erties: d^{20}_{15} 0.8564; n^{20}_D 1.4885. *p*-Isobutyltoluene has been reported[6] to have a boiling point of 191–192° (752 mm.); n^{20}_D 1.4888; d^{20}_{4} 0.8509. The semicarbazone of the acetyl derivative melts at 140–141° (141–142° reported).

Anal. Calcd. for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found: C, 89.34; H, 10.58.

Fraction 2, upon chilling, deposited crystals, which after recrystallization had a melting point of 125° (yield 0.8 g., 0.25%). The third fraction after refractionation boiled at 127–129° (1.8 mm.) and had an index of refraction n^{20}_D 1.5581; yield 71 g. (20.2%) of phenyltolylbutanes.

Anal. Calcd. for $C_{17}H_{20}$: C, 91.01; H, 8.99. Found: C, 91.30; H, 8.92.

Rearrangement of α,α-Dimethyldibenzyl in Toluene.—Two hundred grams (0.95 mole) of α,α-dimethyldibenzyl was added to 19 moles of toluene and 1.9 moles of aluminum chloride. After stirring for 5 hours at 25–30°, during which period the reaction mixture became brown, it was decomposed and worked up in the usual manner. Upon vacuum distillation, the following main fractions were obtained: fraction 1, b.p. 38–57° (1.8 mm.), 45 g.; fraction 2, b.p. 115–125° (1.8 mm.), 32 g.; fraction 3, b.p. 125–149° (1.8 mm.), 70 g.; residue, 30 g.

Fraction one upon redistillation at atmospheric pressure boiled at 192–194° (757 mm.). The yield of 31 g. (22%) of *p*-isobutyltoluene had the following physical properties; d^{20}_{15} 0.8562; n^{20}_D 1.4880. The second fraction when chilled yielded 2.0 g. of crystals m.p. 125° (yield 1%). The third fraction was very carefully refractionated to yield 49 g. (22%) of phenyltolylbutanes boiling at 126–129° (1.8 mm.); n^{20}_D 1.5554.

Anal. Calcd. for $C_{17}H_{20}$: C, 91.01; H, 8.99. Found: C, 90.91; H, 9.19.

Friedel-Crafts Reaction on Benzyldimethylcarbinyl Chloride.—One hundred sixty-nine grams (1 mole) of benzyldimethylcarbinyl chloride was added to a vigorously stirred mixture of 266 g. (2 moles) of aluminum chloride in 1560 g. (20 moles) of benzene during a two-hour period keeping the reaction temperature at 5–10°. The mixture was stirred for one-half hour after the addition was completed and then poured on ice. After washing free of acid and recovering the excess solvent, the product was distilled. The portion of the distillate boiling at 112–115° (2.0 mm.) contained crystals. After processing in the usual manner, 15.8 g. (7.5%) of *meso*-2,3-diphenylbutane and 42.5 g. (20%) of α,α-dimethyldibenzyl were obtained.

BROOKLYN, N. Y.

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

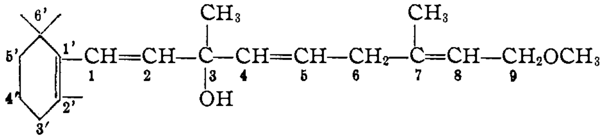
Synthesis of Polyenes. II. Allylic Rearrangements and Dehydrations in Substituted β-Ionols

BY WILLIAM OROSHNIK, GEORGE KARMAS AND ALEXANDER D. MEBANE

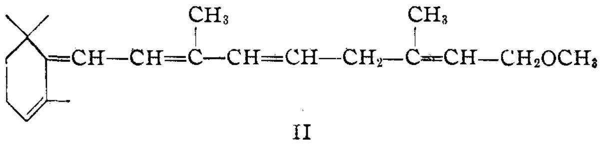
RECEIVED JANUARY 21, 1952

β-Ionols have been found, as a rule, to rearrange and dehydrate chiefly to *retro*ionylidene rather than β-ionylidene compounds. A notable exception was found in the case of the propargylic β-ionol, XIV. Possible mechanisms to explain these reactions, as well as the accompanying steric changes, are presented and discussed.

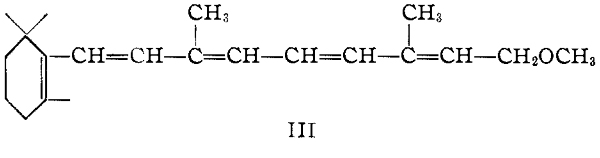
In Part I of this series[1] it was shown that the substituted β-ionol, 4,5-*cis*-I, undergoes a very facile allylic rearrangement and dehydration under the influence of acids, to give 4,5-*cis*- and 4,5-*trans*-II as well as a small quantity of vitamin A methyl ether, III.



I

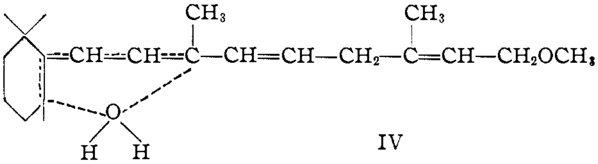


II



III

The rearrangement appears to follow the course established for simple divinylcarbinols, in which the hydroxyl group migrates toward the more alkylated double bond.[2] Braude and Jones,[3] on the basis of kinetic studies, have proposed a mechanism for this type of isomerization wherein an oxonium ion is formed in the initial stage and then isomerizes intramolecularly. In the case of I, which has a 4,5-*cis*-configuration, this mechanism would account only for the formation of 4,5-*cis*-II, since the transition state, IV, does not involve the 4,5-double bond.



IV

The simultaneous formation of the *trans*-isomer was previously thought to result from the stereoisomerizing effect of the dehydrating agent on the preformed *cis*-II.[1] However, it has now been found, by following the reaction spectrophotometrically, that the *cis–trans* ratio of the product is constant throughout the reaction, and is characteristic of the reaction medium. Thus, another mechanism involving the 4,5-double bond must be operating simultaneously. A reasonable explanation is afforded by assuming the formation of a carbonium ion which can be represented by resonance forms V and VI.[4]

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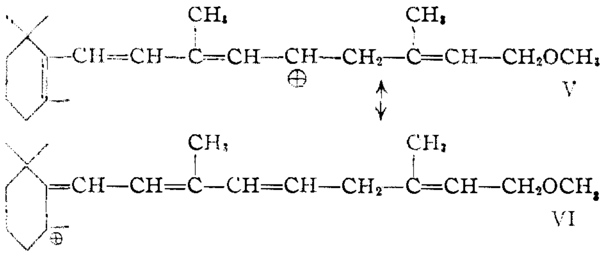
[1] W. Oroshnik, G. Karmas and A. D. Mebane, THIS JOURNAL, 74, 295 (1952).

