Macrocyclic Diterpene Hydroxy Ethers from Tobacco and Cigarette Smoke

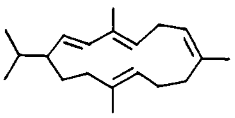
R. L. ROWLAND, ALAN RODGMAN, J. N. SCHUMACHER, DONALD L. ROBERTS, LAWRENCE C. COOK, AND W. E. WALKER, JR.

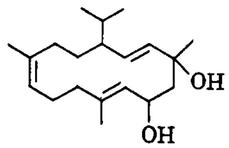
Research Department, R. J. Reynolds Tobacco Company, Winston-Salem, North Carolina

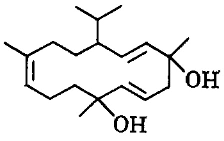
Received June 5, 1963

Diterpene ethers, isolated from tobacco and cigarette smoke, have been characterized as 12-isopropyl-1,5,9-trimethyl-5,8-oxido-3,9,13-cyclotetradecatrien-1-ol (α-IV) and two diastereoisomers of 12-isopropyl-1,5-dimethyl-9-methylen-5,8-oxido-3,13-cyclotetradecadien-1-ol (α- and β-V) by correlation with the previously characterized α-4,8,13-duvatriene-1,3-diol (α-II).

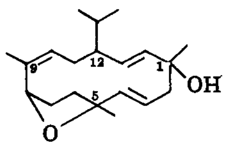
Within the past year, five naturally occurring diterpenes have been characterized as monocyclic compounds containing a C-14 ring. Cembrene (I), an unsaturated hydrocarbon isolated from *Pinus albicaulis*, was shown to be 14-isopropyl-3,7,11-trimethyl-1,3,6,10-cyclotetradecatetraene.[1] We reported earlier the isolation of four macrocyclic diterpene diols from tobacco leaf. Diterpenes designated α-4,8,13-duvatriene-1,3-diol (α-II) and β-4,8,13-duvatriene-1,3-diol (β-II) were characterized as diastereoisomers of 12-isopropyl-1,5,9-trimethyl-4,8,13-cyclotetradecatriene-1,3-diol (II).[2,3] The allylic isomers of II, designated α-3,8,13-duvatriene-1,5-diol (α-III) and β-3,8,13-duvatriene-1,5-diol (β-III), were shown, to be diastereoisomers of 12-isopropyl-1,5,9-trimethyl-3,8,13-cyclotetradecatriene-1,5-diol (III).[3,4]


I

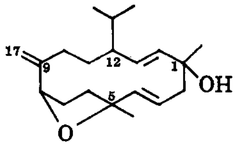

II


III

From tobacco and from tobacco smoke, we have isolated three additional diterpenes. At this time we wish to describe the characterization of these isomers, assigned the names α-5,8-oxido-3,9,13-duvatrien-1-ol (α-IV) and α- and β-5,8-oxido-3,9(17),13-duvatrien-1-ol (α- and β-V), as 12-isopropyl-1,5,9-trimethyl-5,8-oxido-3,9,13-cyclotetradecatrien-1-ol (IV) and 12-isopropyl-1,5-dimethyl-9-methylen-5,8-oxido-3,13-cyclotetradecadien-1-ol (V), respectively.



IV



V

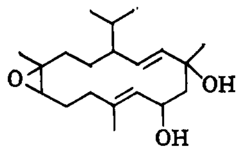
Isolation of the diterpene hydroxy ethers was accomplished by extraction of tobacco with organic solvents (methanol or hexane) followed by chromatographic separations of the extract. α-IV and α-V have been isolated from aged flue-cured, burley, and Turkish tobaccos while β-V was isolated from aged burley and Turkish tobaccos.

Elemental analysis of α-IV, m.p. 95–96°, $[\alpha]^{27}\text{D}$ +86°, indicates the formula $(C_{10}H_{16}O)_n$. The mass spectrum shows a parent mass of 304, which agrees with the formula $C_{20}H_{32}O_2$. Active hydrogen determinations show that only one of the oxygen atoms is present in a hydroxyl group.

The spectral properties of α-IV exhibited similarities to the macrocyclic diterpenes II and III. The infrared spectrum of α-IV includes a hydroxyl band at 2.9 and a strong band at 10.3 μ, characteristic of *trans* disubstituted double bonds. The n.m.r. spectrum[5] shows an isopropyl group (6 protons, 9.15), two $C\mathit{H}_3\text{-}\underset{|}{\overset{|}{C}}OR$ groups (6 protons, 8.70), one $C\mathit{H}_3\overset{|}{C}{=}\underset{|}{C}$ group (3 protons, 8.50), one $—\underset{|}{\overset{|}{C}}\mathit{H}OR$ (1 proton, 5.5), and five olefinic protons (4.3–4.65 τ). Absence of selective ultraviolet absorption above 220 mμ establishes the absence of conjugated double bonds.

