according to infrared spectral analysis, of only 1-*p*-menthene, partly racemized.

Forty ml. of *d*-limonene was introduced into the flask in order to determine the activity of the recovered catalyst. After two hours at reflux the optical rotation decreased from $\alpha^{25}\text{D}$ +103° to $\alpha^{25}\text{D}$ +20°, which indicated that the catalyst was active. The limonene and its reaction product was then removed from the catalyst by flash distillation under reduced pressure and the previously recovered 1-*p*-menthene was reintroduced into the reaction flask. After 25 hours at reflux the optical rotation dropped to $\alpha^{25}\text{D}$ +10°. After 22 hours longer at reflux the liquid product was removed and analyzed according to the method described previously.[1] The composition of the product is given in Table I.

TABLE I

COMPOSITION OF PRODUCTS FROM THE ISOMERIZATION OF *p*-MENTHENES

Starting *x*-*p*-Menthene x =	Reaction time, hr.	Composition of reaction product *p*-Menthene, %			
		1-(I)	2-(II)	3-(III)	8(9)-(IV)
1-(I)	22	32	0	63	5
2-(II)	5	64	3	32	1
2-(II)	20	32	0	63	5
3-(III)	40	24	0	68	6

(+)-*trans*-2-*p*-**Menthene** (II).—Twenty ml. of II was refluxed in the presence of a catalyst prepared from 3 g. of sodium, 1.5 ml. of *o*-chlorotoluene and 15 ml. of toluene. After 5 hours the reflux temperature increased from 169 to 175° while the optical rotation dropped to $\alpha^{25}\text{D}$ +2°. A sample was withdrawn for infrared spectral analysis, while the remainder of the product was continued at reflux for an additional 15 hours. The compositions of the two reaction products are given in Table I.

3-*p*-Menthene (III).—The catalyst was prepared from 5 g. of sodium and 3 ml. of chlorotoluene in 30 ml. of toluene. Forty ml. of III was refluxed for 40 hours in the presence of the catalyst. During the reaction the temperature rose from 166 to 168.5°. The composition of the product is given in Table I.

EVANSTON, ILLINOIS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

On the Geometrical Configuration of the Olefinic Components of Poison Ivy Urushiol. The Synthesis of a Model Compound

BY BERNARD LOEV[1] AND CHARLES R. DAWSON

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A new synthesis of 3-alkenyl veratroles has been developed and used for the synthesis of 3-(*cis*-nonadecenyl-10′)-veratrole, a homolog of dimethylurushenol, the dimethyl ether of the monoölefinic component of the toxic principle of poison ivy. On the basis of a comparison of the infrared spectra and the melting points of the diastereoisomeric glycols of the above homolog with those of dimethyl urushenol obtained from poison ivy, the latter compound has been assigned the *cis* configuration. Inspection of the infrared spectra of the ethers of urushadienol and urushatrienol obtained from poison ivy indicates that the olefinic bonds of the di- and triolefinic components are also in the *cis* configuration.

The allergenic principle of poison ivy is a mixture of four compounds, each of which has the skeletal structure of 3-pentadecylcatechol (hydrourushiol), the minor component. The other three components contain one, two and three olefinic bonds, respectively, in the 15-carbon side chain. Recently the natural mixture has been methylated, separated by chromatography on alumina, and the positions of unsaturation of the olefinic components established.[2]

In the dimethyl ether form, the components of poison ivy "urushiol" are relatively inactive as allergens.[3] The removal of the methyl ether groups to restore the activity is not feasible because of the marked sensitivity of such alkenyl phenols to polymerization under the acid conditions required for demethylation. Consequently, the individual olefinic components of poison ivy "urushiol" cannot be made available for clinical study until either a method is developed for separating them in their free phenolic form or a method is developed for their synthesis. The latter route has already proven convenient for the saturated component, hydrourushiol (3-pentadecylcatechol),[4] and a method for the synthesis of the monoölefinic component, urushenol,[5] recently has been completed.[6]

