carried out, and the crude hydrocarbons were combined for distillation.

Ferric Chloride-catalyzed Reaction Moderated with Nitromethane.—The method was the same as that employed previously except that 20 cc. of nitromethane was placed in the flask before the addition of *t*-amyl chloride.

Aluminum Chloride-catalyzed Reaction Moderated with Nitromethane.—To 0.037 mole (5 g.) of $AlCl_3$ and 2 moles (156 g.) of benzene was added 20 cc. of nitromethane, followed by the drop-wise addition of 1 mole (106.5 g.) of *t*-amyl chloride at room temperature; a rise in temperature was not noticed during the course of the experiment. The product was hydrolyzed in the usual manner.

The above experiment was repeated with 10 g. of $AlCl_3$ instead of 5 g., and the mixture was stirred vigorously during the addition of *t*-amyl chloride.

Aluminum Chloride-catalyzed Reaction between Benzene and *t*-Amyl Alcohol.[11]—One mole (88 g.) of *t*-amyl alcohol ($n^{20}D$ 1.4052, b.p. 102° (750 mm.)) reacted at room temperature and high speed stirring with 4 moles (312 grams) of benzene, the reaction being catalyzed by one-half mole (66.7 g.) of $AlCl_3$; the reaction was exothermic, but no attempt was made to cool the mixture. After two-thirds of the alcohol had been added, the mixture separated into two layers, the bottom layer being very dense. Stirring was again started (with considerable difficulty), and the remainder of the alcohol was added with little evolution of HCl. The reaction mixture was poured into a hydrochloric acid–ice-water mixture and then washed with alkali and steam distilled.

Hydrogenation of *t*-Amylbenzene.—High purity *t*-amylbenzene (129 g.) was hydrogenated over nickel-on-kieselguhr catalyst at 200° and 1800 p.s.i. The hydrogenate (90 g.) was distilled at atmospheric pressure on a column rated at 20 theoretical plates. The observed boiling point was not constant, probably due to a little unchanged *t*-amylbenzene; therefore, the crude *t*-amylcyclohexane was percolated through silica gel, and redistilled before physical properties were measured.

***t*-Amylcyclohexane from *p*-*t*-Amylphenol.**—*p*-*t*-Amylphenol (800 g. or 4.9 moles), supplied by Sharples Chemicals Inc., was dissolved in 1000 cc. of ethylcyclohexane and hydrogenated over nickel-on-kieselguhr catalyst at 200° and 1800 p.s.i. Ethylcyclohexane was removed by distillation, and the hydrogenate was then distilled under vacuum to yield 643 g. (3.8 moles, a 78% yield) of *p*-*t*-amylcyclohexanol (b.p. 112° (9 mm.), $n^{20}D$ 1.4763). Some fractions solidified in the receiver and the index of refraction was taken on the liquid portion only.

The alcohol, diluted with ethylcyclohexane, was dehydrated by passing it through a 2.5 × 100 cm. tube of 4–8 mesh alumina at 325° at a rate of one drop per 3 seconds. The dehydrated product (3.05 moles or 465 g.) distilled at 202° (747 mm.), had a refractive index range of 1.4641 to 1.4674, and amounted to a 91% yield.

Hydrogenation of 381 g. (2.50 moles) of the cycloölefin over nickel-on-kieselguhr at 150° gave 318 g. of crude *t*-amylcyclohexane almost all of which distilled at constant temperature. The yield was 83% on this step or 59% overall.

COLUMBUS, OHIO RECEIVED JULY 3, 1951

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(11) *Cf.* R. C. Huston and T. Y. Hsieh, THIS JOURNAL, **58**, 439 (1936).

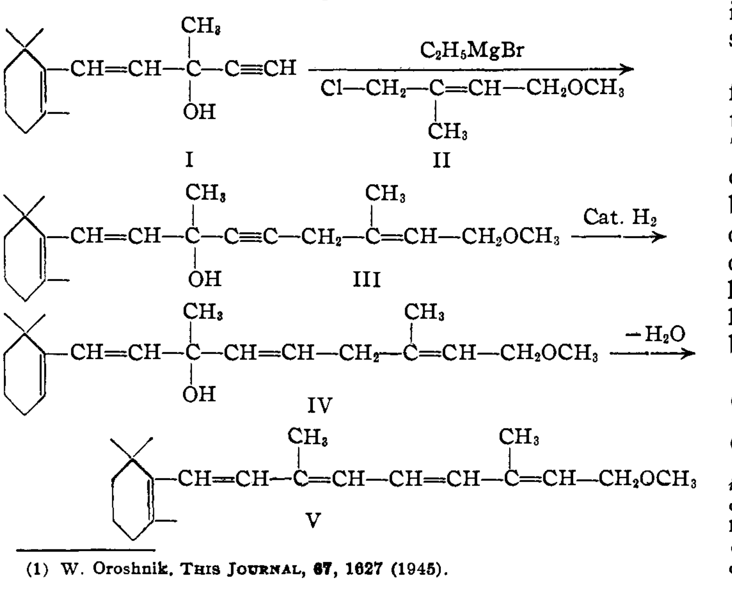
[CONTRIBUTION FROM THE DIVISION OF ORGANIC CHEMISTRY OF THE ORTHO RESEARCH FOUNDATION]

Synthesis of Polyenes. I. *Retro*vitamin A Methyl Ether. Spectral Relationships between the β-Ionylidene and *Retro*ionylidene Series

BY WILLIAM OROSHNIK, GEORGE KARMAS AND ALEXANDER D. MEBANE

A synthesis designed to give vitamin A methyl ether yielded this product in only minor quantity. Structural elucidation of the major product revealed a new series of polyenes isomeric with the β-ionylidene series in that the conjugated system is removed one carbon atom back into the ring. Members of this series may therefore be called *retro*ionylidene compounds. *Retro*vitamin A methyl ether was found to be biologically inactive. Its *cis* isomer represents an experimental contradiction to Pauling's rule. The absorption spectra of the triene, tetraene and pentaene members of this series have been correlated with their structures. On comparison with the spectra of other polyenes they appear normal while those of the β-ionylidene series are found to be hypsochromically displaced. The anomalous nature of the vitamin A spectrum, which has apparently not been generally recognized, is demonstrated.

In 1945, in a preliminary report,[1] a route for the synthesis of vitamin A methyl ether was presented which involved the following transformations



Although the desired product was obtained in only very small yields, we wish to report the details of this synthesis since it led to a new series of polyenes isomeric with the α- and β-ionylidene series.

The coupling of the Grignard reagent from ethynyl-β-ionol (I)[2] with methoxytiglyl chloride (II)[3] was accomplished in 75–85% yields with cupric chloride as catalyst.[4] The resulting acetylenic carbinol (III), originally reported as dehydrating upon distillation, was found to be distillable without decomposition if scrupulously freed of halides beforehand. Catalytic semihydrogenation of its acetylenic bond produced IV in almost quantitative

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(1) W. Oroshnik, THIS JOURNAL, **67**, 1627 (1945).

(2) W. Oroshnik and A. D. Mebane, *ibid.*, **71**, 2026 (1949).

(3) W. Oroshnik and R. A. Mallory, *ibid.*, **72**, 4608 (1950).

(4) J. P. Danehy, D. B. Killian and J. A. Nieuwland, *ibid.*, **58**, 611 (1936). These authors discovered the copper catalyzed condensation of simple alkylacetylenic Grignard reagents with allylic chlorides. The present work represents its first application to acetylenic carbinols and conjugated enynes.

yield. The absorption curves of I, III and IV (Fig. 1), and the 31% yield of geronic acid obtained upon ozonolysis of IV, show that the β-ionol group remained intact during these reactions.

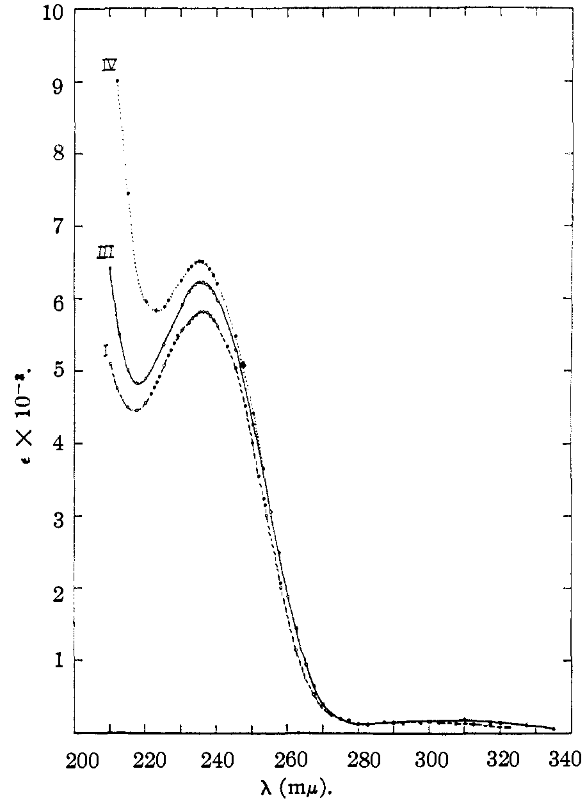


Fig. 1.—Ultraviolet absorption spectra of I, III and IV, illustrating the β-ionol chromophore.