Catalytic hydrogenation of α-IV yielded the saturated compound, $C_{20}H_{38}O_2$, indicating that α-IV contains three double bonds and two rings. Like α-IV, the hydrogenation product contains only one active hydrogen atom and shows no carbonyl absorption in its infrared spectrum. Hexahydro α-IV was not oxidized by chromic oxide in pyridine. Accordingly, α-IV must contain one tertiary hydroxyl and one ether group.

The expectation that one of the rings is a cyclic ether was verified by synthesis of α-IV from α-II. Synthesis of α-IV was accomplished in 50% yield *via* reaction of α-4,8,13-duvatriene-1,3-diol (α-II)[2] with perbenzoic acid and subsequent conversion of the intermediate epoxide to α-IV by a variety of acidic dehydration conditions.


VI

---

[1] W. G. Dauben, W. F. Thiessen, and P. R. Resnick, *J. Am. Chem. Soc.*, **84**, 2015 (1962).

[2] D. L. Roberts and R. L. Rowland, *J. Org. Chem.*, **27**, 3989 (1962).

[3] Nomenclature used in the series of compounds isolated from tobacco is based upon the name duvane for the structure 12-isopropyl 1,5,9-trimethylcyclotetradecane. The α- and β-designations have no absolute stereochemical significance. The diol isolated from tobacco in largest quantity was assigned the α-designation (α-II). Compounds subsequently shown to have the same configuration at the 1-position have likewise been assigned the α-designation.

[4] R. L. Rowland and D. L. Roberts, *J. Org. Chem.*, **28**, 1165 (1963).

[5] N.m.r. values are reported in τ units: G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

The initial product from reaction of α-II with perbenzoic acid showed elemental analyses and a mass spectrum for $C_{20}H_{34}O_3$, which agrees with an epoxide of α-II. Reaction of α-II with one equivalent of perbenzoic acid could result in formation of three epoxides, with epoxidation occurring at the double bonds in the 4-, 8-, or 13-positions.

Selection of VI for the structure of α-II epoxide was accomplished from the n.m.r. spectrum. The n.m.r. spectrum of α-II epoxide shows peaks at 9.15 (6 protons, isopropyl multiplet), 8.80 (3 protons, $\mathrm{C}H_3\overset{\overset{O}{\diagup\diagdown}}{\mathrm{C{-}C}}$), 8.62 (3 protons, $\mathrm{C}H_3\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{OR}$), 8.20 (3 protons, $\mathrm{C}H_3\overset{|}{\mathrm{C}}\mathrm{{=}C}$), 7.06 (1 proton, $\overset{\overset{O}{\diagup\diagdown}}{\mathrm{C}H\mathrm{{-}C}}$), 5.50 (1 proton, $-\overset{|}{\mathrm{C}}H\mathrm{OH}$), and 4.47–4.60 τ (3 olefinic protons). The epoxide which would result from epoxidation of the double bond in the 13-position of α-II was readily eliminated from consideration since it would contain two olefinic protons and two methyl groups attached to olefinic carbon.

Choice between structure VI, in which epoxidation had occurred at the double bond in the 8-position, and the compound which would have resulted from epoxidation of the double bond in the 4-position was made from consideration of the n.m.r. absorption of the methyl group attached to olefinic carbon. In the n.m.r. spectra of α-II and derivatives of α-II,[2] the 5-methyl group shows a split peak at 8.36 and the 9-methyl group shows a broad peak at 8.50 τ. The epoxide of α-II exhibits a split peak at 8.20 τ indicating that the 5-methyl group is attached to ethylenic carbon. Consequently, structure VI was assigned to the epoxide of α-II.[6]

Conversion of epoxide α-VI to α-IV was observed with acid, under conditions favorable for dehydration. Moderate yields of α-IV were obtained in reactions with anhydrous magnesium sulfate in refluxing toluene and with iodine in refluxing benzene. Convenient conversion of α-VI to α-IV was accomplished by room temperature contact of α-VI in chloroform solution with dilute aqueous sulfuric acid.