It has been demonstrated previously[3] that the position and length of the side chain of alkyl catechols has important bearing on the degree and incidence of allergenic response observed after such catechols are applied to the skin of persons sensitive to poison ivy. The role of the double bond in the side chain, however, has received very little attention. The pure alkenyl phenols of varying degree of unsaturation have not been available for clinical study. That the double bond does have an important role is suggested by the fact that hydrourushiol is less active than urushiol as judged by the patch test. Nothing is known as yet in respect to the relationship between the olefinic structure of an alkenyl catechol and its ability to *induce* sensitization in persons not previously sensitized. This type of activity is of great interest because of its possible relationship to desensitization. If sensitization involves a specific reaction between the alkenyl catechol and certain proteins in the skin, then structural details such as the geometrical configuration of the olefinic bonds in the side chain

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(1) Pennsylvania Salt Mfg. Co., Philadelphia, Pa. This paper is based on a portion of the thesis submitted by Bernard Loev in 1952 to Columbia University in partial fulfillment of the requirements for the Ph.D. degree in chemistry.

(2) W. F. Symes and C. R. Dawson, THIS JOURNAL, **76**, 2959 (1954).

(3) H. Keil, D. Wasserman and C. R. Dawson, *J. Exptl. Med.*, **80**, 275 (1954).

(4) D. Wasserman and C. R. Dawson, THIS JOURNAL, **68**, 534 (1946).

(5) For simplicity in differentiating the olefinic components, it seems advisable to modify the name urushiol as originally used by Majima (*Ber.*, **55**, 172 (1922)). The term urushiol will hereafter be used to refer to the natural mixture, and the terms hydrourushiol (or 3-pentadecylcatechol), urushenol, urushadienol and urushatrienol, will be used to refer to the saturated, mono-, di- and triolefinic components.

(6) B. Loev and C. R. Dawson, to be published.

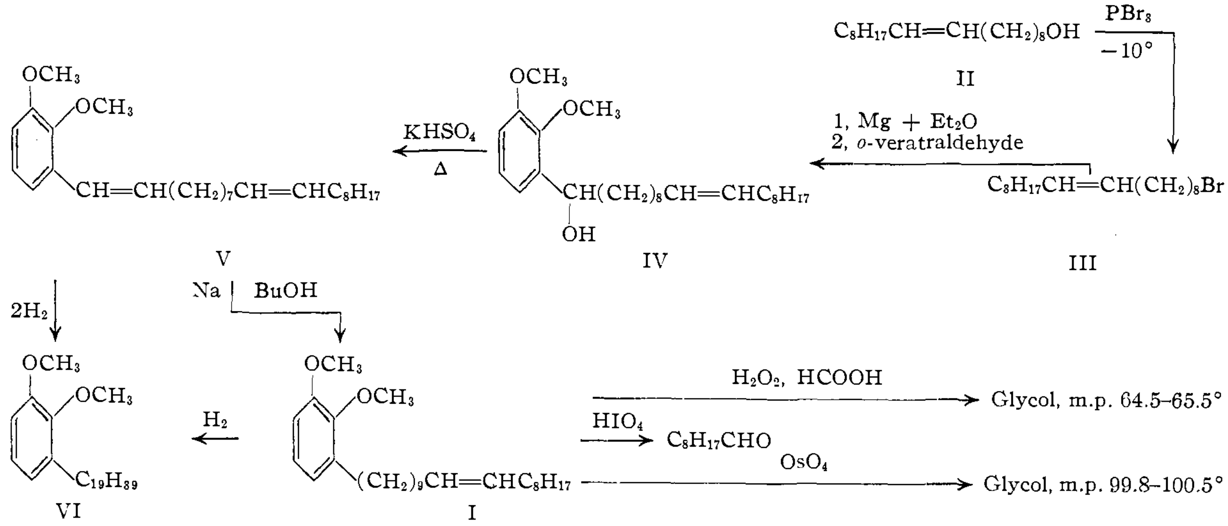

Fig. 1.—Schematic diagram of the synthesis of 3-(*cis*-nonadecenyl-10′)-veratrole (I).