[2] I. M. Heilbron, E. R. H. Jones, J. T. McCombie and B. C. L. Weedon, *J. Chem. Soc.*, 85 (1945).

[3] E. A. Braude and E. R. H. Jones, *ibid.*, 128 (1946).

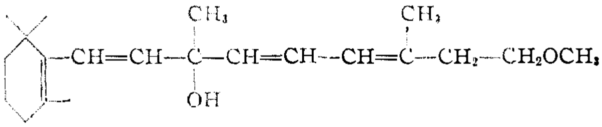
[4] Because of the tendency toward conjugation, the contribution of resonance forms of the type $—CH=CH—\overset{CH_3}{\underset{\oplus}{\overset{|}{C}}}—CH=CH—$ was considered as negligible.

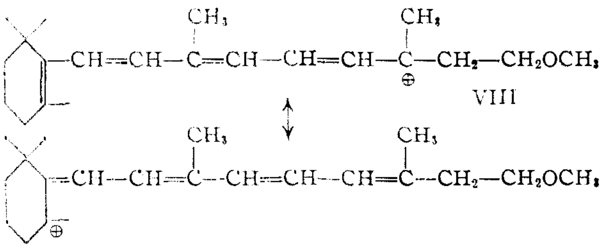

V

VI

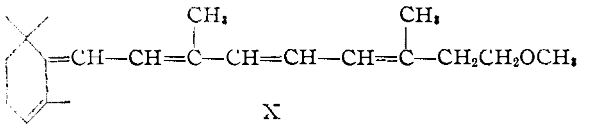
From the results obtained, resonance form VI is apparently the more stable. Upon discharge of the ion through elimination of a β-hydrogen on ring carbon 3′, the preferential configuration assumed at the 4,5-double bond would be the *trans*-, since the *cis*-structure is accompanied by considerable steric hindrance.[1] This proposed mechanism explains the greater proportion of *trans*-isomer obtained with the more strongly acid dehydrating agents.[1]

Since the failure of I to give appreciable yields of vitamin A methyl ether appeared to be due to the greater stability of tertiary as compared to secondary carbonium ions, other isomers of I, from which more stable β-ionylidene resonance forms might be realized, were examined. In carbinol VII, for example, the expected resonance forms, on carbonium ion formation, are VIII and IX, which, being tertiary, would presumably be of similar stability. On the basis of this assumption, nearly equal amounts of *retro*vitamin A methyl ether, X, and vitamin A methyl ether, III, would be expected from VII on dehydration.


VII


VIII

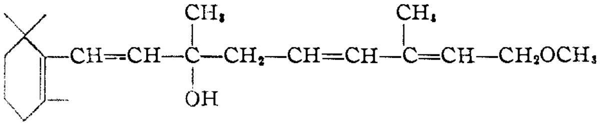
IX

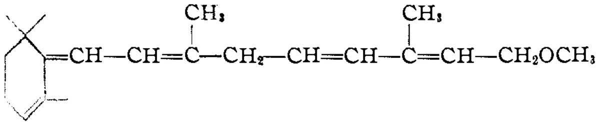

X

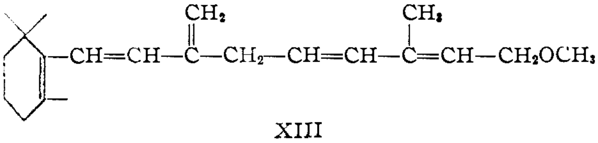
The carbinol, VII, was therefore synthesized in both 4,5-*cis*- and 4,5-*trans*-forms. As expected, because of the two bivinyl groups, it proved even more sensitive to acids than I. But, surprisingly, the product obtained on dehydration contained only about 3% vitamin A methyl ether and more than 90% *retro*vitamin A methyl ether, X. The latter was isolated in a much higher state of stereochemical purity than achieved previously[1] by conjugating the isolated 7,8-double bond in II. The fact that it was obtained in its 4,5-*trans*-form only, irrespective of whether *cis*- or *trans*-VII was the starting material, leaves no doubt as to the prevalence of a carbonium ion mechanism involving the 4,5-double bond. If one may judge from the intensity of the transient red color formed on contact with acid, the *trans*-carbinol undergoes carbonium ion formation much faster than the *cis*-isomer.

Here, as in the case of I, the *retro*ionylidene rather than the β-ionylidene ion is apparently still the more stable form. This implies of course that form VIII, in spite of its tertiary character, has a higher energy content. One reason for this may be the fact that β-ionylidene compounds suffer from steric hindrance involving the 6′-methyl and 2-hydrogen, which results in non-coplanarity between the ring and side-chain. This is reflected in the large hypsochromic displacement of their ultraviolet absorption spectra.[1] The *retro*ionylidene compounds exhibit normal spectra.[1]

The substituted β-ionol, XI, which is isomeric with both I and VII, was also synthesized and investigated for its dehydration products. Dehydration proceeded much more slowly than in the case of I or VII, which was not surprising in view of the absence of the divinylcarbinol system. As pointed out by Braude and Jones,[3] the tendency of two vinyl groups in a divinylcarbinol to conjugate represents a very potent driving force for allylic rearrangement. The dehydration product contained only a little vitamin A methyl ether. The major product exhibited an ultraviolet absorption curve, λ_{max} 286 mμ, typical of an unhindered conjugated triene and very similar to that of *retro*-ionylidene-ethane, λ_{max} 284 mμ.[1] There can be little doubt, therefore, that its structure is XII, for the only alternative triene, XIII, theoretically possible, being of the β-ionylidene type, could hardly be expected to show a λ_{max} higher than 265 mμ (*cf.* β-ionylidene-ethanol, λ_{max} 265 mμ[5]). Furthermore, ozonolysis gave no geronic acid, which would be required for structure XIII. An additional product, λ_{max} 299 mμ, whose structure


