of XIX, for example, show the same $\lambda_{max.}$

(19) W. Oroshnik, G. Karmas and R. A. Mallory, THIS JOURNAL, **76**, 2325 (1954).

VI. The fact that no rearrangement products of XIX (*i.e.*, conjugated trienol) were observed is consistent with the generalizations made above in connection with the behavior of VI and of XII on dehydration; *i.e.*, with a longer conjugated system and a tertiary carbonium ion, loss of a proton by the ionic intermediate is preferred to recombination with an anion.

It is interesting to note the relative prototropic immobility of the unconjugated ring-side-chain system in the α-ionylidene series. Exhaustive treatment of VI and of XIX in various alkaline media failed to induce a shift of either the ring double bond or the first side-chain double bond. The same situation was encountered with α-vitamin A methyl ether which was always recovered substantially unchanged from such treatments. As was pointed out above, these experiments indicate an unusual stability for the 1'-hydrogen in the α-ionylidene system.[20] However, with the presence of activating groups in the molecule, prototropic isomerizations of α-ionylidene to β-ionylidene compounds can be accomplished. This is seen in the small yields of β-carotene obtained by the alkali treatment of α-carotene,[21] and in the easy isomerization of α-ionone to β-ionone in the presence of alkali.[22] The activating groups in these cases are the conjugated decaene system and the vinylogous keto groups, respectively.

Experimental

Absorption Spectra.—The ultraviolet absorption spectra were determined in 95% ethanol with a Beckman DU spectrophotometer. The infrared spectra were determined on the neat compounds with a Baird double-beam spectrophotometer by Samuel P. Sadtler and Son, Inc., Philadelphia, Pa.

Preparation of VI.—A solution of 23.6 g. of the acetylenic carbinol V,[9] 0.5 g. of zinc acetate dihydrate and 10 ml. of piperidine in 150 ml. of methanol was hydrogenated with 5.0 g. of Raney nickel paste[23] on a Parr shaker at atmospheric pressure. The rate of hydrogen uptake averaged about 100 ml./min. but at the theoretical end-point dropped sharply. The reaction was interrupted then, and the solution filtered from the catalyst and worked up with water and petroleum ether. After drying with anhydrous potassium carbonate and concentrating under vacuum, the product was distilled. About 0.5 g. each of forerun and tail fractions were arbitrarily cut. The main fraction, 21.5 g., was collected at 105–115° (0.001 mm.), $n^{20}D$ 1.5040.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.34; H, 10.81.

As expected from the lack of conjugation, the product showed no absorption bands between 210 and 400 mμ.

α-Vitamin A Methyl Ether by Dehydration of VI.—A solution of 15.0 g. of VI and 140 mg. of iodine in 250 ml. of benzene was refluxed with an automatic water separator for 105 minutes. It was then cooled under nitrogen, washed with sodium thiosulfate solution and dried with anhydrous potassium carbonate. Removal of the benzene under vacuum left 14.0 g. of a dark amber liquid showing the spectrum of α-vitamin A methyl ether, $\lambda_{max.}$ 311 mμ, $E^{1\%}_{1\ cm.}$ 382, and another band at 235 mμ, $E^{1\%}_{1\ cm.}$ 272. The latter corresponds to the carbinol expected from XVI or XVII. From the extinction at 311 mμ, the α-vitamin A methyl ether content is calculated to have been 20%.

The crude product was chromatographed on a 3 × 90-cm. column of Alcoa F-20 alumina, developing with petroleum ether and eluting with increasing proportions of ether in petroleum ether. After removal of a small amount of extraneous polyenic material, the eluates showed the spectrum of α-vitamin A methyl ether but with some additional absorption at 230 mμ. Collection into the desired fraction was begun only when the ratio $E_{230\ m\mu}/E_{311\ m\mu}$ dropped from 0.3 to 0.01. The end of this fraction was indicated by a very sudden rise in extinction at 235 mμ.