may be of great importance. For this reason it has seemed advisable not only to determine the geometrical configurations of the olefinic components of poison ivy "urushiol," but to determine also the effect of certain experimental conditions on the geometrical stability of such olefinic bonds. The experimental conditions that were of particular interest were those that have been used in the synthesis of the monoölefinic component, urushenol.[6]

The use of infrared absorption spectra for the determination of the geometrical configuration of olefinic bonds has received much attention.[7] As a result it is now clear that absorption at 10.4 μ is characteristic of a *trans*-olefin. The absence of this absorption band indicates a *cis*-olefin (when an olefinic linkage is known to be present). Weak absorption at 13–14 μ often is found for a *cis*-olefin; however, it is not sufficiently dependable for structure assignment.

In order to apply the infrared analysis to the problem at hand, a procedure has been developed for the synthesis of 3-alkenyl veratroles of known configuration. It has been used for the synthesis of 3-(*cis*-nonadecenyl-10′)-veratrole (I), a homolog of dimethylurushenol. The route of synthesis, starting with geometrically pure *cis*-oleyl alcohol (II), is shown in Fig. 1. By a comparison of the infrared spectra and various derivatives of this synthetic model olefin of known configuration with those of the poison ivy dimethylurushiol olefins, the geometrical configurations of the latter have been deduced. Furthermore, the configuration of the olefinic bond supplied by the oleyl alcohol was checked at each step of the synthesis and the results are shown in Fig. 2. As can be seen in Fig. 2, the carefully purified oleyl alcohol was geometrically pure (*cis*) judging from the absence of absorption at 10.4 μ.

The oleyl alcohol (II) was converted to the bromide III at −10°. Even at this low temperature, a small amount of acid-catalyzed isomerization occurred, for a small *trans* absorption at 10.4 μ can be seen (Fig. 2, III). This small *trans* absorption will be noted in each of the succeeding compounds.

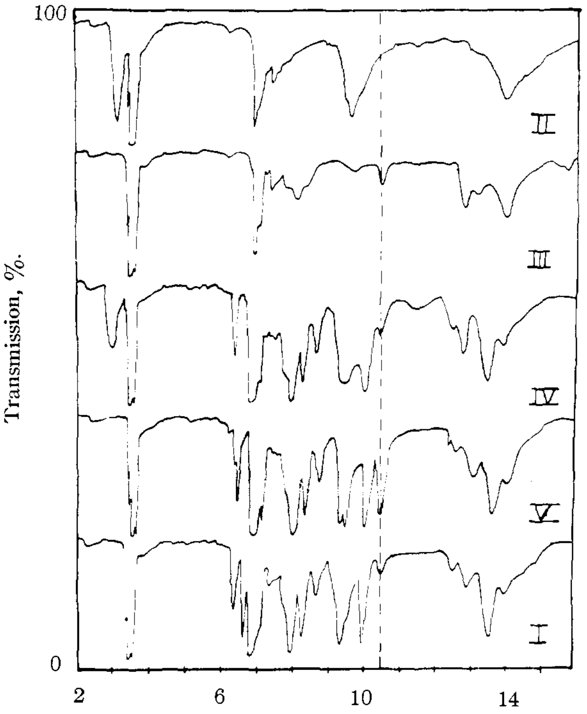

Fig. 2.—Infrared spectra: oleyl alcohol, II; oleyl bromide, III; 3-(1′-hydroxynonadecenyl-10′)-veratrole, IV; 3-(nonadecadienyl-1′,10′)-veratrole, V; 3-(nonadecenyl-10′)-veratrole, I.