The carbinol IV dehydrated very readily with any of the reagents commonly used for this purpose. The product from glacial acetic acid reported in the original communication was found by bioassay to have a vitamin A activity of 20,000 units per gram. Although the product was very inhomogeneous, as indicated by the large differences in refractive index and ultraviolet absorption maxima between successive fractions arbitrarily cut during distillation, it nevertheless appeared to consist entirely of isomers of vitamin A methyl ether since all fractions showed the same elementary analysis. When phenyl isocyanate was used as the dehydrating agent, the product was much more homogeneous ($\lambda_{max.}$ 317 mμ) and had a vitamin A activity of 100,000 units per gram as measured by bioassay. Upon alumina chromatography it yielded a fraction spectroscopically identical with vitamin A methyl ether, in amounts approximating those indicated by the bioassay. Extracts of the livers of the rats used in the bioassay showed the spectrum of vitamin A methyl ether, with no evidence of the presence of the 317-mμ isomer. Extracts of the livers of rats used as negative controls showed no absorption in the range 250–350 mμ.[5]

Although the carbinol IV was subjected to a large variety of dehydrating agents, the highest reproducible yields of vitamin A methyl ether (3%) were obtained with phenyl isocyanate. It is of interest to note that the rat appears to be able to accomplish this dehydration *in vivo*, for IV itself showed a biological activity of 10,000 units per gram.

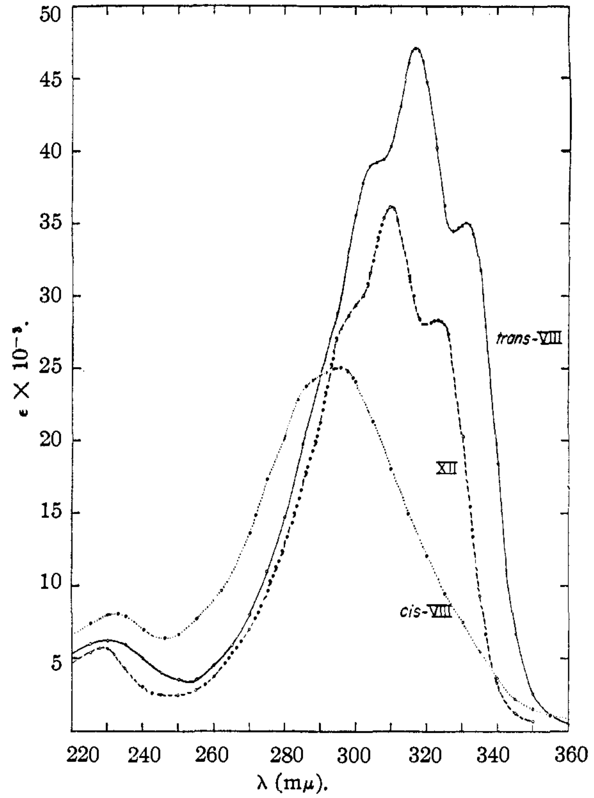
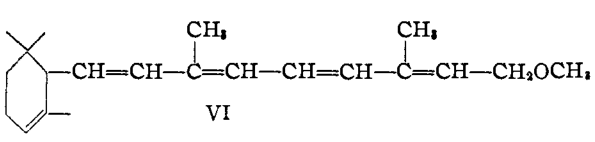


Fig. 2.—Ultraviolet absorption spectra of *cis*- and *trans*-VIII and their acetylenic analog XII.

The major product ($\lambda_{max.}$ 317 mμ) obtained upon dehydration of IV was shown by quantitative hydrogenation to be a pentaene. The presence of the vitamin A skeleton was demonstrated by fission of the perhydrogenated ether to a bromide and conversion of the latter to the same isothiuronium picrate obtained from perhydrovitamin A bromide. According to its absorption spectrum, $\lambda_{max.}$ 317 mμ, only four of the double bonds in the pentaene were conjugated. It has been suggested by other workers[6] that this may have resulted from the rearrangement of the β-ionyl to the α-ionyl system. This would give VI, α-vitamin A methyl ether. However, this possibility was dismissed upon failure to detect any isogeronic acid among the ozonolysis products.[7] The absence of geronic acid as well similarly disposed of the possibility of dehydration across the 3-methyl group to the cross-conjugated tetraene VII.



$$\text{—CH=CH—}\overset{\text{CH}_3}{\overset{|}{\text{C}}}\text{=CH—CH=CH—}\overset{\text{CH}_3}{\overset{|}{\text{C}}}\text{=CH—CH}_2\text{OCH}_3$$

VI

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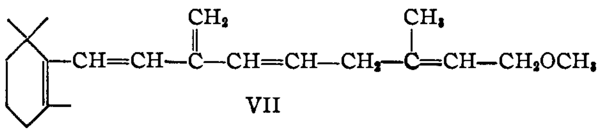
[5] The above-mentioned bioassays and liver extractions were performed by the Division of Biochemistry of this Institute.

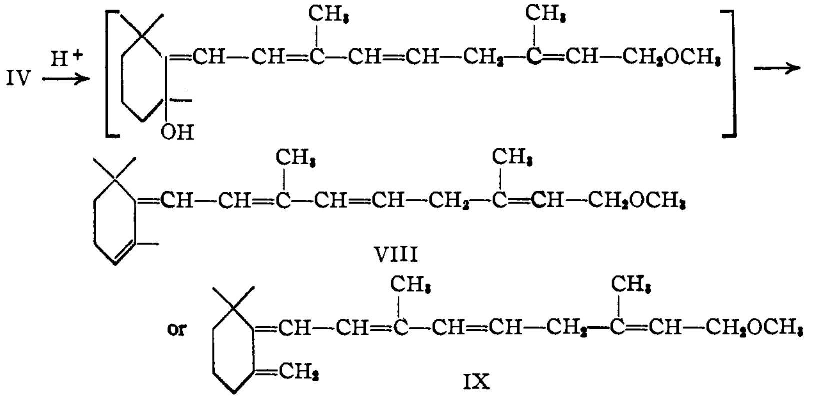
[6] J. Cymerman, I. M. Heilbron, E. R. H. Jones and R. N. Lacey, *J. Chem. Soc.*, 502 (1946).

[7] Moreover, α-vitamin A methyl ether, which has been synthesized in this Laboratory, has the spectral constants $\lambda_{max.}$ 311 mμ, ε 57,200. Its synthesis will be described in a future publication.



VII

The only remaining possible mode of dehydration to give a conjugated tetraene is that involving a precursory allylic rearrangement of the β-ionol hydroxyl group into the ring

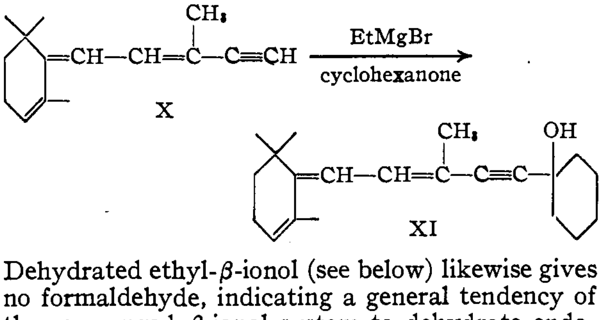


VIII

or

IX

While ozonolysis for formaldehyde would ordinarily be used to distinguish between VIII and IX, it proved of no diagnostic value in this specific case, for although a 22% yield of formaldehyde was obtained, the same yield was obtained from its progenitor IV, which has no terminal vinyl group. Evidently the *allylic methoxyl* group is the source of this formaldehyde, inasmuch as comparable yields could also be obtained from methoxytiglyl chloride (II) and from methyl γ,γ-dimethylallyl ether, while *ethoxy*tiglyl chloride[3] gave none. This question of endocyclic *vs.* exocyclic dehydration of the rearranged β-ionol system was brought up in a previous publication in connection with the structure of dehydrated ethynyl-β-ionol (X).[2] The condensation product of X with cyclohexanone has now been proved, by the absence of formaldehyde on ozonolysis, to be the endocyclic isomer (XI).



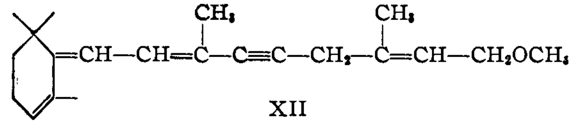
X

XI

Dehydrated ethyl-β-ionol (see below) likewise gives no formaldehyde, indicating a general tendency of the rearranged β-ionol system to dehydrate endocyclically.

The assumption that IV dehydrates analogously, giving VIII, was confirmed by the 30% yield of α,α-dimethylglutaric acid obtained upon ozonolysis of the product. The inhomogeneity of some samples of VIII, such as that obtained with glacial acetic acid, will be shown below to be due not to the exocyclic isomer but to stereoisomerism.

The acetylenic carbinol III dehydrates with even greater facility than its ethylenic analog IV. The product, unlike that obtained from IV, was chromatographically homogeneous. Inasmuch as an identical product was obtained by coupling the Grignard reagent from X with methoxytiglyl chloride, this compound must be the endocyclic isomer XII.



XII

Semihydrogenation of the acetylenic bond in XII gave, instead of the expected VIII, $\lambda_{\max.}$ 317 mμ, an isomeric compound, $\lambda_{\max.}$ 296 mμ. The conversion of the latter to VIII by catalytic quantities of iodine or strong acid indicated a *cis–trans* relationship between the two isomers. This stereoisomerism must result from the configuration around the 4,5 double bond[8] only, since the 1′,3-diene parts of the isomers, having been formed in both cases by allylic rearrangement of a β-ionol group, are undoubtedly sterically identical. On the basis of its absorption spectrum, its stereochemical instability, and the fact that its 4,5-double bond was formed by catalytic semihydrogenation,[9] the 296-mμ compound is clearly the 4,5-*cis* isomer of VIII. Hence the 317-mμ compound is the corresponding *trans*-isomer. The appearance of a 4,5-*trans* product upon dehydration of IV, whose 4,5 double bond is *cis*, is evidently due to the stereoisomerizing effect of the dehydrating agent. It was found, in fact, that although essentially *trans* products were formed by dehydrating with strong acids, iodine or catalyzed phenyl isocyanate, large proportions of *cis*-VIII resulted with phosphorus oxychloride–pyridine or glacial acetic acid. Although the isolation of the pure *cis* isomer from such *cis–trans* mixtures could not be accomplished by chromatography, which yielded only rich-in-*cis* fractions, its presence was demonstrable in two ways: (a) catalysis with iodine or strong acids converted the mixture into essentially *trans*-VIII; (b) the absorption curve of such mixtures could be quantitatively duplicated by mixing appropriate quantities of pure *cis*- and pure *trans*-VIII.