XI


XII


XIII

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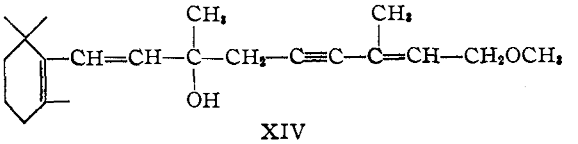
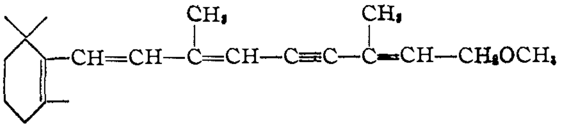
[5] Distillation Products, Inc., British Patents 633,711 (1949) and 650,302 (1951). It is shown here that "β-ionylideneacetic ester" prepared by the usual method [P. Karrer, *et al.*, *Helv. Chim. Acta*, **15**, 878 (1932)] is a mixture of conjugated and unconjugated esters and therefore any "β-ionylidene-ethanol" obtained therefrom [λ_{max} 274 mμ: N. Milas and T. Harrington, THIS JOURNAL, **69**, 2247 (1947); λ_{max} 285 mμ: N. L. Wendler, *et al.*, *ibid.*, **73**, 719 (1951)] is likewise a mixture of conjugated and unconjugated alcohols. β-Ionylidene-ethanol prepared from pure β-ionylideneacetic ester shows λ_{max} 265 mμ.

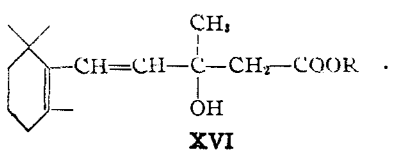
has not yet been ascertained, was also obtained in appreciable proportion.

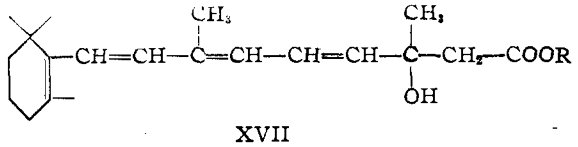
Compound XIV, the acetylenic precursor of XI, on the other hand, dehydrated exclusively in the "forward" direction, giving only 5,6-dehydrovitamin A methyl ether, XV. This was characterized by ozonolysis to geronic acid and by its ultraviolet absorption spectrum which, when compared with that of vitamin A, showed the hypsochromic and hypochromic effects to be expected upon substituting an acetylenic group for an interior ethylenic group in a conjugated polyene. Its homogeneity was confirmed by chromatography. Milas and his co-workers[6] have also reported a 5,6-dehydrovitamin A methyl ether, of spectral properties that differ substantially from those reported herein. It is unlikely that their product was homogeneous, since, in spite of extensive attempts at purification, chromatography was omitted, and their published curve shows extraneous absorption in the region 350–380 mμ.


XIV


XV

Although the behavior of XI upon dehydration can be readily explained in terms already discussed for I and VII, the exclusively "forward" dehydration of its acetylenic analog, XIV, indicates that some other operative factors are involved. One of these is undoubtedly the very much higher electron-attracting nature of the acetylenic group as compared to the vinyl group.[3] Several other β-ionols and vinylogs thereof are known to undergo "forward" dehydration and are similarly characterized by the presence of a strong electron-attracting group on the carbon beta to the hydroxyl group. Best known among these are β-ionolacetic ester, XVI, and its isoprenylog, XVII, which give moderately good yields of β-ionylideneacetic ester and vitamin A acid ester, respectively. However,


XVI


XVII

each is accompanied by an isomeric unconjugated ester which, judging from the published ultraviolet absorption data, λ_{max} 284 mμ[5] and $\lambda\lambda_{max}$ 330, 348 and 365 mμ,[5,7] is undoubtedly the corresponding *retro*ionylidene compound.

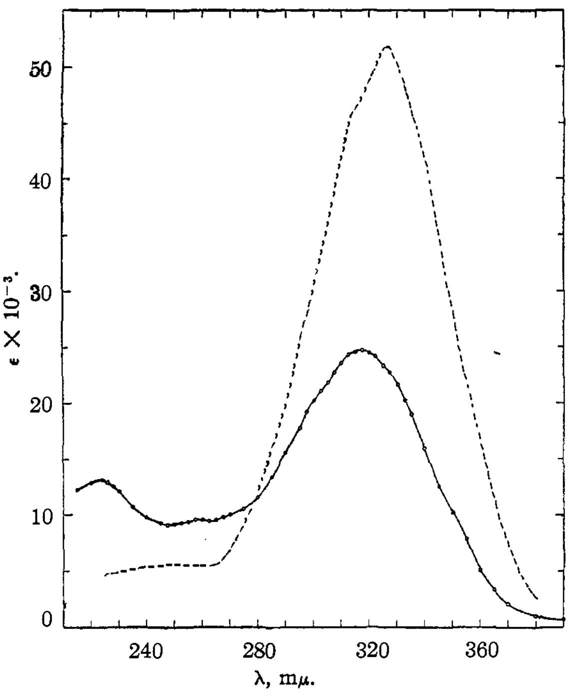
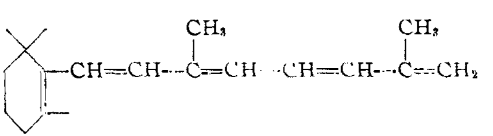
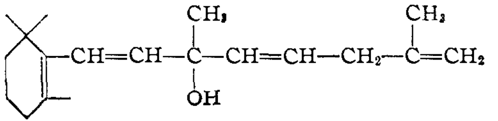
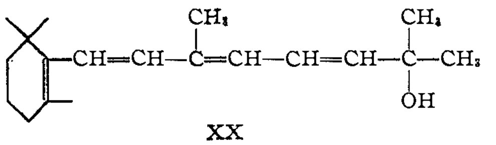


Fig. 1.—Ultraviolet absorption spectra, in alcohol, of 5,6-dehydrovitamin A methyl ether, XV (—), and vitamin A acetate (- - -).