The Grignard reaction between oleyl bromide and *o*-veratraldehyde caused no isomerization, since the spectrum of the resulting alcohol IV shows no increase in absorption at 10.4 μ. Dehydration of IV, by heating with potassium bisulfate, gave the diolefin V, showing a strong absorption at 10.4 μ. Most of this *trans* absorption can be attributed to

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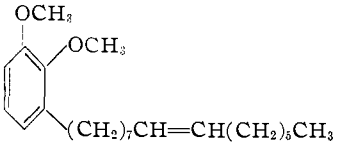
[7] R. S. Rasmussen, R. R. Brattain and P. S. Zucco, *J. Chem. Phys.*, **15**, 135 (1947); N. Sheppard and D. M. Simpson, *Quart. Rev.*, **6**, 1 (1952).

the styrene double bond, for most of the absorption at 10.4 μ disappeared on selective reduction of the double bond conjugated with the ring. The spectrum of I, produced by sodium–butanol reduction of V, shows only the weak absorption attributable to the small amount of *trans*-olefin that was present in the 9′-position in the oleyl bromide (III). This result shows that no perceptible geometrical isomerization of the isolated double bond occurred during the dehydration step. The selective reduction of the styrene double bond by sodium–alcohol[8] has been confirmed by degradation and by comparison of the ultraviolet absorption spectra of V and I. The diolefin V exhibited a strong absorption band at 259 mμ, characteristic of styrene compounds, whereas I showed no band at this wave length.

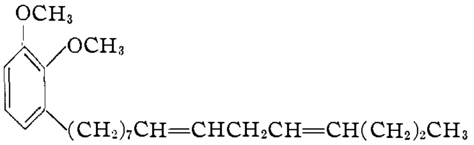
On catalytic hydrogenation of I to give VI, the small absorption at 10.4 μ completely disappeared. Ozonolysis of I gave nonanal, isolated as the methone derivative. Oxidation of I with osmium tetroxide, a *cis*-hydroxylating agent,[9] gave a glycol, m.p. 99.8–100.5°; oxidation of I with performic acid, a *trans*-hydroxylating agent,[10] gave the diastereoisomer, m.p. 64.5–65.5°. These hydroxylation results are in agreement with the common observation that *trans*-hydroxylation of a *cis* olefin generally gives a lower melting glycol than is obtained by *cis*-hydroxylation of the same *cis*-olefin.[10,11]

This new method of synthesis of alkenyl veratroles, involving the selective reduction of one of two olefinic bonds in the side chain, *i.e.*, the olefinic bond conjugated with the ring, has several advantages over the earlier method[12] developed in these laboratories. The configuration of the resulting olefinic bond in the side chain is established at the *start* of the synthesis by the use of alkenyl halides of known configuration. Such alkenyl halides are readily prepared by conventional methods.[13] The position, the number and the geometrical configurations of the olefinic bonds are more readily varied than by the earlier method. Furthermore, the experimental procedures throughout the synthesis are less difficult and less time consuming in this new method.

Samples of poison ivy dimethylurushenol (VII) and dimethylurushadienol (VIII), made available by a previous investigation in these laboratories,[2] have been examined in the infrared spectrophotometer. The spectra clearly show that each of the olefinic linkages in these compounds has the *cis* configuration, *i.e.*, there is no absorption at 10.4 μ.[14] A comparison of the infrared spectra of dimethylhydrourushiol and the free phenol, hydrourushiol reveals why a spectral determination of the geometrical configuration of alkenyl phenols must be carried out with the ether derivatives rather than the free phenols. The free phenolic hydroxyl group absorbs in the region of 10.4 μ.



VII



VIII

Performic acid oxidation of the chromatographically pure poison ivy dimethylurushenol previously has been shown to give a glycol, m.p. 66.8–68.2°[2]; hydroxylation by means of osmium tetroxide has now been carried out giving the diastereoisomer, m.p. 94–95°. The similarity in melting points of these glycols with those of the homolog already described is very striking (Table I). The assignment of a *cis* configuration to the poison ivy dimethylurushenol is thus also supported by chemical evidence.