The desired eluates were washed with water, dried with anhydrous potassium carbonate and distilled. The product, a very viscous lemon-yellow liquid, was collected at 110–120° (0.001 mm.); yield 2.0 g.; $n^{20}D$ 1.5924; $\lambda_{max.}$ 311 mμ, ε 57,200, $E^{1\%}_{1\ cm.}$ 1,900.

Anal. Calcd. for $C_{21}H_{32}O$: C, 83.94; H, 10.74; methoxyl, 10.33. Found: C, 83.77; H, 10.87; methoxyl, 10.08.

Preparation of the Conjugated Enyne XX (By G. Karmas).—A Grignard reagent was prepared in the conventional manner from 19.7 g. of 4-methyl-6-methoxyhex-2-en-1-yne,[11] 200 ml. of dry ether and 105 ml. of 1.53 *M* ethylmagnesium bromide. To this solution, cooled to −10°, was added, with stirring, a solution of 30 g. of α-ionone in 100 ml. of dry ether. After standing overnight at room temperature, the reaction mixture was hydrolyzed at −20° with 30% ammonium acetate solution. The ether layer was removed, filtered through some anhydrous potassium carbonate and concentrated under vacuum. Distillation yielded 15 g. of product collected at 125–135° (0.001 mm.); $n^{22}D$ 1.5208; $\lambda_{max.}$ 234.5 mμ, ε 15,800.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.71; H, 10.19; methoxyl, 9.80. Found: C, 79.94; H, 10.09; methoxyl, 9.33.

Reduction of the Enyne XX to 4,5-*trans*-XIX.—A solution of 18.0 g. of XX in 150 ml. of dry ether was added at 0° to a stirred suspension of 2.1 g. of commercial lithium aluminum hydride in 200 ml. of dry ether. The mixture was then refluxed for three hours, cooled to −20° and hydrolyzed with 100 ml. of 70% methanol. The precipitated alumina was filtered off with the aid of a little Super-Cel, and the filtrate washed thoroughly with water, dried with anhydrous potassium carbonate and concentrated under vacuum. Distillation yielded 16.4 g. of product collected at 120–124° (0.005 mm.); $n^{25}D$ 1.5234; $\lambda_{max.}$ 241 mμ, ε 25,400, $E^{1\%}_{1\ cm.}$ 798.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76; methoxyl, 9.74. Found: C, 79.54; H, 10.69; methoxyl, 9.51.

Reduction of the Allene XVIII to 4,5-*trans*-XIX.—The procedure was that described in Part III[9] for the chromous hydroxide reduction of the β-analog of XVIII. From 45 g. of XVIII and the proportionate quantities of chromous acetate, sodium hydroxide, ethanol and water, there was obtained 42.0 g. of product collected at 115–120° (0.001 mm.); $n^{25}D$ 1.5168; $\lambda_{max.}$ 241 mμ, $E^{1\%}_{1\ cm.}$ 615.

Since the product analyzed 1% high in carbon, a portion was chromatographed on Alcoa F-20 alumina and again distilled; $n^{20}D$ 1.5189; $\lambda_{max.}$ 241 mμ, $E^{1\%}_{1\ cm.}$ 667.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.19; H, 10.72.

Prototropic Rearrangement of VI to 4,5-*trans*-XIX.—A solution of 59.8 g. of VI and 168 g. of sodium methoxide, in one liter of methanol, was refluxed for six hours. It was then cooled under nitrogen and worked up in the usual fashion with water and petroleum ether. After drying with anhydrous potassium carbonate and concentrating under vacuum the product was distilled. A 2.0-g. forerun coming over between 60 and 105° (0.001 mm.) was discarded. Following this, the distillate progressively increased in extinction at 241 mμ, and in refractive index. On reaching $n^{20}D$ 1.5150 this fraction was cut; yield 4.3 g., $n^{20}D$ 1.5130; $\lambda_{max.}$ 241 mμ, $E^{1\%}_{1\ cm.}$ 534. From the analysis below and the fact that further alkali treatment enriched the 241 mμ content, this fraction was judged to be a mixture of the unconjugated and conjugated isomers VI and XIX.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76; methoxyl, 9.74. Found: C, 79.43; H, 10.89; methoxyl, 9.30.