Upon heating *trans*-VIII with alcoholic alkali, a method used to conjugate isolated ethylenic bonds,[10] it was almost completely converted to a new compound, $\lambda\lambda_{\max.}$ 333, *348* and 367 mμ. The same compound was obtained when an alumina chromatogram of *trans*-VIII stood at room tempera-

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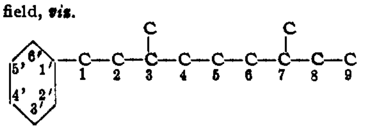
[8] The numbering system in this paper is that customarily used in the vitamin A field, *viz.*



[9] As a rule, catalytic semihydrogenation of an acetylenic bond with Raney nickel or palladium yields the *cis* olefin. The only known exceptions to this rule, tolane and acetylenedicarboxylic acid, may be accounted for by the facile stereoisomerization of the olefinic products. [K. N. Campbell and B. K. Campbell, *Chem. Revs.*, **31**, 148 (1942)].

[10] D. T. Mowry, W. R. Brode and J. B. Brown, *J. Biol. Chem.*, **142**, 671 (1942).

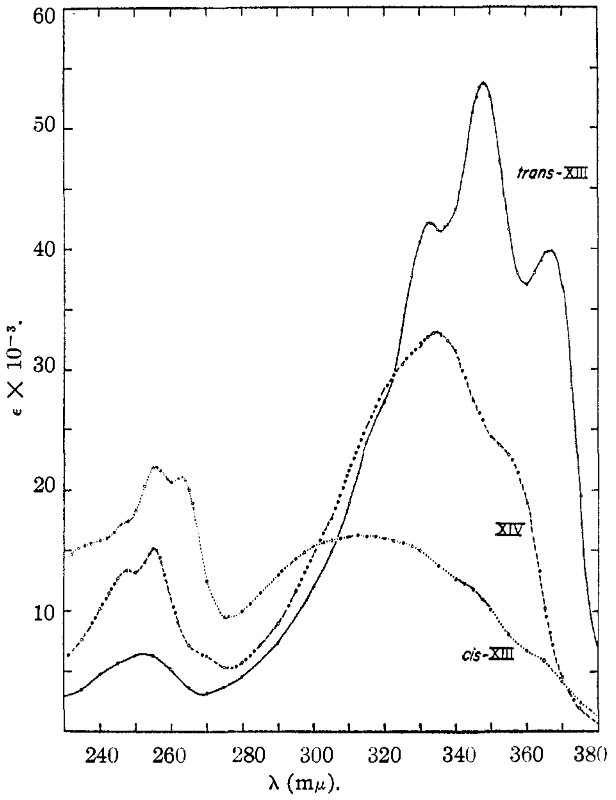
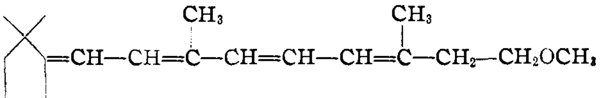
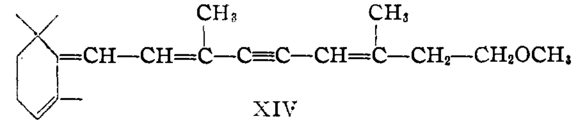


Fig. 3.—Ultraviolet absorption spectra of *cis*- and *trans*-XIII and their acetylenic analog XIV.

ture for several days. Spectrally this compound corresponds to the next higher vinylog of *trans*-VIII. The absence of geronic acid and formaldehyde upon ozonolysis confirms its structure as XIII. A small quantity of by-product isolated chromatographically from the above reaction mixture showed absorption maxima at 350, 368 and 388 mμ. Its insignificant methoxyl content and its absorption curve indicate anhydrovitamin A. Presumably this resulted through demethanolation of XIII.



XIII



XIV

Since XIII differs from vitamin A methyl ether only in that the conjugated pentaene system is displaced one carbon atom into the ring, it seems appropriate to refer to it as *retro*vitamin A methyl ether. Biological assays showed it to possess no more than a trace of vitamin A activity when fed at a level of 0.045 mg. per day.[11,12]

The isolated ethylenic bond in XII similarly moved into conjugation upon treatment with alkali or upon an alumina column, but with much greater facility than that in *trans*-VIII. The product, XIV, was chromatographically homogeneous. Catalytic semihydrogenation of its acetylenic bond yielded *cis*-XIII, which was also obtained when the isolated ethylenic bond in *cis*-VIII moved into conjugation on an alumina column or upon heating with alkali. In the latter instance a considerable amount of *trans*-XIII was also formed; since *cis*-XIII is unaffected by alkali, this must have resulted from the stereoisomerization of the 4,5-bond in *cis*-VIII before, or simultaneously with, the shift of the 7,8-bond.

The absorption curves of *cis*-XIII and its acetylenic analog XIV are distinguished by very high *cis*-peaks at 255 mμ, which indicate a bending of the chromophore in both compounds.[13] While this bending around the 4,5-bond is obvious in *cis*-XIII, it can only be seen readily in XIV with the aid of Fisher–Hirschfelder–Taylor models, which show a small but distinct bend around the acetylenic bond.

The extreme hypochromic and hypsochromic (35 mμ) degradation of the main peak in *cis*-XIII with respect to *trans*-XIII, as well as the absence of fine structure, must be due to the break in coplanarity resulting from steric hindrance between the 3-methyl group and the 6-hydrogen atom, since an unhindered *cis* configuration alone would be expected to produce a hypsochromic effect in the main band of only about 7 mμ.[14] The *cis* configura-

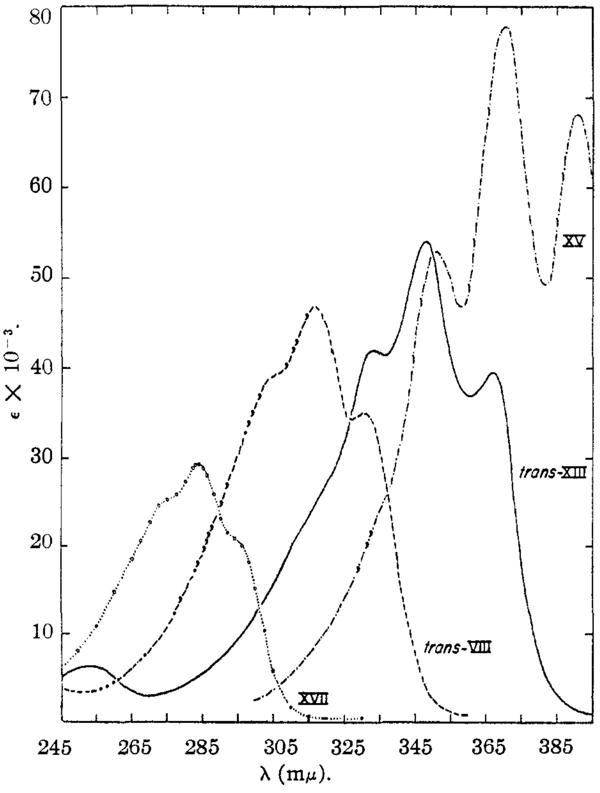


Fig. 4.—Ultraviolet absorption spectra in the *retro*ionylidene series: triene through hexaene members.

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[11] Bioassays of this compound were performed by the Food Research Laboratories, Inc., Long Island City, New York, N. Y.

[12] Several synthetic and naturally occurring compounds having an ultraviolet absorption spectrum very similar to that of XIII have been reported during the past few years. One of these, having approximately 10% of the biological activity of vitamin A [E. Shantz, *J. Biol. Chem.*, **182**, 515 (1950)], has been suggested as the alcohol corresponding to XIII. The structure of these compounds will be the subject of a forthcoming paper in this series.

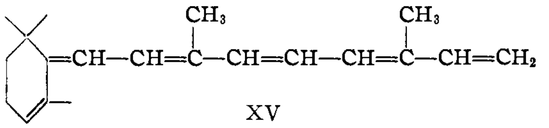
[13] L. Zechmeister, *Chem. Revs.*, **34**, 298 (1944).

[14] J. H. Pinckard, B. Wille and L. Zechmeister, THIS JOURNAL, **70**, 1938 (1948).

tion and accompanying steric hindrance in *cis*-XIII is of the type which Pauling considered sufficiently unstable to be non-existent in polyenes.[15] This compound, therefore, represents the second exception to be found to Pauling's rule.[16] Although steric hindrance is absent in XIV because of the linearity of the acetylenic group, there still appears to be sufficient inhibition of resonance, presumably due to the interior acetylenic group, to produce a marked hypsochromic effect (13 mμ) with respect to *trans*-XIII, as well as a decrease in fine structure and extinction coefficient.

In *cis*-VIII, models show hindrance to coplanarity similar to that present in *cis*-XIII, but to a lesser degree. This is in accord with the observed absence of fine structure, the lowered extinction of the main band, and the large hypsochromic effect (21 mμ) with respect to *trans*-VIII. In XII steric hindrance is absent, and the absorption curve shows fine structure and only small hypochromic and hypsochromic effects as compared to *trans*-VIII. The terminal acetylenic group thus appears to cause less inhibition of resonance than does the interior acetylenic group. Simple enynes usually show only hypochromic degradation as compared to their analogous dienes, but in some cases a hypsochromic effect is also observed.[17] While there is insufficient evidence as yet available to permit generalization concerning the effect of an acetylenic bond in a polyene chromophore, there is little doubt that such groups produce some inhibition of resonance.