TABLE I

GLYCOL MELTING POINTS

Olefin	Hydroxylating agents HCO_3H	 OsO_4
Dimethylurushenol of poison ivy	66.8–68.2°	94.0–95.0°
Synthetic homolog (I)	64.5–65.5°	99.8–100.5°

Experimental[15]

Oleyl Alcohol (II).—The oleyl alcohol (commercial) was carefully purified by fractional crystallization at −40° from acetone, followed by distillation, b.p. 182–184° (1.5 mm.), $n^{27.5}$D 1.4582.[16]

Anal. Calcd. for $C_{18}H_{36}O$: C, 80.53; H, 13.52. Found: C, 80.25; H, 13.59.

A sample of II, on catalytic reduction, absorbed the theoretical quantity of hydrogen, giving octadecyl alcohol.

Oleyl Bromide (III).—A solution of the alcohol II in carbon tetrachloride (at −10°) was converted (with PBr_3) to the bromide III employing a standard procedure.[17] The oleyl bromide distilled as a colorless liquid, b.p. 185–187° (1.5 mm.), n^{25}D 1.4718 (54%).

Anal. Calcd. for $C_{18}H_{35}Br$: C, 65.24; H, 10.65; Br, 24.12. Found: C, 65.21; H, 10.63; Br, 24.26.

3-(1′-Hydroxynonadecenyl-10′)-veratrole (IV).—To the Grignard reagent prepared from 100 g. (0.302 mole) of oleyl bromide (III) in 100 cc. of ether, was added a solution

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(8) A. Klages, *Ber.*, **35**, 2633 (1902); **35**, 2646 (1902).

(9) R. Criegee, *Ann.*, **522**, 75 (1936); A. R. Bader, THIS JOURNAL, **70**, 3938 (1948).

(10) D. Swern, G. N. Billen, T. W. Findley and J. T. Scanlan, *ibid.*, **67**, 1786 (1945); D. Swern, L. P. Witnauer and H. B. Knight, *ibid.*, **74**, 1655 (1952); D. Swern, *ibid.*, **70**, 1235 (1948).

(11) G. Braun, *ibid.*, **51**, 228 (1929); W. F. Huber, *ibid.*, **73**, 2730 (1951); H. Wittcoff, O. A. Moe and M. H. Iwen, *ibid.*, **70**, 742 (1948).

(12) D. Wasserman and C. R. Dawson, *J. Org. Chem.*, **8**, 73 (1943).

(13) K. Ahmad, F. M. Bumpus and F. M. Strong, THIS JOURNAL, **70**, 3391 (1948).

(14) These spectra are available in the dissertation of Bernard Loev, a microfilm copy of which may be obtained from the Columbia University Library. Unfortunately, insufficient dimethylurushatrienol was available for spectrophotometric analysis. However, the infrared spectrum of the dibenzyl ether of urushatrienol, having double bonds in the 8-, 11-, 14-positions of the side chain, recently has been taken by K. Markiewitz in these laboratories. No absorption at 10.4 μ was observed.

(15) The infrared spectra of compounds I to V were determined with a Baird infrared recording spectrophotometer, model B, using an 0.025-mm. cell. The spectra VI to X were determined with a Perkin–Elmer double beam infrared recording spectrophotometer, model 12, using an 0.001″ cell. These latter spectra were obtained through the courtesy of W. Tarpley and C. Vitiello of the Chemistry Division of the Schering Corporation, N. J. Spectra of the solids were taken as Nujol mulls.

(16) D. Swern, H. B. Knight and T. W. Findley, *Oil and Soap*, **21**, 113 (1944).