The main fraction, which followed, was collected at 110–120°, yield 45.0 g., $n^{20}D$ 1.5170; $\lambda_{max.}$ 241 mμ, $E^{1\%}_{1\ cm.}$ 612.

(20) The possibility that the prototropic stability of the 1'-hydrogen may, in part, be due to the extensive methylation around it, should not be overlooked. This can constitute a considerable block to the approach of an anion.

(21) P. Karrer and E. Jucker, *Helv. Chim. Acta*, **30**, 266 (1947).

(22) H. Köster, *Ber.*, **77B**, 553 (1944).

(23) This weight actually refers to a wet cake of Raney nickel, obtained by pressing an aqueous paste between two layers of filter paper. The aqueous paste was purchased from the Raney Catalyst Co., Chattanooga 2, Tenn.

Anal. Found: C, 79.45; H, 10.76; methoxyl, 9.61.

A tail fraction of 1.2 g., $n^{20}D$ 1.5176, arbitrarily cut from the main, likewise analyzed properly for $C_{21}H_{34}O_2$ but showed $\lambda_{max.}$ 238 mμ, $E^{1\%}_{1\,cm.}$ 673.

α-Vitamin A Methyl Ether by Dehydration of 4,5-*trans*-XIX.—A 15.0-g. sample of pure 4,5-*trans*-XIX as obtained from the reduction of XVIII was dehydrated with iodine by the procedure described above for the dehydration of VI. Removal of the benzene under vacuum left 14.2 g. of dark amber-colored liquid; $\lambda_{max.}$ 311 mμ, $E^{1\%}_{1\,cm.}$ 926. The extinction corresponds to an α-vitamin A methyl ether content of 48.8%.

Alumina chromatography and subsequent distillation as described above under the dehydration of VI, yielded 4.5 g. of α-vitamin A methyl ether identical in all respects with the specimen obtained from VI.

The results were essentially the same with samples of 4,5-*trans*-XIX obtained by the other two routes.

Dehydration of 4,5-*trans*-XIX was also readily accomplished by allowing a solution of 10.0 g. of the carbinol in 300 ml. of glacial acetic acid to stand at room temperature for three hours. Working up with water and petroleum ether and concentrating under vacuum yielded 10.0 g. of crude product of $\lambda_{max.}$ 311 mμ, $E^{1\%}_{1\,cm.}$ 806.

Stereoisomerization of the Tetraene Glycol X.—A specimen of X was prepared by the lithium aluminum hydride reduction of the corresponding 1,2-dehydro compound,[24] as described by Attenburrow, *et al.*[5] The product, after two recrystallizations from cyclohexane, melted at 126–134° and showed $\lambda_{max.}$ 307.5 mμ, ε 52,400. Attenburrow, *et al.*, report m.p. 122–127°, $\lambda_{max.}$ 307 mμ, ε 58,000. These data, especially the wide melting ranges, leave no doubt that the reduction product in each case was a mixture of stereoisomers.

A solution of 2.4 g. of the glycol and 25 mg. of iodine in 625 ml. of benzene was stirred under nitrogen at room temperature in moderate artificial light. The shift of $\lambda_{max.}$ from 307.5 to 309.5 mμ was completed during the first half-hour but stirring was allowed to continue an additional half-hour to assure equilibrium. The solution then was washed with sodium thiosulfate solution, dried with anhydrous potassium carbonate, and concentrated under vacuum to a sirup. This was taken up in 5 ml. of warm benzene, diluted to 30 ml. with cyclohexane, and stored overnight under nitrogen at 0°. A portion of the glycol which precipitated was then recrystallized from benzene–cyclohexane. The all-*trans* product consisted of rather large canary-yellow crystals as compared to the almost white mono-*cis* isomer; m.p. 124–125°[25]; $\lambda_{max.}$ 309.5 mμ, ε 59,800.