The results of this work as well as those in the preceding paper of this series illustrate the great ease with which the *retro*ionylidene system is formed. It now becomes clear that dehydration of a β-ionol or vinylog thereof can take two competitive courses: (a) the formation of the *retro*ionylidene system, and (b) the formation of the β-ionylidene system. The former always predominates, unless kept to a minimum by the action of other factors such as those mentioned above. Unfortunately, this principle has not been previously recognized and as a result many workers claiming to have synthesized compounds of the β-ionylidene type have actually had *retro*ionylidene compounds, as can be judged from the reported


XVIII


XIX


XX

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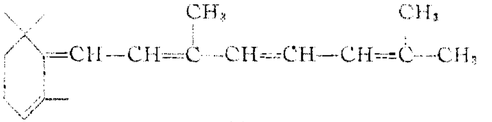
[6] N. A. Milas, *et al.*, THIS JOURNAL, **70**, 1597 (1948).

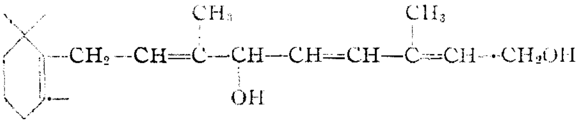
[7] O. Schwarzkopf, *et al.*, *Helv. Chim. Acta*, **32**, 443 (1949); 115th Meeting, American Chemical Society, San Francisco, California, March 27–April 1, 1949.

absorption data. Notable among these is the case of the hydrocarbon, XVIII, which is alleged to result from the dehydration of XIX[5] and of XX.[9] It is obvious from the absorption spectral correlations presented in Part I of this series[1] that XVIII should show light absorption properties very similar to those of vitamin A, whereas the published curves, $\lambda\lambda_{max}$ 332, **348,** 367 mμ, and $\lambda\lambda_{max}$ 332, **346,** 364 mμ, leave no doubt that the compound obtained actually had the structure XXI. Proof of this, with a critical examination of other similar instances, will be presented in a forthcoming publication.



XXI

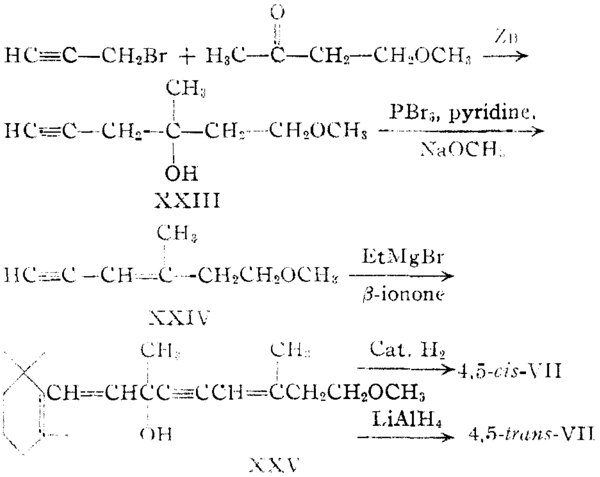
It is interesting to note that the only really successful synthesis of vitamin A[10] started with a carbinol (XXII) in which *retro*ionylidene formation was structurally impossible.



XXII

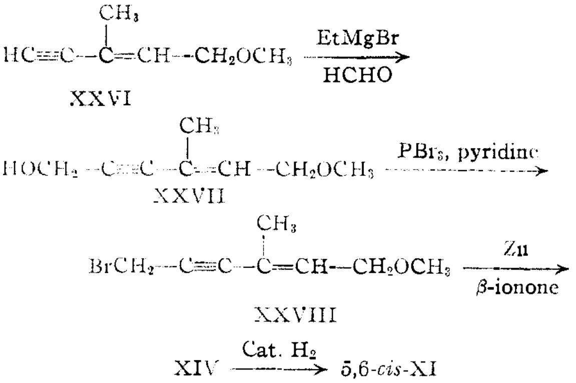
The synthesis of VII was carried out by the reaction sequence shown in Chart I. The distinction between the 4,5-*cis*- and 4,5-*trans*-isomers is based primarily on the assignment of the *cis*-configuration to the catalytically semihydrogenated enyne.[11] Although the crude product contained considerable overhydrogenated as well as unhydrogenated material, the desired product, λ_{max} 243 mμ, ϵ 21,900, could be isolated in fairly pure state by chromatography on alumina. Semihydrogenation with lithium aluminum hydride,[12] on the other hand, proved remarkably specific, producing VII in very high yield and in a practically pure state. The chromatographed product in this case showed λ_{max} 241 mμ, ϵ 27,800. This was assigned the *trans*-structure on the basis of the fact that *trans*-mono- and diolefins are hypsochromically displaced with respect to their *cis*-isomers and show higher extinction.[13]

CHART I



The reaction sequence (Chart II) furnishing the carbinol XI has been reported in the patent literature by Isler.[14] In view of the absence in the cited reference of sufficient experimental details

CHART II



$$HC{\equiv}C{-}\overset{CH_3}{\overset{|}{C}}{=}CH{-}CH_2OCH_3 \xrightarrow[HCHO]{EtMgBr}$$

XXVI

$$HOCH_2{-}C{\equiv}C{-}\overset{CH_3}{\overset{|}{C}}{=}CH{-}CH_2OCH_3 \xrightarrow{PBr_3,\ pyridine}$$

XXVII

$$BrCH_2{-}C{\equiv}C{-}\overset{CH_3}{\overset{|}{C}}{=}CH{-}CH_2OCH_3 \xrightarrow[\beta\text{-ionone}]{Zn}$$

XXVIII

$$XIV \xrightarrow{Cat.\ H_2} 5,6\text{-}cis\text{-}XI$$

TABLE I

ULTRAVIOLET ABSORPTION DATA[a]

Compound	λ_{max} (mμ)	ϵ_{max}
I	236	6,500
4,5-*cis*-II	296	25,000
	306	39,000
4,5-*trans*-II	**317**	**47,000**
	331	34,500
4,5-*cis*-VII[b]	243.5	25,100[c]
4,5-*trans*-VII	241	27,800[c]
	332.5	48,800
X[d]	348	65,900
	367	53,100
5,6-*cis*-XI	229	14,600[e]
XII	286	.....
XIV	229	17,000[c]
XV[e]	317	24,800
XXIV	226	13,000
XXV	235	19,500[c]
XXVI	223	11,300
XXVII	227	12,000
XXVIII	234[f]	17,500

[a] Measured in 95% ethanol (unless otherwise indicated) with a Beckman spectrophotometer. [b] The spectral data reported here are those of a sample obtained with chromous hydroxide.[20] [c] It should be borne in mind that this value contains a contribution of approximately 6,000 from the β-ionol chromophore (*cf.* I above). [d] The extinctions of the previously reported sample[1] at 333, 348 and 367 mμ were, respectively, 42,100, 53,700 and 39,600. [e] Milas, *et al.*,[6] report λ_{max} 322 mμ, ϵ 53,700. [f] Measured in hexane.