The polyenes VIII and XIII are tetraene and pentaene members of what may be called the *retro*-ionylidene series. Anhydrovitamin A (XV) represents a typical hexaene member. Its normal position in this spectral series tends to confirm the assigned structure,[18] which has not yet been proven by degradative studies. What is probably a heptaene member of this series (XVI) has been obtained[19] as a dehydration product of axerophthylideneisopropanol.


XV

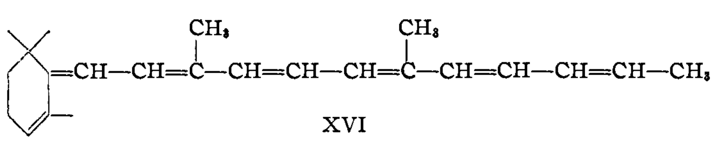

XVI

TABLE I

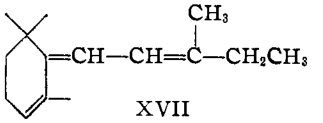
ULTRAVIOLET ABSORPTION DATA[a]

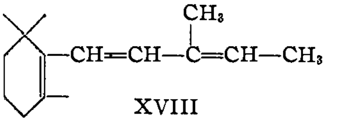
Compound	$\lambda_{max.}$ (mμ)	$\epsilon_{max.}$
I	236	5,800
III	236	6,200
IV	236	6,500
	306[b]	39,000
trans-VIII	**317**	**47,000**
	331	34,500
cis-VIII	296	25,000
	298[b]	26,700
X	**307**	**31,300**
	318[b]	25,000
	300[b]	29,500
XII	**310**	**36,100**
	323	28,300
	333	42,100
trans-XIII	**348**	**53,700**
	367	39,600
cis-XIII	**255**	**21,900**
	313	**16,200**
	255	**15,000**
XIV	**335**	**33,000**
	353[b]	23,700
	275[b]	25,300
XVII	**284**	**29,300**
	294[b]	21,000

[a] Solvent: 95% ethanol. [b] Inflection.

In order to prepare a triene member of the series, ethyl-β-ionol was dehydrated to XVII. Karrer and Benz[20] have also reported the dehydration of ethyl-β-ionol and their spectral data are qualitatively in agreement with those reported herein. However, structure XVIII, which they assign to the dehydration product, is unsupported by ozonolysis data. Ozonolysis of the product obtained in the present work yielded no significant amount of formaldehyde and only 15% of geronic acid as compared to 40% obtainable from ethynyl-β-ionol. Hence, it appears that dehydration of ethyl-β-ionol yields a mixture of XVII and XVIII with the former predominating. A pure sample of XVII, obtained by chromatography, gave no geronic acid on ozonolysis. Other workers[21] have dehydrated methyl-β-ionol and assigned the structure *nor*-XVIII to the product without recourse to ozonolysis. From the absorption data ($\lambda_{max.}$ 281.5 mμ) the product undoubtedly was essentially the *retro* isomer, *nor*-XVII.

On comparison with unhindered polyenes (Table


XVII


XVIII

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(15) L. Pauling, *Fortschr. Chem. org. Naturstoffe*, **3**, 203 (1939).

(16) The first exception to this rule was found in *cis-cis-β*-methylmuconic acid [P. Karrer, R. Schwyzer and A. Neuwirth, *Helv. Chim. Acta*, **31**, 1210 (1948)]. Upon consideration of this datum, Pauling later showed by a rough quantitative treatment of the resonance energy involved, that the above type of *cis* configuration would be expected to be more stable in the lower polyenes than in higher polyenes such as carotenoids [L. Pauling, *Helv. Chim. Acta*, **32**, 2241 (1949)].

(17) J. D. Chanley and H. Sobotka, THIS JOURNAL, **71**, 4140 (1949).

(18) P. Meunier, R. Dulou and A. Vinet, *Compt. rend.*, **216**, 907 (1943); *Bull. soc. chim. biol.*, **25**, 371 (1943).

(19) I. M. Heilbron, A. W. Johnson and W. E. Jones, *J. Chem. Soc.*, 1561 (1939); E. G. E. Hawkins and R. F. Hunter, *Biochem. J.*, **38**, 34 (1944).

(20) P. Karrer and J. Benz, *Helv. Chim. Acta*, **31**, 1048 (1948).

(21) H. Sobotka, H. H. Darby, D. Glick and E. Bloch, THIS JOURNAL, **67**, 403 (1945); F. B. Kipping and F. Wild, *J. Chem. Soc.*, 1239 (1940).

TABLE II

SPECTRAL COMPARISON OF POLYENES OF THE β-IONYLIDENE SERIES WITH NORMAL POLYENES

Compound	Number of substituents	$\lambda_{max.}$ (mμ)[a]	$\epsilon_{max.}$	Est. $\lambda_{max.}$ for equal substitution[b]
Dienes				
β-Ionol[2]	4	234	5,200	234
Ethyl-β-ionol[2]	4	231[c]	5,500	231
Vinyl-β-ionol[d]	4	235	5,700	235
Ethynyl-β-ionol (I)	4	236	5,800	236
Carbethoxymethyl-β-ionol[e]	4	235	5,600	235
Tris*nor*-β-ionol[17]	3	233	24,000	238
Menthadiene[f]	3	235	10,700	240
2-Vinylcyclohexene[f]	2	230	8,500	240
β-Phellandrene[f]	2	232	9,200	242
3-Isopropylidenecyclohexene[g]	4	242	9,950	242
Trienes				
β-Ionylidene-ethanol[h]	5	265	11,800	265
1,3,5-Hexatriene[i]	0	257	34,200	282
3-Methyl-1,3,5-octatrien-7-ol[j]	2	267	40,500	282
Alloöcimene[k]	4	277	43,000	282
Deca-4,6,8-trien-1-yn-3-ol[l]	2	268	55,000	283
XVII	5	284	29,300	284
Tetraenes				
Hydroxyester from "C_{18} ketone" and ethyl bromoacetate[m]	5	290	28,000	290
1,3,5,7-Octatetraene[n]	0	290	....	315
2,4,6,8-Decatetraene-1-ol[o]	2	299	64,000	314
"α-Vitamin A" methyl ether (VI)[7]	4	311	57,200	316
trans-VIII	5	317	47,000	317
Pentaenes				
Vitamin A[p] (V)	6	325	49,900	325
1,3,5,7,9-Decapentaene[q]	0	319	65,000	349
trans-XIII	6	348	53,700	348
Hexaenes				
Axerophthylideneisopropanol[19]	6	354	40,800[v]	354
2,4,6,8,10,12-Tetradecahexaene[r]	2	360	69,300	374
Anhydrovitamin A[s] (XV)	5	370	78,000	375
Dihydrocrocetin[t]	4	365	74,000	375
Heptaenes				
1,3,5,7,9,11,13-Tetradecaheptaene[q]	0	368	....	398
XVI[u,19]	6	395	101,000	395

[a] The solvent used was ethanol unless otherwise stated. [b] In order to permit a real comparison, the $\lambda\lambda_{max.}$ of the less substituted members of each group are here "corrected" to the number of substituents carried by the most highly substituted member of the group. A bathochromic effect of 5 mμ for each substituent was assumed (*cf.* Woodward, note *g*). [c] The unusually low $\lambda_{max.}$ for this compound is difficult to understand. [d] This compound, hitherto unreported, was prepared by the semihydrogenation of ethynyl-β-ionol: b.p. 91–92° (0.8 mm.), $n^{20}{}_D$ 1.5022. Calcd. for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.68; H, 10.95. [e] W. G. Young, L. J. Andrews and S. J. Cristol, THIS JOURNAL, 66, 520 (1944). The spectral data were obtained from a sample prepared in this Laboratory. [f] H. Booker, L. K. Evans and A. E. Gillam, *J. Chem. Soc.*, 1453 (1940). Menthadiene and vinylcyclohexene exhibit the same type of cyclization as the β-ionols, but lack steric hindrance. [g] R. B. Woodward, THIS JOURNAL, **64**, 72 (1942). [h] British Patent 633,711 (1949), p. 13. It is shown here that "β-ionylideneacetic ester" obtained by the usual method [Karrer, *et al.*, *Helv. Chim. Acta*, **15**, 878 (1932)] is a mixture of conjugated and unconjugated esters and hence any β-ionylidene-ethanol obtained therefrom ($\lambda_{max.}$ 274 mμ: Milas and Harrington, THIS JOURNAL, 69, 2247 (1947)) cannot be considered pure. [i] G. F. Woods and L. H. Schwartzman, THIS JOURNAL, **70**, 3394 (1948); solvent, cyclohexane. [j] G. W. H. Cheeseman and I. M. Heilbron, *et al.*, *J. Chem. Soc.*, 2031 (1949). [k] Private communication from Dr. L. A. Goldblatt, U. S. Dept. of Agric., Naval Stores Res. Div., New Orleans, La. These data are for "alloöcimene A" (the "B" isomer has $\lambda_{max.}$ 272 mμ, $\epsilon_{max.}$ 44,600); solvent, isoöctane. [l] I. M. Heilbron, E. R. H. Jones and J. T. McCombie, *J. Chem. Soc.*, 134 (1944). [m] O. Schwarzkopf, *et al.*, *Helv. Chim. Acta*, **32**, 450 (1949); solvent, hexane. [n] G. F. Woods and L. H. Schwartzman, THIS JOURNAL, **71**, 1396 (1949); solvent, cyclohexane. [o] T. Reichstein and G. Trivelli, *Helv. Chim. Acta*, 15, 1074 (1932). [p] C. D. Robeson and J. G. Baxter, THIS JOURNAL, **69**, 136 (1947). [q] A. D. Mebane, unpublished work. [r] R. Kuhn, *Angew. Chem.*, **50**, 703 (1937); solvent, chloroform. A solvent correction of −6 mμ has been applied in the last column [see L. F. Fieser, *J. Org. Chem.*, 15, 930 (1950)]. [s] O. Isler, W. Huber, A. Ronco and M. Kofler, *Helv. Chim. Acta*, **30**, 1927 (1947). E. M. Shantz, J. D. Cawley and N. D. Embree [THIS JOURNAL, 65, 901 (1943)] report a molecular extinction of 98,000. [t] K. W. Hausser and A. Smakula, *Z. angew. Chem.*, **47**, 663 (1934); **48**, 152 (1935). [u] Solvent, cyclohexane. [v] Not measured on a purified specimen.