(17) J. Boeseken and A. H. Belinfante, *Rec. trav. chim.*, **45**, 914 (1926).

of 40.2 g. (0.242 mole) of 2,3-dimethoxybenzaldehyde (*o*-veratraldehyde) in 100 cc. of ether. After the addition was complete, the solution was refluxed 30 minutes, and then hydrolyzed by pouring into cold ammonium chloride solution. The ethereal layer was washed, dried and the solvent removed. The residual oil was dissolved in 400 cc. of hot ethanol, and then the solution was filtered. On chilling the filtrate, a white, waxy solid precipitated, and was removed by decantation. The solid, 6 g., was insoluble in acetone (probably it is the coupling product, 9,27-hexatriacontadiene). The ethanol was distilled leaving 106.5 g. of a pale yellow liquid, which did not solidify on cooling. The oil was distilled, b.p. 233–235° (0.5 mm.), giving 64 g. (63%) of the alcohol IV as a pale yellow liquid having a slight bluish fluorescence; n^{24}D 1.4960.

Anal. Calcd. for $C_{27}H_{46}O_3$: C, 77.46; H, 11.08. Found: C, 77.47; H, 11.04.

3-(Nonadecadienyl-1′,10′)-veratrole (V).—The alcohol IV, 57 g., was heated to 150°. Two grams of freshly fused potassium bisulfate was added and the temperature was raised to 190°. After a five-minute induction period vigorous boiling occurred; the temperature was maintained at 185–200° until the dehydration was complete (about 10 minutes). The resulting golden colored liquid was extracted once with 95% ethanol in which it was insoluble (to remove any non-dehydrated IV, which is soluble in alcohol). The diolefin V distilled as a pale yellow liquid with blue fluorescence, b.p. 244–247° (0.8 mm.), n^{25}D 1.5069, yield about 90%.

Anal. Calcd. for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.75; H, 11.04.

A sample of V, on catalytic reduction, using 5% palladium-on-charcoal, slowly absorbed the theoretical quantity of hydrogen, giving **3-nonadecylveratrole**, m.p. 45.5–47.0° (from ethanol).

3-(Nonadecenyl-10′)-veratrole (I).—During a period of 30 minutes, sodium (14.4 g. 0.625 mole) was added to a boiling solution of 25 g. (0.0625 mole) of the diolefin V dissolved in 200 cc. of dry butanol. The color of the solution soon changed from yellow to colorless. On cooling the solution resumed its yellow color. Cold water was slowly added, then the alcohol solution was washed several times with saturated salt solution, dried, and the solvent removed, *in vacuo*, leaving 31.5 g. of a pale yellow oil. The oil was distilled, b.p. 222–224° (0.4 mm.), giving I as a very pale yellow oil, 21.6 g. (86%), n^{24}D 1.4884.

Anal. Calcd. for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.22; H, 11.52.

A solution of I in ethyl acetate, at −40°, was ozonized. The ozonide was catalytically reduced over 5% palladium-on-charcoal. The nonanal was steam distilled and the distillate extracted with ether, dried and concentrated. A 0.3-g. sample of the residual oily nonanal was mixed with 1.2 g. of freshly recrystallized methone and 6 cc. of water. Sufficient alcohol was then added to make the solution homogeneous. After refluxing for five minutes, the solution was chilled and a crystalline precipitate (0.47 g.) was obtained. The precipitate was recrystallized from methanol–water to give colorless plates, m.p. 80–81°, showing no depression in melting point when mixed with an authentic sample of nonanal dimedon derivative.[18]

Anal. Calcd. for $C_{25}H_{40}O_4$: C, 74.21; H, 9.97. Found: C, 74.38; H, 10.02.

A sample of I, on catalytic reduction, absorbed one equivalent of hydrogen, giving **3-nonadecylveratrole (VI)**, m.p. 47–48°, identical to that obtained by reduction of V.

Anal. Calcd. for $C_{27}H_{48}O_2$: C, 80.14; H, 11.96. Found: C, 79.96; H, 12.06.