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[8] E. M. Shantz, THIS JOURNAL, **68**, 2553 (1946).

[9] P. Karrer and J. Benz, *Helv. Chim. Acta*, **31**, 1607 (1948).

[10] O. Isler, W. Huber, A. Ronco and M. Kofler, *ibid.*, **30**, 1911 (1947).

[11] K. N. Campbell and B. K. Campbell, *Chem. Revs.*, **31**, 148 (1942).

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

[13] P. L. Nichols, S. F. Herb and R. W. Riemenschneider, *ibid.*, **73**, 247 (1951); J. R. Platt, H. B. Klevens and W. C. Price, *J. Chem. Phys.*, **17**, 466 (1949).

[14] O. Isler, U. S. Patent 2,540,118 (1951).

and of characterizing data for the carbinol and its intermediates, the procedure is fully described in the experimental part.

Although XIV showed the expected absorption properties of conjugated enynes, its semihydrogenation product, 5,6-*cis*-XI, did not exhibit the hyperchromic and bathochromic effects usually observed in going from a conjugated enyne to the corresponding diene. Models of 5,6-*cis*-XI show pronounced steric hindrance between the 7-methyl and 4-methylene groups when the 6,7-single bond is *s-trans* and between the 8-hydrogen and 4-methylene groups when this single bond is *s*-cis. Clearly this is the cause of the spectral degradation observed. The same type of steric hindrance occurs in 4,5-*cis*-II between the 3-methyl and 6-methylene groups, and likewise causes pronounced spectral degradation.[1]

Experimental

4-Methoxy-2-butanone.—The preparation of this ketone by the boron trifluoride-catalyzed addition of methanol to methyl vinyl ketone has already been reported in yields of 45–61%.[15] The following procedure gave yields of 87%. To a solution of 387 g. (5.53 moles) of dried and redistilled methyl vinyl ketone in 1.2 liters of anhydrous methanol was added 15 ml. of boron trifluoride etherate. The resulting exothermic effect was controlled to 50° by intermittent cooling. The mixture was allowed to stand at room temperature overnight and then refluxed for two hours. On cooling, 30 g. of anhydrous sodium acetate was added to destroy the boron trifluoride–methanol complex. Most of the methanol was then distilled off at 80 mm. and the residue diluted with three volumes of ether and filtered to remove the precipitated salts. The filtrate and methanol distillate were combined and distilled atmospherically; yield 490 g.; b.p. 138–140°; n^{20}D 1.4050.

Propargylmethyl-β-methoxyethylcarbinol (XXIII).—About 15 ml. of a solution consisting of 83.7 g. (0.82 mole) of methoxybutanone, 50 g. (0.42 mole) of propargyl bromide, 0.2 g. of copper ethyl acetoacetate, 15 ml. of benzene and 100 ml. of dry ether was added to 60.0 g. (0.92 mole) of iodine-activated zinc dust.[16] After initiation of reaction by 20–30 minutes of warming, the mixture was vigorously stirred, and the remainder of the reactants added at a rate sufficient to maintain refluxing. Following an additional 30 minutes of refluxing, the mixture was hydrolyzed at −10° with 250 ml. of 5 *N* sulfuric acid, the excess zinc filtered off, and the ether layer separated. The aqueous layer was reextracted twice with 200-ml. portions of ether. The combined ether extracts were washed with enough 15% aqueous ammonia to dissolve zinc salts present, and finally dried with anhydrous potassium carbonate. Two fractionations through a 15-inch jacketed Vigreux column yielded 20.1 g. (33.7%) of product; b.p. 82–84° (15 mm.); n^{20}D 1.4552.

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.59; H, 9.92. Found: C, 67.83; H, 9.86.

4-Methyl-6-methoxy-3-hexen-1-yne (XXIV).—To a stirred solution of 35.4 g. (0.13 mole) of phosphorus tribromide in 195 ml. of dry pyridine maintained at 0°, was added dropwise 46.4 g. (0.33 mole) of the above carbinol, XXIII. The mixture was then refluxed with vigorous stirring for 90 minutes. Dehydrobromination was completed by the addition of 200 ml. of 5 *M* methanolic sodium methoxide and refluxing for an hour. The cooled mixture was then poured onto ice and water, layered with pentane, and acidified with 6 *N* sulfuric acid. The aqueous layer was reextracted three times with pentane, and the combined extracts washed with dilute sodium bicarbonate and dried with anhydrous potassium carbonate. After concentrating atmospherically through a 5-ball Snyder column, the product was fractionated through a 15-inch jacketed Vigreux column. Two refractionations were necessary to produce a pure product; b.p. 83–85° (50 mm.); n^{20}D 1.4713. The yields were 35–45%.

Anal. Calcd. for $C_8H_{12}O$: C, 77.35; H, 9.74. Found: C, 77.21; H, 9.76.

Carbinol XXV.—A solution of 13.6 g. (0.11 mole) of enyne XXIV in 250 ml. of dry ether was treated with a 2% excess of 1.5 *M* ethylmagnesium bromide. Grignard formation was rather slow and 15 hours of refluxing was required to complete the reaction. The acetylenic Grignard reagent precipitated as a tacky, gummy mass. After the addition of 23.3 g. (0.12 m.) of pure β-ionone (λ_{max} 296 mμ, ε10,500), the mixture was stirred for 16 hours at room temperature, and then hydrolyzed at −20° with 30% ammonium acetate. (Acid hydrolysis must be avoided since XXV dehydrates with great ease.) The ethereal layer was separated, dried with anhydrous potassium carbonate and concentrated under vacuum to a sirup. This was distilled at 0.001 mm. from an ordinary Claisen flask, immersed up to its side-arm in an oil-bath.[17] The product, a very light yellow viscous oil, was collected at 115–130°; n^{20}D 1.5212; yield 20.0 g. (57%).