II), the absorption characteristics of *retro*vitamin A and its *trans*-vinylogs appear normal, showing fine band structure, high extinction and proper location of the absorption maxima. On the other hand, the data show that β-ionyl and β-ionylidene compounds are, without exception, hypsochromically displaced. Thus the spectrum of vitamin A, which has generally been considered as typical of a conjugated pentaene, *is actually atypical*, being hypsochromically displaced by more than 20 mμ. This spectral degradation is clearly due to the steric hindrance which occurs, as models show, between the 6′-methyl group and the 2-hydrogen atom. The dienes, trienes and tetraenes of this series show a hypochromic effect as well, but the higher members exhibit more nearly normal extinction. Braude[22] has recently offered an interesting explanation for the spectral degradation observed with β-ionone semicarbazone, an explanation which may well be applicable to vitamin A and the higher members of the β-ionylidene series. He considers that the noncoplanarity of the ring and side-chain, resulting from the above-mentioned steric hindrance, should set up a side-chain partial chromophore. This effect is manifested in β-ionone by the appearance of a second peak at 223 mμ, with concomitant hypochromic degradation of the main band. In β-ionone semicarbazone, the second band is thought by Braude to lie sufficiently close to the main band to overlap with it. The plausibility of Braude's hypothesis can readily be seen by considering the chromophore in α-ionone semicarbazone ($\lambda_{max.}$ 264 mμ, $\epsilon_{max.}$ 31,000)[23] as structurally equivalent to the side-chain partial in the β-isomer. Since the hypochromically degraded main band in the latter

[22] E. A. Braude, *et al.*, *J. Chem. Soc.*, 1890 (1949).

[23] Y.-R. Naves and P. Ardizio, *Helv. Chim. Acta*, **31**, 1427 (1948); W. G. Young, *et al.*, THIS JOURNAL, **66**, 855 (1944).

would be expected to occur around 300 mμ, the resultant band should appear around 282 mμ, with a molecular extinction below 31,000. β-Ionone semicarbazone has $\lambda_{max.}$ 282 mμ; $\epsilon_{max.}$ 22,300.[23]

If this interpretation is applied to the vitamin A spectrum, the latter would be considered as the resultant of two chromophores: (a) the fully resonating side-chain tetraene structurally equivalent to that in VI ($\lambda_{max.}$ 311 mμ; $\epsilon_{max.}$ 57,000)[7] and (b) the sterically inhibited total pentaene with a main band of low extinction at < 348 mμ. The resultant maximum would therefore be expected to occur between 311 and 348 mμ with a molecular extinction below 57,000. The observed constants for vitamin A, $\lambda_{max.}$ 325 mμ and $\epsilon_{max.}$ 49,900, are in accord with this expectation.

Surprisingly, Fisher–Hirschfelder–Taylor models show that steric hindrance similar to that found in the β-ionylidene compounds should likewise be present in *retro*vitamin A and its vinylogs. This is in contradiction to the spectral data, which are unquestionably those of unhindered resonating systems. The explanation probably lies in the distortion of the cyclohexenylidene ring as compared to the cyclohexenyl ring.[24] The models, with their fixed valence-bond angles, cannot show this. The accompanying strain, aside from labilizing the electronic system of the chromophore,[25] evidently brings the 6′-methyl groups out of the radius of steric interference with the 2-hydrogen atom.

Experimental

Acetylenic Carbinol (III).—A stirred solution of 21.8 g. of ethynyl-β-ionol[2] in 350 ml. of anhydrous ether was treated at 10–15° with 136 ml. (2% excess) of 1.5 *M* ethylmagnesium bromide and then refluxed until evolution of ethane ceased (30 to 60 min.). After cooling to 10°, 15.5 g. (15% excess) of methoxytiglyl chloride[3] and 0.5 g. of anhydrous cupric chloride were added, and the solution was again refluxed for four hours. The addition of the cupric chloride was followed by a series of color changes from brown through burgundy to blue, lasting one-half hour. A second layer usually appeared about two hours after the beginning of reflux. The mixture was stirred an additional twelve hours at room temperature, then cooled to −20° and hydrolyzed with 30% ammonium acetate solution. The ether layer was removed and, after adding 100 ml. of diethylamine, was concentrated under vacuum to about 200 ml. After several days at room temperature, the concentrate was worked up with water and petroleum ether and dried with anhydrous potassium carbonate. The mixture was distilled from a simple Claisen flask immersed to its side-arm in an oil-bath. The product, a viscous yellow oil, was collected at 110–120° (0.001 mm.) (receiver pressure), $n^{20}\text{D}$ 1.5110.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19; methoxyl, 9.81. Found: C, 79.52, 79.63; H, 10.24, 10.22; methoxyl, 9.87, 9.86.

Several precautions must be followed in the above procedure. To assure freedom from *in situ* dehydration, iodide Grignard reagents, hydrolysis of the reaction mixture with dilute acids or concentration in the absence of amine must be avoided. While practically all the chloride reacts with the diethylamine within a few hours, the last traces, which can still cause some dehydration during distillation, are removed only upon several days' standing. Warming with the amine is inadvisable, since it tends to cause an isomerization (to be discussed in the second paper of this series).

Ethylenic Carbinol (IV).—A reaction mixture such as the one above, after only an overnight treatment with diethylamine, was worked up with water and petroleum ether, dried with anhydrous potassium carbonate and concentrated under vacuum to a sirup. This was dissolved in 150 ml. of methanol containing 10 ml. of piperidine, 0.5 g. of zinc acetate dihydrate and 3.0 g. of Raney nickel,[26] and hydrogenated in a Parr shaker at atmospheric pressure. Absorption proceeded at the rate of 50–100 cc./min. but dropped to 3–30 cc./min. for the last 100 cc. of hydrogen. While the exact rate obtained varied with the age of the catalyst and the amount of unreacted ethynyl-β-ionol, the sharp drop in rate at the semihydrogenation point always appeared when the piperidine–zinc acetate poison was used. When the theoretical amount of hydrogen, based on the total acetylenes present, had been absorbed, the mixture was filtered, worked up with water and petroleum ether and distilled. The product, a yellow oil, was collected at 105–115° (0.001 mm.), $n^{20}\text{D}$ 1.5090.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76; methoxyl, 9.74. Found: C, 79.37, 79.25; H, 10.63, 10.74; methoxyl, 9.52, 9.59.

The yield in the hydrogenation, as determined with a sample of the pure acetylenic carbinol, III, appears to be the theoretical.

Ozonolysis gave 31% geronic acid and 22% formaldehyde. Under similar conditions, methoxytiglyl chloride gave 15% and methyl γ,γ-dimethylallyl ether[3] 16% of formaldehyde. The lower yields of formaldehyde from these two compounds are presumably due to over-ozonization facilitated by the complete solution of the ozonide in the carbon tetrachloride. (The ozonide of IV is insoluble in carbon tetrachloride.) Ethoxytiglyl chloride[3] gave only 3.5% of formaldehyde.[12]

Dehydration of IV: Preparation of *cis-trans*-VIII.—These experiments illustrate the varying properties of *cis* and *trans* isomers obtainable with different dehydrating agents. All products described in this section analyzed properly for $C_{21}H_{32}O$.

(a) **Glacial Acetic Acid.**—A solution of 21 g. of IV in 100 ml. of glacial acetic acid was kept under nitrogen at room temperature for 12 hours. The solution was poured into water and extracted with petroleum ether. After washing with bicarbonate and drying with anhydrous potassium carbonate, distillation yielded: (a) 1.7 g. distilling at 95–110° (0.001 mm.); $n^{20}\text{D}$ 1.5601; λ_{max} 303 mμ, ϵ_{max} 23,100. (b) 16.1 g. at 110–115° (0.001 mm.); $n^{20}\text{D}$ 1.5656; λ_{max} 305 mμ, ϵ_{max} 29,500; λ_{max} 317 mμ, ϵ_{max} 30,000. The yield was 90%.

When catalyzed with 50 mg. of *p*-toluenesulfonic acid, the reaction was complete in 4–6 hours. The product in this case showed higher extinction at 317 mμ.

(b) **Phosphorus Oxychloride–Pyridine.**—A solution of 25 g. of IV in 125 ml. of toluene was added to a solution of 15 g. of phosphorus oxychloride and 75 ml. of pyridine in 100 ml. of toluene and the resulting mixture stirred under nitrogen at room temperature for 12 hours. It was then poured into ice-water, and stirred for one hour below 20° to hydrolyze the excess phosphorus oxychloride. After working up as above, the yield was 17.8 g. (75%), $n^{20}\text{D}$ 1.5656; λ_{max} 303 mμ, ϵ_{max} 23,400; λ_{max} 317 mμ, ϵ_{max} 22,500.