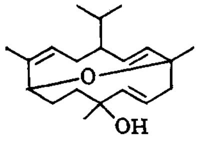
The conversion of epoxide α-VI ($C_{20}H_{34}O_3$) to α-IV ($C_{20}H_{32}O_2$) involves the elimination of water. This reaction cannot, however, be a simple dehydration. Dehydration of α-VI would be expected to yield an epoxide containing conjugated double bonds. The n.m.r. and ultraviolet spectra of α-IV show the absence of conjugated double bonds. The presence of an epoxide ring in α-IV is prohibited by the observations: (1) the ether ring of α-IV remains intact during catalytic hydrogenation; (2) α-IV was recovered from attempted reduction with lithium aluminum hydride; and (3) the n.m.r. spectrum of α-IV shows no absorption at 6.8–7.2 τ, the range expected for epoxide protons ($\overset{\overset{O}{\diagup\diagdown}}{\mathrm{{-}C}H\mathrm{{-}C}}$). Accordingly, the epoxide ring of α-VI must be changed during the dehydration reaction to an ether ring containing more than two carbon atoms.

Assignment of structure to α-IV has been approached by consideration of all mechanisms by which α-VI could be converted to a compound possessing the chemical and physical properties of α-IV. These properties of α-IV, as reported earlier, require the following structural features: three double bonds, none of which is conjugated; five olefinic protons; one methyl group attached to olefinic carbon; one tertiary alcohol grouping, $\mathrm{CH_3}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{OH}$; and a cyclic ether containing the partial structure, $\mathrm{CH_3}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{O}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{H}$. Also utilized in the consideration of possible structures for α-IV was the absence of a methylene group located between two double bonds, $\mathrm{C{=}C}\mathrm{C}H_2\mathrm{C{=}C}$. N.m.r. absorption at 7.1 τ has been reported[7] for a methylene group between two olefinic double bonds; α-IV shows no absorption between 5.7 and 7.5 τ.

Transformation of epoxide α-VI to the cyclic ether α-IV could occur only by reaction of the allylic alcohol systems with the epoxide ring (with allowance for rearrangement before or after the reaction). Three reaction mechanisms are discussed subsequently.

Application to VI of the accepted mechanism of reaction of an alcohol with the epoxide ring[8] could lead to four dihydroxy ethers, $C_{20}H_{34}O_3$. Subsequent dehydration could lead to twelve monohydroxy ether structures, $C_{20}H_{32}O_2$, each containing a seven-, eight-, or nine-membered ether ring. Consideration of the structural requirements for α-IV allows elimination of each of these twelve structures.

Since none of the structures resulting from dehydration following intramolecular reaction of the allylic hydroxyl groups with the epoxide ring of VI was acceptable for α-IV, consideration also was given to products which would result by this mechanism plus an allylic rearrangement. Two structures, VII and IV, which agree with the spectral properties of the hydroxy ether could be formed in such manner. Epoxide ring opening by the 1-hydroxyl group to form a 1,8-oxide bridge, dehydration to form the 9-double bond, and allylic rearrangement of the 3-hydroxyl group would yield VII. Structure IV could result from the sequence: allylic rearrangement of 3-hydroxyl to 5-hydroxyl, epoxide opening by the 5-hydroxyl group, and dehydration to form the 9-double bond.



VII

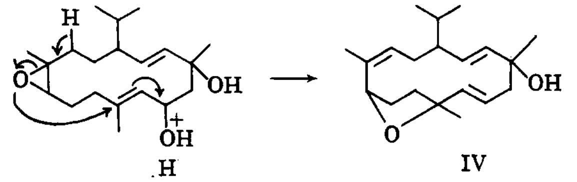
A second mechanism considered for conversion of α-VI to α-IV consists of a concerted allylic displacement of the alcohol group by epoxide oxygen. This

---

[6] We feel that the assignment of structure VI is well justified from this consideration of the n.m.r. spectrum. It is interesting to note that the alternative 4,5-oxide structure also may be eliminated on the basis that we have been unable to propose any structure agreeing with the properties of α-IV which would be derived from the 4,5-oxide. The development of structure of α-IV has been possible, however, by proceeding from the epoxide structure VI, as described subsequently.

[7] L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Inc., New York, N. Y., 1959, p. 60.

[8] R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).

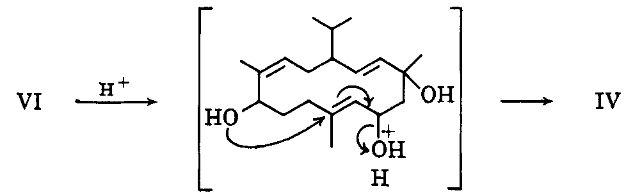


VI IV

mechanism is suggested by its similarity to the rearrangement of carotene epoxides to furanoid compounds.[9] In chloroform containing traces of mineral acid, carotene epoxides (VIII) were rearranged to IX. This rearrangement differs from dehydration of VI to IV only in that the displaced allylic oxygen function is also the epoxide oxygen.