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19; methoxyl, 9.81. Found: C, 79.59; H, 9.94; methoxyl, 9.72.

Chromatography produced no change in the physical properties or analysis.

4,5-*cis*-VII.—A solution of 10.2 g. of XXV in 200 ml. of methanol containing 10 ml. of piperidine and 0.5 g. of zinc acetate was shaken under hydrogen in the presence of 5.0 g. of Raney nickel.[18] The rate of absorption, which was 40 cc. per minute at the start, gradually decreased, but there was no sharp change at the semihydrogenation endpoint. The reaction was then stopped and worked up in the usual manner. Distillation yielded 9.2 g. of product, collected at 105–120° (0.002 mm.). The results were essentially the same with a specially poisoned palladium catalyst.[19]

The product was dissolved in 100 ml. of petroleum ether and poured onto a 3 × 30-cm. column of Alcoa F-20 alumina (80–200 mesh). On developing with increasing proportions of ether in petroleum ether there was obtained one main band (slightly fluorescent under ultraviolet light) preceded by a narrow yellow band. The first eluates of the main band showed λ_{max} 236 mμ. On continued elution this λ_{max} rose to 244 mμ and then finally dropped to 236 mμ again. Only eluate of $\lambda_{max} \geqslant 243$ mμ was collected. Distillation yielded 4.5 g. of product at 105–112° (0.002 mm.); n^{20}D 1.5204; λ_{max} 243 mμ; ε 21,900[20]; Carr–Price color, red-violet.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76; methoxyl, 9.74. Found: C, 79.08; H, 10.95; methoxyl, 9.31.

4,5-*trans*-VII.—A solution of 9.0 g. of carbinol XXV in 75 ml. of dry ether was added, at 0°, to a suspension of 1.0 g. of lithium aluminum hydride in 100 ml. of dry ether. The resulting clear solution was refluxed for three hours. The excess hydride was then destroyed with 5 ml. of ethyl acetate and the mixture hydrolyzed by pouring into 20% potassium hydroxide at 0°. (Hydrolyzing with acids must be avoided because of the ease of dehydration of VII.) The small amount of undissolved alumina was filtered off, and the ether layer separated and dried with anhydrous potassium carbonate. Upon distillation 8.0 g. of product was collected at 120–125° (0.001 mm.); n^{20}D 1.5255; Carr–Price color, red-violet. On an alumina column the product proved to be chromatographically homogeneous.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76; methoxyl, 9.74. Found: C, 79.01; H, 10.67; methoxyl, 9.54.

Dehydration of VII.—A 5.0-g. chromatographed sample of either 4,5-*cis*- or 4,5-*trans*-VII was dissolved in 75 ml. of

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[15] D. B. Killian, G. F. Hennion and J. A. Nieuwland, THIS JOURNAL, **58**, 893 (1936); N. A. Milas, *et al.*, *ibid.*, **70**, 1597 (1948).

[16] This is produced by gently heating 200 g. of acid washed and dried zinc dust with 0.5 g. of iodine in a loosely stoppered erlenmeyer flask, until iodine vapors are no longer perceptible.

[17] All subsequent distillations at 0.001–0.005 mm. were carried out in this manner.

[18] 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.

[19] We are indebted to Dr. J. A. Aeschlimann, Hoffmann-LaRoche, Inc., Nutley, N. J., for a sample of this catalyst.

[20] A much purer sample of this *cis*-isomer was obtained from XXV by semihydrogenation with chromous hydroxide. Its spectral data are in Table I. The chromous hydroxide procedure will be described in a subsequent publication.

glacial acetic acid containing 2.5% anhydrous potassium acetate and 0.1 g. of hydroquinone. Solution of the *trans*-isomer was accompanied by a brilliant rose color which faded within 20 seconds to a bright yellow. With the *cis*-isomer the color was only a faint pink, and required five minutes to fade. After standing under nitrogen overnight, the solution was poured into water and extracted with petroleum ether. The extract was washed with sodium bicarbonate, dried with anhydrous potassium carbonate and distilled. The *trans*-isomer yielded 67% of distillable product as compared to 84% from the *cis*-isomer. In both cases the product, collected at 120–130° (0.001 mm.), showed $n^{20}D$ 1.642. The ultraviolet absorption curves were practically identical: $\lambda\lambda_{max}$ 333, **348**, 367 mμ; ϵ_{max} 57,000.

Anal. Calcd. for $C_{21}H_{32}O$: C, 83.94; H, 10.74; methoxyl, 10.33. Found: C, 83.97; H, 10.78; methoxyl, 10.05.

A solution of 4.3 g. of the product in 50 ml. of petroleum ether was chromatographed as described under *cis*-VII. The first band eluted showed $\lambda\lambda_{max}$ 348, **367**, 387 mμ suggestive of anhydrovitamin A (3.5%).[21] The second and main band, $\lambda\lambda_{max}$ 333, **348**, 367 mμ, amounted to 90% of the total. The third and last band eluted had λ_{max} 326 mμ and the typical shape of the vitamin A curve (3.0%). The above percentages are based on weights after vacuum evaporation of the solvents.

Distillation of the middle 50% of the main band gave 2.7 g. of the purest sample of *retro*vitamin A methyl ether, X, so far obtained. It was collected as a lemon-yellow product at 120–125° (0.002 mm.); $n^{20}D$ 1.65–1.66. Light absorption data are in Table I. The analytical figures were essentially the same as those above.

3-Methyl-5-methoxy-3-penten-1-yne (XXVI).—The preparation of this compound through the action of phosphorus tribromide on methylvinylethynylcarbinol, followed by sodium methoxide treatment, has been previously described by Isler.[22] The procedure described below is simpler and gives comparable yields (72%). A mixture of 50 g. (0.52 mole) of methylvinylethynylcarbinol, 200 ml. of ether and 100 ml. of concd. hydrochloric acid was shaken under nitrogen for three hours at room temperature, and was then poured into three volumes of water and extracted twice with petroleum ether. The combined extracts were dried with anhydrous potassium carbonate and added at 0° to a solution of 65 g. of sodium methoxide in 350 cc. of methanol. The petroleum ether was then distilled off and the residue was poured into 1500 ml. of water. The product was twice extracted with petroleum ether, dried with anhydrous potassium carbonate, and distilled through a ten-inch jacketed Vigreux column; b.p. 74–76° (100 mm.); $n^{20}D$ 1.4538; weight 41.5 g. Isler[22] reports b.p. 73–75° (100 mm.) and $n^{22.5}D$ 1.4552.