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.60. Found: C, 78.45; H, 10.51.

Biological Assays.—The assays and liver extractions were performed by the Biochemistry Division of this Institute and the Food Research Laboratories, Inc., Long Island City, New York.

Acknowledgment.—The author is indebted to Mr. Joseph Grodsky for the microanalyses and to Mr. Walter Gall for technical assistance.

(24) The author is indebted to Dr. B. A. Hems, Glaxo Laboratories, Ltd., Greenford, Middlesex, England, for a generous supply of the intermediate necessary for the synthesis of the dehydro compound.

(25) Partial polymerization or some other reaction appears to occur during the heating for about one-third of the melting point sample did not fuse.

RARITAN, NEW JERSEY

[CONTRIBUTION FROM THE DIVISION OF APPLIED BIOLOGY, NATIONAL RESEARCH LABORATORIES]

Production of Formic Acid During Oxidation of Carbohydrates with Lead Tetraacetate[1,2]

BY A. S. PERLIN

RECEIVED MAY 24, 1954

The rate of oxidation of formic acid to carbon dioxide by lead tetraacetate in acetic acid was found to be markedly increased in the presence of potassium acetate. The accelerated reaction was used to study production of formic acid during the lead tetraacetate oxidation of methyl glycopyranosides. By measuring evolved carbon dioxide with the Warburg respirometer the course of the reactions was conveniently followed on the micro scale. In glacial acetic acid, the glycosides consumed the expected two moles of oxidant but, with the hexose series, much less than the theoretical one mole of formic acid was found. Evidence is presented suggesting that the formic acid not accounted for was present as the 6-O-formyl ester. In aqueous acetic acid, the extent of ester formation was reduced and over-oxidation of the glycosides also was observed.

In theory, formic acid is produced during the oxidation of many carbohydrates with lead tetraacetate, *e.g.*, when the compounds contain hydroxyl groups on three adjacent carbon atoms.[3] Little is known of this aspect of the oxidations, however, because of the lack of a convenient method of analysis. Moreover, the stoichiometry of the oxidations is obscured when the formic acid is not determined since the latter itself consumes lead tetraacetate.[4] Grosheintz[5] has noted that when oxidations are conducted in aqueous acetic acid,[6] formic acid is quantitatively oxidized to carbon dioxide and consumes an extra mole of oxidant. Although this finding suggests an index of formic acid production in carbohydrate oxidations with lead tetraacetate, it has been used only to a limited extent, *e.g.*, in the degradative assay of radioactive sugars.[7]

An examination of Grosheintz' reaction in this Laboratory showed that the rate of evolution of carbon dioxide was accelerated markedly by the addition of potassium or sodium acetate (Fig. 1) (see also reference 8). The reaction was carried out in the Warburg respirometer,[9] and the evolved gas measured manometrically. An accelerated oxidation also was evident in glacial acetic acid though more potassium acetate was required to attain the same rate. Thus at a concentration of 1.5 moles of acetate per mole of oxidant in 90% acetic acid and of 3 moles per mole in glacial acetic acid, the reaction was complete in 10 to 15 minutes. These rates

(1) Presented in part before the Division of Carbohydrate Chemistry, 124th Meeting, American Chemical Society, Chicago, Ill., 1953.

(2) Issued as N.R.C. No. 3401.

(3) R. Criegee, *Ann.*, **495**, 211 (1932).

(4) R. C. Hockett, M. T. Dienes, H. G. Fletcher and H. E. Ramsden, THIS JOURNAL, **66**, 467 (1944).

(5) J. M. Grosheintz, *ibid.*, **61**, 3379 (1939).

(6) E. Baer, J. M. Grosheintz and H. O. L. Fischer, *ibid.*, **61**, 2607 (1939).

(7) S. Abraham, *ibid.*, **72**, 4050 (1950).

(8) A. S. Perlin, *Anal. Chem.*, **26**, 1053 (1954).

(9) O. Warburg, "Uber der Stoffwechsel der Tumoren," Berlin, Springer, 1926.