(c) **Phenyl Isocyanate.**—The commercial product always contained traces of acidic impurities, which were removed by adding cautiously a few ml. of a Grignard reagent and distilling rapidly at 20 mm. To a solution of 33 g. of IV in 150 ml. of purified phenyl isocyanate was added 2 ml. of 1.5 *M* ethylmagnesium bromide (15–20 mg. of ferric acetylacetone or ferric thiocyanate was equally effective), and the mixture stirred at 95° for three hours. There was a continuous precipitation of diphenylurea during the reaction. (In the absence of catalyst, no significant amount of diphenylurea was observed. The reaction mixture, after working up as described below, yielded a viscous oil which decomposed on distillation. It was not further investigated.) The bulk of the excess phenyl isocyanate was then removed at 1–2 mm. and the residue diluted with 500 ml. of petroleum ether. After filtering off the diphenylurea the solution was concentrated and distilled. Superheating was necessary toward the end to decompose some phenylurethan present. The distillate, which contained some diphenylurea, was again diluted with petroleum ether,

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(24) W. Hückel, "Theoretische Grundlagen d. organischen Chemie," 2nd ed., Vol. I, 1934, p. 72.

(25) G. N. Lewis and M. Calvin, *Chem. Revs.*, **25**, 273 (1939).

(26) 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, Tennessee.

chilled for several hours, refiltered and redistilled. The yield was 28.6 g. (92%), $n^{20}\mathrm{D}$ 1.5875; $\lambda_{\max}$ 317 mμ; $\epsilon_{\max}$ 37,700.

A solution of 7.8 g. of this product in 100 ml. of petroleum ether was chromatographed on a 3 × 35 cm. column of Alcoa F-20 alumina, developing with increasing proportions of ether in petroleum ether and inspecting intermittently with ultraviolet light.[27] A small red-fluorescing zone at the bottom of the column gave a blue Carr–Price test and showed the spectrum of anhydrovitamin A. The main zone which followed was white-fluorescing. It showed at first the spectrum of *trans*-VIII, then, as elution progressed, that of *trans*-XIII. The Carr–Price test, which was violet for this fraction, then changed to blue again, and the spectrum of the eluate showed a single maximum at 327 mμ. This eluate gave 0.1–0.2 g. of a concentrate, corresponding to about 1% of vitamin A methyl ether in the original preparation. Bio-assays of the original preparation showed 3% vitamin A methyl ether.

(d) **Alcoholic Hydriodic Acid.**—A solution of 10.7 g. of IV in 150 ml. of 95% ethanol containing 3.5 ml. of concd. HI was kept at room temperature for 12 hours. The mixture was worked up with water and petroleum ether and distilled. The yield was 9.6 g. (96%), $n^{20}\mathrm{D}$ 1.5847; $\lambda_{\max}$ 317 mμ; $\epsilon_{\max}$ 40,600.

Using, instead, an equivalent amount of hydrobromic acid, the product had $\epsilon_{\max}$ 38,500; with hydrochloric acid, 36,200; with *p*-toluenesulfonic acid, 34,200.

trans-VIII.—The purest sample of this isomer was obtained by chromatographic purification of the last two-thirds of the distillate from (c) or (d). A 5.9-g. sample was dissolved in 50 ml. of petroleum ether and passed through a 3 × 30 cm. column of 60–100 mesh "Florisil." On development with 2% ether–petroleum ether, a broad cobalt-blue zone was formed, which was preceded by a narrow zone of deeper blue. The latter was dug out, and the remaining main zone was eluted with 10% ether–petroleum ether until the eluate gave only a weak blue Carr–Price test. The column was still blue-green when 3.5 g. (78%) had been recovered. On distillation this gave 3.1 g. of a pale yellow product, collected at 118–120° (0.001 mm.); $n^{20}\mathrm{D}$ 1.5907.

Anal. Calcd. for $C_{21}H_{32}O$: C, 83.94; H, 10.74; methoxyl, 10.33; $\models$ = 5. Found: C, 83.98, 83.70; H, 10.79, 10.80; methoxyl, 10.04, 10.13; $\models$ = 4.9.

Ozonolysis gave 22% formaldehyde and 30% α,α-dimethylglutaric acid. No geronic acid or isogeronic acid was detected.

cis-VIII.—A solution of 31.4 g. of XII (see below) in 150 ml. of methanol containing 10 ml. of piperidine, 1.0 g. of zinc acetate dihydrate and 3.0 g. of Raney nickel[26] was hydrogenated in a Parr shaker at atmospheric pressure. The rate of absorption during the major part of the reaction was 25 cc./min. but at the end had dropped to 2 cc./min. After absorption of the theoretical amount of hydrogen, the mixture was worked up with water and petroleum ether. Distillation yielded 29.4 g. (90%) of product collected at 93–98° (0.001 mm.); $n^{20}\mathrm{D}$ 1.5566.

Anal. Calcd. for $C_{21}H_{32}O$: C, 83.94; H, 10.74; methoxyl, 10.33. Found: C, 83.84, 83.98; H, 10.77, 10.89; methoxyl, 10.11, 10.06.

Chromatography upon a "Florisil" column showed a constant absorption spectrum. The recovered compound, upon distillation, had $n^{20}\mathrm{D}$ 1.5610 but the same spectral properties.

Stereoisomerization of ***cis*-VIII.** (a) **With Iodine.**—A solution of 5.5 g. of pure *cis*-VIII and 0.35 g. of iodine in 200 ml. of isoheptane was allowed to stand at room temperature for one hour. The reaction was then stopped by the addition of 50 ml. of pyridine and the mixture refluxed for one hour (85–90°) to remove organic iodo compounds. After washing with water and dilute acid, the solution was dried and distilled. The product, 3.5 g., was collected at 102–115° (0.001 mm.); $n^{20}\mathrm{D}$ 1.5756; $\lambda_{\max}$ 317 mμ; $\epsilon_{\max}$ 35,000.

(b) **With Hydrobromic Acid.**—An 11.5-g. sample of *cis–trans*-VIII ($n^{20}\mathrm{D}$ 1.5700, $\lambda_{\max}$ 317 mμ, $\epsilon_{\max}$ 28,200) was dissolved in 150 ml. of ether containing one ml. of concd. HBr. After shaking vigorously for one hour, the solution was allowed to stand overnight at room temperature. Working up in the usual way yielded 9.9 g. of product, $\lambda_{\max}$ 317 mμ; $\epsilon_{\max}$ 38,800, $n^{20}\mathrm{D}$ 1.5923. The absorption curve had a small peak at 367 mμ, showing that some conjugation of the 7,8-double bond had occurred. This accounts for the rather high refractive index.

The analysis of the products obtained under (a) and (b) corresponded to $C_{21}H_{32}O$.

Proof of the Vitamin A Skeletal Structure of VIII.—A solution of 8.0 g. of *trans*-VIII in 100 ml. of methanol was completely hydrogenated at 45 lb. pressure with 2.0 g. of Adams catalyst. Absorption of hydrogen was very slow toward the end and required additional portions (3.0 g.) of catalyst. Distillation through a 6-inch Vigreux column yielded 5.0 g. of perhydro ether boiling at 130–135° (0.1 mm.); $n^{20}\mathrm{D}$ 1.4693. This was refluxed for 48 hours in a mixture of 30 ml. of 48% HBr and 50 ml. of glacial acetic acid. It was worked up with water and petroleum ether, dried and concentrated. Dry hydrogen bromide was then passed through the concentrate at 140–150° for four hours. Distillation of the product after neutralization and drying yielded 4.0 g. of perhydro bromide boiling at 130–135° (0.05 mm.), $n^{20}\mathrm{D}$ 1.4848.

One-half gram of the bromide was refluxed with 0.4 g. of thiourea in 10 ml. of ethanol for six hours; picric acid (0.4 g.) was added to the warm solution, and the picrate was precipitated with water. The air-dried picrate was leached thoroughly with petroleum ether and recrystallized three times from methanol–water; m.p. 115–116°.

Anal. Calcd. for $C_{27}H_{44}N_5SO_7$: C, 55.64; H, 7.61; N, 12.02. Found: C, 55.83; H, 7.65; N, 11.81.

Authentic perhydroaxerophthyl bromide, prepared from vitamin A according to Karrer and Morf,[28] gave an isothiuronium picrate melting at 117–118°, after three recrystallizations from methanol–water.

Anal. Found: C, 55.65; H, 7.79; N, 11.99.

The mixed melting point of the two specimens was 115–117°.

XII, **The Acetylenic Analog of VIII.** (a) **By Dehydration of III.**—A solution of 27.0 g. of III in 150 ml. of glacial acetic acid containing 25 mg. of *p*-toluenesulfonic acid was kept under nitrogen at room temperature for 24 hours. The solution was worked up in the usual manner and the product distilled, collecting at 115–118° (0.001 mm.); $n^{20}\mathrm{D}$ 1.5740. The yield was 80%.

Anal. Calcd. for $C_{21}H_{30}O$: C, 84.51; H, 10.13; methoxyl, 10.40. Found: C, 84.50, 84.38; H, 10.15, 10.12; methoxyl, 10.40, 10.35.

This was chromatographed on "Floridin" and proved to be homogeneous.

(b) **By Coupling X with II.**—A solution of 20.0 g. of X (see below) in 300 ml. of anhydrous ether was treated with 68 ml. of 1.5 *M* ethylmagnesium bromide. No cooling precautions were taken. Reaction was very slow, requiring at least 12 hours of refluxing for completion. Thereafter, the procedure was the same as described under III, except that only an overnight treatment with amine was given. The product had $n^{20}\mathrm{D}$ 1.5734. Spectrally and analytically it was identical with that obtained under (a). The yield was 45%.