4-Methyl-6-methoxy-4-hexen-2-yne-1-ol (XXVII).—A solution of 16.5 g. (0.15 mole) of enyne XXVI in 200 ml. of dry ether was treated with 2% excess 1.59 *M* ethylmagnesium bromide. As in the case of XXIV, Grignard formation was slow and overnight refluxing was necessary to complete the reaction. Formaldehyde vapor, generated by strongly heating 13.5 g. (0.45 mole) of dry paraformaldehyde, was then delivered to the very vigorously stirred Grignard reagent with the temperature maintained at 0°. Following a subsequent half-hour of stirring at 0°, the mixture was hydrolyzed with 30% ammonium acetate and the ether layer separated. After re-extracting the aqueous layer and combining and drying the extracts with anhydrous potassium carbonate, the product was fractionated through an eight-inch jacketed Vigreux column; b.p. 85–87° (1.0 mm.); $n^{20}D$ 1.4960; yield 12.6 g. (60%). Isler[14] reports $n^{22}D$ 1.496.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.57; H, 8.63. Found: C, 68.44; H, 8.36.

1-Bromo-4-methyl-6-methoxy-4-hexen-2-yne (XXVIII).—To a stirred solution of 12.6 g. (0.09 mole) of the above enynol, XXVII, and 2 ml. of pyridine in 70 ml. of dry ether was added dropwise at 0° 13.0 g. (0.048 mole) of phosphorus tribromide. The mixture was refluxed with stirring for one hour and then hydrolyzed with ice-water. The ether layer was separated, washed with sodium bicarbonate and dried with anhydrous magnesium sulfate. Fractionation through a jacketed ten-inch Vigreux column yielded 10.6 g. (58%) of the desired bromo compound; b.p. 68–70° (1.0 mm.); $n^{20}D$ 1.5261. Isler[14] reports $n^{21}D$ 1.524.

Anal. Calcd. for $C_8H_{11}BrO$: C, 47.35; H, 5.46; Br, 39.38. Found: C, 47.20; H, 5.44; Br, 39.25.

Carbinol XIV.—A few ml. of a solution of 10.7 g. (0.055 mole) of pure β-ionone and 20 g. (0.1 mole) of the above bromide in 75 ml. of dry ether were added to 20 g. of granulated zinc and 5 mg. of copper ethyl acetoacetate. Upon initiation of reaction by a few minutes of warming, the mixture was stirred vigorously while the remainder of the reactants was added at a rate sufficient to maintain gentle refluxing. Refluxing was continued for an additional 15 minutes. The mixture was then hydrolyzed at −10° with enough 15% ammonium hydroxide to dissolve the basic zinc salts. The ether layer was separated and added to 500 ml. of 10% methanolic sodium hydroxide to destroy the unreacted bromo compound. (If this is omitted, distillation is accompanied by extensive dehydration.) After standing overnight at room temperature, the mixture was poured into a liter of water, washed twice with water, once with 5% acetic acid, and finally with sodium bicarbonate solution. After drying with anhydrous magnesium sulfate, the solution was distilled. The desired product was collected at 105–110° (0.001 mm.); $n^{22}D$ 1.5223; yield 11.0 g. (63%). Isler[14] reports $n^{20}D$ 1.515 for an undistilled concentrate.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 80.00; H, 10.19.

5,6-*cis*-XI.—A solution of 7.5 g. of carbinol XIV in 150 ml. of methanol was shaken under hydrogen at atmospheric pressure in the presence of a specially poisoned palladium catalyst.[19] With 1.0 g. of catalyst, absorption occurred at the rate of 100 cc. per minute and was stopped when the equivalent amount of hydrogen for semihydrogenation had been consumed. No distinct slow-down at the semihydrogenation end-point was observed. Working up in the usual manner yielded 6.5 g. of product collected at 110–120° (0.001 mm.); $n^{20}D$ 1.5172. Isler[14] reports $n^{20}D$ 1.512 for an undistilled concentrate.

Similar results were obtained with Raney nickel poisoned with piperidine and zinc acetate. The absorption curves of the two products were practically identical: λ_{max} 229 mμ, ε 13,000.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76; methoxyl, 9.74. Found: C, 79.85; H, 10.47.

An 8.5-g. sample of the product was chromatographed as described under *cis*-VII. Eluate of the main band, which was scarcely fluorescent under ultraviolet light, showed initially only end absorption, then a peak at 229 mμ, which became more pronounced with continued elution. Only the middle 50% of this eluate was accepted. Distillation gave 4.4 g. of product at 114–120° (0.002 mm.); $n^{20}D$ 1.5175; Carr–Price color, prussian blue. Ultraviolet absorption data are in Table I.

Anal. Found: C, 79.50; H, 10.42; methoxyl, 9.50.

Dehydration of 5,6-*cis*-XI.—A solution of 6.1 g. of the carbinol in 80 ml. of glacial acetic acid containing 0.1 g. of hydroquinone and 2% anhydrous potassium acetate was allowed to stand under nitrogen at room temperature. There was no color change accompanying solution as in the case of VII. Spectrophotometric examinations made intermittently showed dehydration to be progressing very slowly. After 48 hours the mixture was worked up with water and petroleum ether, the extract dried with anhydrous potassium carbonate and concentrated under vacuum to about 100 cc. The absorption spectrum indicated that about half the original carbinol remained unchanged.

The petroleum ether solution was then chromatographed as described under *cis*-VII. After discarding the first eluates, which contained two minor bands, progressive elution with increasing proportions of ether in petroleum ether gave in order: (a) 1.0 g. of a substance absorbing maximally at **299** mμ, mixed with appreciable *retro*ionylidene triene; (b) 1.0 g. *retro*ionylidene triene, XII, λ_{max} 286 mμ; (c) 0.15 g. of product showing the typical curve of vitamin A, λ_{max} 325 mμ; (d) 2.4 g. of unchanged XI.