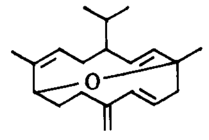
VIII IX

A third mechanism for conversion of epoxide VI to IV would involve the isomerization of the oxide function to an allylic alcohol,[10] a reaction which has been observed under conditions similar to those effective in preparation of α-IV from α-VI. Formation of α-IV could then result from allylic displacement of the 3-hydroxyl group by the newly formed 8-hydroxyl.

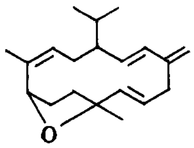


The preceding considerations of reactions whereby a cyclic ether could be formed from α-VI have led to only two structures acceptable for α-IV, structure VII and structure IV.

Elimination of structure VII was possible by consideration of the product isolated from dehydration of α-IV. Mild dehydration conditions (potassium hydrogen sulfate in refluxing dioxane for 3 hr., or *p*-toluenesulfonic acid in refluxing benzene for 3 min.) yielded an unsaturated ether, $C_{20}H_{30}O$, m.p. 41–42°. The ultraviolet absorption showed a maximum at 236 mμ (log ε 4.40). The n.m.r. spectrum showed peaks at 9.13 (6 protons, isopropyl), 8.70 (3 protons, $CH_3\overset{|}{\underset{|}{C}}OR$), 8.50 (3 protons, $CH_3\overset{|}{C}=\underset{|}{C}$), 7.08 (2 protons, $C=CCH_2$-$\underset{|}{C}=C$), 5.50 (1 proton, $-\overset{|}{C}HOR$), 5.04 (2 protons, $C=CH_2$), and 3.90–4.9 τ (5 olefinic protons). N.m.r. peaks for one vinyl methyl group and seven olefinic protons would require the dehydration product derived from structure VII to be an ether of structure X. However, structure X does not contain a methylene group between two double bonds, $C=CCH_2C=C$, required by n.m.r. absorption for two protons at 7.08 τ.[7] Consequently, structure VII is not acceptable for the ethereal alcohol isolated from tobacco.



X

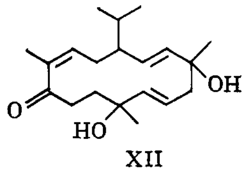


XI

The properties of the ether formed by mild dehydration of α-IV are in agreement with structure XI. The dehydration of α-IV to XI with formation of an exocyclic double bond is in agreement with previous observation that elimination of the 1-hydroxyl by dehydration of the α isomers in the duvatriene family (*i.e.*, dehydration of α-4,8,13-duvatrien-1-ol-3-one) yields an exocyclic double bond.[2] Structure XI includes the $C=CCH_2C=C$ grouping, the absence of which eliminates structure X from consideration. Accordingly, the structure 12-isopropyl-1,5,9-trimethyl-5,8-oxido-3,9,13-cyclotetradecatrien-1-ol (IV) is proposed for α-IV.

It is important to note that the 1-hydroxyl group is not involved in the reaction sequence α-II → α-VI → α-IV. Accordingly, the configuration at the 1-position is identical in α-II and α-IV; *i.e.*, both compounds are of the α-series.

Oxidation of α-IV yielded an interesting product. Although hexahydro α-IV was recovered in 90% yield from attempted chromic oxide–pyridine oxidation, α-IV was oxidized by chromic oxide in pyridine. The oxidation product, $C_{20}H_{32}O_3$, contains two active hydrogen atoms. Strong infrared absorption at 6.05 μ and maximum ultraviolet absorption at 235 mμ (log ε 4.0) indicate an α,β-unsaturated ketone. The n.m.r. spectrum shows the presence of an isopropyl group, two $CH_3\overset{|}{\underset{|}{C}}OR$ groups, one $CH_3\overset{|}{\underset{|}{C}}=C$ group, and five olefinic protons. Structure XII, resulting from cleavage of the ether ring of α-IV, is proposed for the oxidation product.



XII

A second ethereal diterpene isolated from tobacco, α-V, is an isomer of α-IV. The mass spectrum, elemental analysis, and active hydrogen determination showed that α-V, m.p. 109–110°, $[\alpha]^{25}D$ +77.4°, possesses the formula $C_{20}H_{31}O(OH)$. Catalytic hydrogenation of α-V yielded a product identical with that obtained by catalytic hydrogenation of α-IV. Consequently, on the basis of the structure assigned to α-IV in the preceding discussion, α-V contains the duvane ring system with the 5,8-oxide bridge, a hydroxyl group of the α-configuration at the 1-position, and three double bonds. Structure assignment for α-V, exclusive of configuration, then requires the location of the double bonds.