Dehydration of Ethynyl-β-ionol, X.[29]—A solution of 18.5 g. of the carbinol in 500 ml. of glacial acetic acid containing 0.5 g. of *p*-toluenesulfonic acid and a trace of hydroquinone was stored under nitrogen at room temperature for 24 hours. (The relatively large volume of solvent was used to minimize polymerization.) The mixture was worked up in the usual manner and the product distilled rapidly, since this trienyne (X) readily polymerizes. It was collected at 65–75° (0.05 mm.); $n^{20}\mathrm{D}$ 1.5821. The yield was 73%.

Anal. Calcd. for $C_{15}H_{20}$: C, 89.94; H, 10.06. Found: C, 89.83, 90.01; H, 10.01, 10.02.

Ozonolysis of its cyclohexanone adduct XI gave 4% formaldehyde[32] and no geronic or isogeronic acid.

***trans*-Retrovitamin A Methyl Ether (*trans*-XIII).** (a) **From** ***trans*-VIII.**—A solution of 50 g. of rich-in-*trans*-VIII ($\epsilon_{\max}$ 38,000) and 41.0 g. of 98% NaOH in 500 ml. of absolute ethanol was refluxed under nitrogen for 16 hours. It was then poured into water, extracted with petroleum

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[27] Light of a G.E. Purple-X bulb was used.

[28] P. Karrer and R. Morf, *Helv. Chim. Acta*, **16**, 625 (1933).

[29] This procedure is superior to one described previously, which gave lower yields and an impure product.[2]

ether, dried and distilled. The product was collected in two fractions: (a) 6.6 g. at 110–125° (0.001 mm.); n^{20}D 1.610; λ_{max} 348 mμ; ϵ_{max} 32,000; (b) 34.0 g. at 125–140° (0.001 mm.); n^{20}D 1.635; λ_{max} 348 mμ; ϵ_{max} 50,800. Both fractions analyzed similarly. The low methoxyl value is to be noted.

Anal. Calcd. for $C_{21}H_{32}O$: C, 83.94; H, 10.74; methoxyl, 10.33. Found: C, 83.93, 83.92; H, 10.80, 10.77; methoxyl, 9.10, 9.35.

A 12.1-g. portion of fraction (b) in 120 ml. of petroleum ether was chromatographed on an alumina (Alcoa F-20, 80–200 mesh) column 4 × 32 cm., developing with 2% ether–petroleum ether, and inspecting intermittently with ultraviolet light.[27] The bottom red-fluorescing yellow zone was eluted and concentrated to about one gram of orange sirup which showed λ_{max} 351, 368 and 388 mμ (methoxyl: found, 1.9%). The remaining yellow-fluorescing colorless zone, which occupied most of the column, was cut out after extrusion of the column, and extracted with methanol. Distillation gave 7.2 g. of pale-yellow liquid collected at 125–130° (0.001 mm.); n^{20}D 1.635; ϵ_{max} 53,700 (348 mμ); and a 0.6-g. tail fraction, n^{20}D 1.640; ϵ_{max} 58,800 (348 mμ). The main fraction was analyzed.

Anal. Calcd. for $C_{21}H_{32}O$: C, 83.94; H, 10.74; methoxyl, 10.33. Found: C, 83.74, 83.68; H, 10.68, 10.80; methoxyl, 10.32, 10.25.

Ozonolysis gave less than 2% formaldehyde[32] and no geronic or isogeronic acid.

(b) **From** *cis*-**VIII.**—A solution of 18.0 g. of *cis*-VIII and 20.5 g. of 98% NaOH in 250 ml. of absolute ethanol was refluxed for 16 hours under nitrogen. The solution was then worked up as described under (a) and the distillate collected in two fractions: (a) 10.5 g., at 100–120° (0.001 mm.); n^{20}D 1.5955; λ_{max} 347 mμ; ϵ_{max} 21,400; (b) 5.0 g., at 125–135° (0.001 mm.); n^{20}D 1.613; λ_{max} 347 mμ; ϵ_{max} 33,400. A plateau of 300 mμ and a high *cis* peak at 261 mμ in the absorption curve of fraction (a) indicated the presence of unchanged *cis*-VIII and *cis*-XIII, respectively.

cis-***Retro*vitamin A** (*cis*-XIII). (a) **By Catalytic Semi-hydrogenation of XIV.**—An 8.4-g. sample of XIV (see below) in 150 ml. of methanol containing 10 ml. of piperidine, 1.0 g. of zinc acetate dihydrate and 2.0 g. of Raney nickel was hydrogenated in a Parr shaker at atmospheric pressure. The steady rate of absorption was 5 cc./min., dropping at the end to 1 cc./min. The product was worked up as usual and distilled. The first half-ml. of distillate, n^{20}D 1.5648, was rejected, and the remainder, 7.2 g., was collected at 112–115° (0.002 mm.); n^{20}D 1.5845; λ_{max} 256 mμ, ϵ_{max} 16,200; λ_{max} 330 mμ, ϵ_{max} 19,400. The last drop of distillate had n^{20}D 1.6070, indicating some degree of non-specific reduction. The peak at 330 mμ is probably due to the presence of unreduced XIV (λ_{max} 335 mμ), for in the chromatographically purified material, described below, the second peak is at 313 mμ.

The distillate, in 100 ml. of petroleum ether, was chromatographed on an alumina column, 3 × 30 cm., developing with 2% ether–petroleum ether. The main zone, which fluoresced dull yellow-orange under ultraviolet light, was spectrally homogeneous during elution with increasing proportions of ether in petroleum ether. It gave 3.7 g. of concentrate, which on distillation yielded 3.4 g. of golden-yellow liquid collected at 100–113° (0.001 mm.); n^{20}D 1.5830.

Anal. Calcd. for $C_{21}H_{32}O$: C, 83.94; H, 10.74; methoxyl, 10.33. Found: C, 83.90, 83.86; H, 10.77, 10.74; methoxyl, 10.36, 10.27.

(b) **By Conjugation of** *cis*-**VIII on Alumina.**—A solution of 7.8 g. of *cis*-VIII in 100 ml. of isoheptane was passed through an alumina column, 3 × 35 cm., and developed with 5% ether–petroleum ether. The white fluorescing main zone was eluted and concentrated to 3.1 g. of a sirup. This was a mixture of unchanged *cis*-VIII with *cis*-XIII as shown by the peaks at 298 mμ and 255–264 mμ, respectively, in the absorption spectrum.

The concentrate was rechromatographed on a 3 × 30 cm. Florisil column. The first 125 ml. of eluate, giving a red-violet Carr–Price test, and showing the spectrum of *cis*-XIII, yielded 1.3 g. on concentration. Further elution gave 1.2 g. of unchanged *cis*-VIII.

Stereoisomerization of *cis*-**XIII.** (a) **With Iodine.**—A solution of 380 mg. of chromatographically pure *cis*-XIII and 4 mg. of iodine in 100 ml. of isoheptane was allowed to stand at room temperature in ordinary artificial light. After 18 hours, the spectrum was that of *trans*-XIII, ϵ_{max} 49,000 (348 mμ).

(b) **With Hydrobromic Acid.**—A solution of 380 mg. of chromatographically pure *cis*-XIII and one drop of concentrated hydrobromic acid in 100 ml. of methanol was heated under pressure at 75° for one hour and allowed to stand overnight at room temperature. The spectrum was that of *trans*-XIII, ϵ_{max} 32,000 (348 mμ).

XIV, The Acetylenic Analog of XIII.—A solution of 20.0 g. of XII in 500 ml. of 1*M* absolute ethanolic NaOH was refluxed for 90 minutes. It was then poured into water, extracted with petroleum ether, dried and distilled, collecting 17.2 g. of golden-yellow product at 115–118° (0.002 mm.); n^{20}D 1.6026.

Anal. Calcd. for $C_{21}H_{30}O$: C, 84.51; H, 10.13; methoxyl, 10.40. Found: C, 84.50, 84.48; H, 10.06, 10.21; methoxyl, 10.44, 10.53.

Alumina chromatography showed the compound to be homogeneous. The properties were unchanged.

Dehydration of Ethyl-β-ionol: XVII.—The product obtained with oxalic acid using the method of Karrer and Benz[20] had an absorption peak at 282 mμ, ϵ_{max} 17,000, in agreement with that reported by these authors. However, our product showed in addition another peak, of about equal height, at 273 mμ. Judging from the broadness of the maximum in the published curve of the above authors, this peak was probably present in their product as well. Dehydration with acetic acid, iodine or ethanolic HBr gave products with increasing proportions of the 282–284 mμ peak and increasing refractive indices (n^{20}D 1.5208–1.5358). The product obtained with phenyl isocyanate contained the highest proportion of XVII. A solution of 27 g. of ethyl-β-ionol, 80 ml. of phenyl isocyanate and 1 ml. of 1.5 *M* ethylmagnesium bromide in 240 ml. of benzene was refluxed for four hours. After concentrating under vacuum, the mixture was diluted with 500 ml. of petroleum ether, filtered from the diphenylurea and distilled. The product, 21.8 g. (86%) distilled at 65–67° (0.1 mm.); n^{20}D 1.5388; λ_{max} 284 mμ, ϵ_{max} 24,400.

Anal. Calcd. for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 87.98, 87.70; H, 11.80, 11.72.

Ozonolysis gave 15% geronic acid and 3.3% formaldehyde.[32]

A 62.1-g. mixture of the isomeric products from oxalic acid, acetic acid and iodine was dissolved in 500 ml. of petroleum ether and passed through a 5 × 100 cm. alumina column. The zones were invisible even under ultraviolet light and the development of the chromatogram was followed spectroscopically, examining the eluate at 50-ml. intervals. After 600 ml., the spectrum was that of XVII and remained constant during further elution with 5% ether–petroleum ether. This eluate was concentrated and distilled, giving 14.0 g. of product boiling at 83–85° (0.6 mm.); n^{20}D 1.5430; λ_{max} 283.5 mμ, ϵ_{max} 29,300.