Fraction (b) was ozonized[1] and gave no geronic acid. Insufficient material was available for distillation and analysis.

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[21] This product is an artifact produced by the alumina column. It was not present in the spectrum of the original.

[22] O. Isler, W. Huber, A. Ronco and M. Kofler, *Festschrift E. C. Barell*, 31 (1946).

5,6-Dehydrovitamin A Methyl Ether (XV).—Dehydration of XIV in glacial acetic acid proved too slow to be practical. Consequently the enynol (7.1 g.) was dissolved in 110 ml. of methanol containing 0.6 cc. of concd. hydrochloric acid and 0.1 g. of hydroquinone and allowed to stand under nitrogen for three days at room temperature. The solution was then diluted with water and the product extracted with petroleum ether, washed with sodium bicarbonate solution and dried with anhydrous potassium carbonate. The extract was concentrated under vacuum to 50 cc. and chromatographed as previously described under *cis*-VII. Under ultraviolet light the column showed a single large red-fluorescent zone preceded by a bright red-fluorescing edge. The column was extruded and the lower two-thirds of the main band was cut out and eluted with methanol. The remainder of the column was rejected although it showed very nearly the same spectrum as the above eluate. After working up in the usual manner, distillation gave 4.1 g. of golden-yellow product at 110–120° (0.001 mm.); $n^{20}\text{D}$ 1.5791.

Anal. Calcd. for $C_{21}H_{30}O$: C, 84.52; H, 10.13; methoxyl, 10.40. Found: C, 84.48; H, 9.99; methoxyl, 10.42.

Ozonolysis[1] gave 21% geronic acid.

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RARITAN, NEW JERSEY

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE MOUNT SINAI HOSPITAL]

p-Hydroxyphenoxy Aliphatic Acids

BY HARRY SOBOTKA AND JOHN AUSTIN

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A new series of water-soluble monoethers of hydroquinone has been prepared including the hydroquinone ethers of lactic acid, of β-hydroxypropionic acid, of α- and γ-hydroxybutyric acid, the hydroquinone acetal of ethyl glyoxalate, and some of their derivatives. Four methods of synthesis have been adapted to the specific conditions encountered.

This report describes the synthesis of a number of monoethers of hydroquinone with aliphatic monohydroxy acids. Of this group one representative only has been previously described, namely, the glycolic acid monoether of hydroquinone,[1] also designated as *p*-hydroxyphenoxyacetic acid and, less correctly, as hydroquinone-O-acetic acid.[2] The homologs of this ether-acid include two subseries, the "α-phenoxy" acids of the general formula $HOC_6H_4OCHRCO_2H$ and the "(non-α)-phenoxy" acids, $HOC_6H_4O(CH_2)_nCO_2H$. The formation of *p*-hydroxyphenoxyacetic acid, according to Carter and Lawrence,[1] could not be verified within a wide range of conditions, nor did we find it possible to obtain it by diazotization of *p*-aminophenoxyacetic acid and elimination of nitrogen.

We therefore developed several methods for the condensation of hydroquinone with one molecule of halogenated aliphatic acids. In order to circumvent the condensation with two molecules, one of the hydroxy groups had to be masked by a group that would not be hydrolyzed by the alkaline reaction required for the condensation. At the same time the masking group had to be so selected as to enable its removal under conditions that would not simultaneously open the other ether linkage. All four methods, subsequently described, apply to the α-halogeno acids as well as to the γ-halogeno acid, γ-chlorobutyric acid. β-Halogenated fatty acids tend to dehydrohalogenate to the corresponding acrylic acids, therefore certain precautions had to be applied to the synthesis of β-(*p*-hydroxyphenoxy)-propionic acid.

The condensation of alkali salts of diphenol monomethyl ethers with halogenoacetic acids was claimed in three patents by Majert and Lederer,[3] but they gave as only example the ortho-isomer, the monocatechol ether of glycolic acid. We have succeeded in the synthesis of a series of *p*-methoxyphenoxy aliphatic acids and esters by condensation of hydroquinone monomethyl ether with halogeno-fatty acids and esters; demethylation with concentrated hydrochloric acid yielded the respective *p*-hydroxyphenoxy acids. In order to avoid the heating with hydrochloric acid or dry hydrogen chloride, we used the benzyl group which may be removed by catalytic hydrogenolysis. Reaction of the sodium salt of monobenzyl hydroquinone with ethyl β-bromopropionate in anhydrous medium exemplifies the extension of the method to β-halogenated acids. The method proved also suitable for the condensation of dichloroacetic acid with two molecules of hydroquinone.

An alternative synthesis of β-(*p*-hydroxyphenoxy)-propionic acid might be accomplished by the condensation of β-propiolactone with the methyl- or benzylmonoether of hydroquinone according to Gresham[4] leading to the methoxy acid (IV) or the benzyloxy acid of which we describe the ethyl ester (XI).

The method of widest scope and operative under the mildest conditions is the condensation of the sodium or potassium salt of arbutin, hydroquinone-β-glucopyranoside, with salts of halogenated acids. The primary condensation products could not be isolated in crystalline form. The glucoside linkage is easily opened by dilute acid or by emulsin (β-glucosidase).

As a further alternative, the procedure of Friess[5] was used for the synthesis of γ-(*p*-hydroxyphenoxy)-butyric acid.

A study of the antioxidant properties of these water-soluble hydroquinone monoethers will be reported separately. The influence of the substituent groups on the stability of the ether linkage is under investigation.

We are indebted for the microanalyses to the Schwarzkopf Microanalytical Laboratories, Middle Village, L. I., N. Y. Miss Franca Nunes contrib-

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(1) W. Carter and W. T. Lawrence, *J. Chem. Soc.*, **77**, 1222 (1900).

(2) "Beilstein," Vol. VI, Berlin, 1923, p. 847.

(3) W. Majert and L. Lederer, German Patent 87336 (1895); German Patent 87668 (1895); German Patent 108241 (1896).

(4) T. L. Gresham, J. E. Jansen, F. W. Shaver, R. A. Bankert, W. E. Beears and M. G. Prendergast, THIS JOURNAL, **71**, 661 (1949).

(5) S. L. Friess, *ibid.*, **71**, 14 (1949).