Hydroxylation of I Using Performic Acid.[10]—To a rapidly stirred mixture of 1 g. of I and 2.1 cc. of formic acid, was added 0.23 cc. of 37.8% hydrogen peroxide. The mixture was placed in a water-bath maintained at 40°. After ten minutes, the mixture started to turn yellow. At the end of three hours, another 0.05 cc. of hydrogen peroxide was added to the mixture, which now consisted of an upper orange, and a lower, light yellow layer. Following another hour of stirring and heating, the mixture was poured into water, extracted with ether, and the ether then removed. The residual oil was heated with 25 cc. of 3 *N* sodium hydroxide and sufficient alcohol to make the solution homogeneous. At the end of one hour, the alcohol was distilled. The oil was poured into dilute hydrochloric acid, extracted with ligroin, and the ligroin then distilled, giving 1.19 g. of tan, solid glycol. The glycol was chromatographed on a small column of alumina, using benzene as eluent. It was recrystallized from petroleum ether as a white, waxy solid, m.p. 64.5–65.5°.

Anal. Calcd. for $C_{27}H_{48}O_4$: C, 74.26; H, 11.08. Found: C, 74.24; H, 11.23.

Hydroxylation of I Using Osmium Tetraoxide.[9]—A solution of 1 g. (0.00394 mole) of osmium tetraoxide in 20 cc. of anhydrous ether (deep red color) was added to a solution of 1.6 g. of I in 25 cc. of anhydrous ether containing 0.8 g. of pyridine. The solution immediately turned reddish-brown in color; a brown scum soon coated the bottom of the flask. After 24 hours standing with occasional shaking, 35 cc. of 10% potassium hydroxide and 3 g. of mannitol were added and the solution was shaken thoroughly. The solution was shaken until the organic layer became colorless (the aqueous layer was now dark red). The organic layer was washed with diluted acid, then water. The ethereal solution was dried and the solvent distilled, leaving 1.45 g. of white solid, m.p. 97–99° (85%). After several recrystallizations from ligroin, there was obtained 1.06 g. (61.6%) of the white crystalline glycol, m.p. 99.8–100.5°. When the oxidation was carried out using piperidine in place of pyridine, hydroxylation still occurred; the yield of crude product was then 57%.

Anal. Calcd. for $C_{27}H_{48}O_4$: C, 74.26; H, 11.08. Found: C, 74.12; H, 11.18.

A sample of this glycol, m.p. 99.8–100.5°, was cleaved with periodic acid.[19] The nonanal was removed by steam distillation and recovered from the distillate by ether extraction. After drying, the ether was removed and the 0.22 g. of oily nonanal was treated with 15 cc. of a saturated solution of 2,4-dinitrophenylhydrazine in alcohol containing 1% hydrochloric acid. On warming a golden precipitate formed; m.p. 87.5–92°. Recrystallization from ethanol gave material melting sharply at 97.5°, showing no depression in melting point when mixed with an authentic sample of the 2,4-dinitrophenylhydrazone of nonanal.

Hydroxylation of the Poison Ivy Dimethylurushenol Using Osmium Tetraoxide.—Oxidation of a sample of dimethylurushenol[2] with osmium tetraoxide, using the procedure described above, gave a white crystalline glycol, m.p. 94–95° (from ligroin).

Anal. Calcd. for $C_{23}H_{40}O_4$: C, 72.59; H, 10.60. Found: C, 72.47; H, 10.70.

A sample of the glycol was cleaved with periodic acid[19] and the heptaldehyde was identified as the 2,4-dinitrophenylhydrazone.

Acknowledgment.—The authors are indebted to the Lederle Laboratories Division of the American Cyanamid Co. for a grant to Columbia University for support of this investigation.

NEW YORK, NEW YORK

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[18] E. C. Horning and M. G. Horning, *J. Org. Chem.*, **11**, 95 (1946).

[19] M. L. Malaprade, *Bull. soc. chim. France*, **1**, 833 (1934).