Anal. Found: C, 87.89; H, 11.82.

Ozonolysis gave no geronic or isogeronic acid and 3.9% formaldehyde.[32]

The first 600 ml. of eluate showed an absorption peak at 270–273 mμ, presumably due to β-ionylideneëthane (XVIII). This was not further investigated.

Carr–Price Colors.—One drop of a chloroform or petroleum ether solution of the compound was added to 0.5 ml. of a saturated chloroform solution of antimony trichloride. Under these conditions, vitamin A and anhydrovitamin A gave a clear blue color stable for three minutes.

III and XII gave an orange-brown or yellow-brown color, changing within two or three minutes to a dull yellowish-green.

IV and *cis*- and *trans*-VIII gave a cobalt blue changing to green.

cis-XIII gave violet changing to rose, *trans*-XIII violet changing to lavender.

XIV gave magenta, fading within a minute to a dull reddish-orange.

Ozonolysis.[30] (a) **Formaldehyde.**—The sample (0.015 *M*) was ozonized at 0° in 75 ml. of carbon tetrachloride,

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(30) The ozonizer, which was powered by a 15-KV transformer, was as described by A. L. Henne and W. L. Perilstein [THIS JOURNAL, **65**, 2183 (1943)]. At a flow rate (measured by rotameter) of 20 liters per hour, the effluent oxygen contained 4.5% by weight of ozone. No condenser or fog-precipitator was used.

the exit gases being bubbled through 100 ml. of water. Ozonization was terminated when the green color of excess ozone appeared; this occurred when about 150% of the theoretical ozone had been passed in. The contents of the water trap were assayed for formaldehyde with chromotropic acid.[31] The carbon-tetrachloride solution was transferred to a round-bottomed flask, washing in the gummy ozonide with 15–25 ml. of glacial acetic acid, and refluxed for an hour with 100 ml. of water. After cooling, the CCl_4 layer was drawn off and twice re-extracted with water; the combined aqueous extracts were then assayed for formaldehyde. Most of the formaldehyde was found here rather than in the water-trap.[32]

(b) **Geronic Acid.**[33]—The aqueous and carbon tetrachloride layers were recombined and refluxed for one hour with 5 ml. of 30% hydrogen peroxide. The mixture was then made alkaline with ammonia and the carbon tetrachloride layer extracted three times with 75-ml. portions of 1% ammonia water. The combined ammoniacal extracts were concentrated under vacuum to about 300 ml., acidified to *p*H 1, and treated with a hot solution of 3.0 g. of 2,4-dinitrophenylhydrazine, 10 ml. of concd. hydrochloric acid, and 3 ml. of water in 30 ml. of glacial acetic acid. After standing at 5° overnight, the crude derivative was filtered off and leached five times at 80° with 50-ml. portions of 3% potassium bicarbonate. The geronic acid derivative was reprecipitated from the cooled, combined filtrates by acidifying to *p*H 1, and filtered off on a sintered glass funnel. It was then redissolved on the filter with a minimum quantity of glacial acetic acid and the filtrate diluted at 60° with six-fifths its volume of hot water. After cooling to 5° the precipitated derivative was filtered off, washed sparingly with 50% acetic acid and dried under vacuum. Some specimens melted as low as 130–134° and others as high as 136–138°.

(c) **α,α-Dimethylglutaric Acid.**—*trans*-VIII (7.2 g.) was ozonized in 50 ml. of carbon tetrachloride and 50 ml. of glacial acetic acid; the time of ozonization was as above. The solution of ozonide was vigorously stirred overnight with 35 ml. of 30% hydrogen peroxide and 50 ml. of 0.2 *N* sulfuric acid,[34] then, with an additional 10 ml. of Superoxol, for two hours at 100°. (The CCl_4 was allowed to escape.) The cooled solution was freed of peroxides with sodium sulfite, and concentrated on the steam-bath at aspirator pressure. The resulting damp solid was taken up in 75 ml. of 20% hydrochloric acid, and extracted with four 50-ml. portions of ether; the dried ether extract was concentrated and distilled. The fraction boiling at 110–145° (0.1 mm.) largely crystallized on standing; a small sample of the crystals, after washing with hexane, melted at 81.5–82.5°. The whole fraction (2.45 g.) was dissolved in 30 ml. of 0.5 *N* NaOH, filtered, and treated with 3.0 g. of benzylisothiourea hydrochloride in 10 ml. of water. After an hour at 5°, the crystalline solid was filtered off, dried at 80° and weighed: 2.35 g., m. p. 172–174°. Recrystallization from aqueous acetone gave microprisms, m. p. 177–178°.

Anal. Calcd. for $C_{15}H_{22}O_4N_2S$: C, 55.19; H, 6.80; N, 8.58. Found: C, 55.29; H, 6.94; N, 8.45, 8.57.

Authentic α,α-dimethylglutaric acid was prepared in the same way as similar α,α-dialkylglutaric acids.[35] The cyanoethylation of isobutyraldehyde[36] (50% aqueous KOH as catalyst, at 70°) gave a 60% yield of γ-formylisocapronitrile, b.p. 82–84° (2 mm.), $n^{25}D$ 1.4355. Alkaline hydrolysis, followed *in situ* by $KMnO_4$ oxidation, furnished in 90% yield crude dimethylglutaric acid melting at 75–79°. The benzylisothiuronium salt, after recrystallization, melted at 175–176°; mixed m.p. with the specimen from ozonolysis, 176–177°.

Anal. Found: C, 55.33; H, 7.01; N, 8.36.

Absorption Spectra.—All absorption spectra were determined in 95% ethanol using a Beckman spectrophotometer.

Acknowledgment.—The authors are indebted to Mr. Robert A. Mallory and Mr. William Häffcke for technical assistance, and to Mr. Joseph Grodsky for the microanalyses.

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[31] D. A. MacFadyen, *J. Biol. Chem.*, **158**, 112 (1945).

[32] Yields of formaldehyde up to 5% were considered insignificant. Anomalous yields of formaldehyde up to 2.5% were obtained from negative controls by G. R. Clemo and J. M. Macdonald (*J. Chem. Soc.*, 1294 (1935)) who used no water trap. Their positive controls gave 20–32% formaldehyde. Y.-R. Naves [*Helv. Chim. Acta*, **31**, 908 (1948)], using a water-trap, obtained 49–65% yields from positive controls. In the present work 1-acetoxy-3-methylbutene-3 (E. Arundale and L. A. Mikeska, U. S. Patent 2,246,285) was used as a positive control and gave 43% formaldehyde.

[33] This procedure is a modification of that of H. H. Strain [*J. Biol. Chem.*, **102**, 144 (1933)].

[34] W. G. Young and S. L. Linden, THIS JOURNAL, **69**, 2042 (1947).

[35] H. A. Bruson and T. W. Riener, *ibid.*, **66**, 57 (1944); J. Cason, *J. Org. Chem.*, **13**, 233 (1948).

[36] French Patent 886,846 (1943); H. A. Bruson and T. W. Riener, U. S. Patent 2,353,687 (1944). The boiling point given by J. F. Walker [U. S. Patent 2,409,086 (1946)] is too high.

RARITAN, NEW JERSEY RECEIVED JANUARY 22, 1951

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE RICE INSTITUTE]

The Bimolecular Displacement of Nitrogen from *p*-Nitrobenzenediazonium Ion[1]

BY EDWARD S. LEWIS AND WILLIAM H. HINDS

In excess acidic sodium bromide solutions *p*-nitrobenzenediazonium ion reacts to give a mixture of *p*-nitrobromobenzene, *p*-nitrophenol and tar. The reaction is pseudo first-order, since the apparent first-order rate constant increases linearly with the bromide ion concentration. This behavior indicates the presence of a second-order displacement of nitrogen by bromide accompanying the recognized first-order decomposition of this diazonium salt. Such an interpretation is supported by the ratio of the yields of *p*-nitrobromobenzene and *p*-nitrophenol as a function of bromide ion concentration. Low concentrations of copper have a large effect on this reaction, but the small quantities unavoidably present could not alone account for the observed kinetics.

Introduction

The decomposition of benzenediazonium ion in dilute solution in water is a first-order reaction leading to phenol,[2] the rate of which is little influenced by the presence of other ions in moderate concentration.[3] In the presence of chloride ion appreciable yields of chlorobenzene are also produced.[2] A two-step mechanism has been proposed[4] to explain these observations. The first is a rate-determining loss of nitrogen from the diazonium ion

$$C_6H_5N_2^+ \longrightarrow C_6H_5^+ + N_2 \qquad (1)$$

This is followed by a fast reaction of the phenyl cation with water to give phenol

$$C_6H_5^+ + H_2O \longrightarrow C_6H_5OH + H^+ \qquad (2)$$

or, in the presence of chloride ion

$$C_6H_5^+ + Cl^- \longrightarrow C_6H_5Cl \qquad (3)$$

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[1] From the Ph.D. Thesis of W. H. Hinds, Rice Institute, May, 1951. Presented in preliminary form at the Southwest Regional Meeting of the American Chemical Society, December, 1950.

[2] M. L. Crossley, R. H. Kienle and C. H. Benbrook, THIS JOURNAL, **62**, 1400 (1940).

[3] H. A. H. Pray, *J. Phys. Chem.*, **30**, 1477 (1926).

[4] W. A. Waters, *J. Chem. Soc.*, 266 (1942).