Comparison of the n.m.r. spectrum of α-V with that of α-IV is of particular interest. α-V was similar to α-IV in showing an isopropyl multiplet (9.13), two methyl groups of the type $CH_3\overset{|}{\underset{|}{C}}OR$ (8.72), and one

---

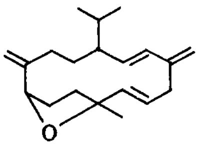
[9] P. Karrer and E. Jucker, *Helv. Chim. Acta*, **28**, 300, 427 (1945).

[10] L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp. 243, 244.

proton of the type —C*H*OR (5.65 τ). The remainder of the n.m.r. spectrum of α-V showed general similarity to the n.m.r. spectrum of α-IV with two major differences: α-V did not show absorption for methyl attached to ethylenic carbon and α-V contained six olefinic protons (4.55–5.25 τ), including the protons of an exocyclic methylene group. The presence of only four methyl groups in the n.m.r. spectrum of α-V, compared to five methyl groups in the n.m.r. spectrum of α-IV, requires that one of the three double bonds of α-V be utilized in attachment of an exocyclic methylene group at the 9-position.

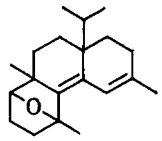
Assignment of the two other double bonds to the 3- and 13-positions was accomplished by further consideration of the n.m.r. spectrum. Absorption of —C*H*OR as a triplet, the appearance of the isopropyl multiplet at 9.13 τ, and the absence of conjugated double bonds eliminate location of double bonds at the 6-, 11-, 12-, and 10-positions, leaving only the 2-, 3-, and 13-positions available for the two double bonds. If the double bonds were located at the 2- and 13-positions, the greatly different environments of the 1- and 5-methyl groups would be expected to result in distinctly different n.m.r. peaks for these two methyls. Instead, the 1- and 5-methyl groups of α-V show absorption as a single peak at 8.72 τ. The equivalence of n.m.r. absorption of the two C*H*$_3$COR groupings is in agreement with locations of the double bonds in the 3- and 13-positions, whereby both methyl groups are in the similar $CH_2C(CH_3)(OR)CH{=}CH$ arrangement. Consequently, the double bonds were assigned to the 3- and 13-positions and the structure 12-isopropyl-1,5-dimethyl-9-methylen-5,8-oxido-3,13-cyclotetradecadien-1-ol (V) was assigned to α-V.

Assignment of structure V was verified by the products obtained by dehydration of α-V. Dehydration of α-V using potassium hydrogen sulfate yielded, as the major product, an unsaturated ether, m.p. 70–71°. The mass spectrum and elemental analysis indicated a molecular formula $C_{20}H_{30}O$. Maximum ultraviolet absorption occurs at 237 mμ (log ε 4.28). The appearance of eight olefinic protons in the n.m.r. spectrum shows that dehydration occurred without cyclization. Of the olefinic protons, four protons are present in terminal methylene groups (5.04 τ), in agreement with predominantly exocyclic dehydration in the α-duvane series. The n.m.r. spectrum (isopropyl multiplet, 9.12; C*H*$_3$COR, 8.70; —C*H*OR, 5.55; and especially C=CC*H*$_2$C=C, 7.07 τ) allows assignment of structure XIII to the dehydration product; from the assignment of structure XIII to the dehydration product, the 3- and 13-positions of the endocyclic double bonds in α-V are confirmed.



XIII

Dehydration of α-V by *p*-toluenesulfonic acid yielded an interesting tetracyclic ether, $C_{20}H_{30}O$, m.p. 50–51°. From consideration of the n.m.r. spectrum (angular methyl, 9.25; isopropyl multiplet, 9.06; C*H*$_3$COR, 8.77; C*H*$_3$C=C, 8.22; —C*H*OR, 6.28; one olefinic proton, 3.98 τ) and the ultraviolet absorption (λ$_{max}$ 251 mμ, log ε 3.99), structure XIV is proposed for the tetracyclic ether.



XIV

A third ethereal diterpene, β-V, isolated from tobacco in trace amounts, is assigned a structure differing from α-V only in configuration at the 1-position. The mass spectrum and elemental analysis showed that β-V, m.p. 108–109°, $[\alpha]^{25}D$ +72.5°, possesses the molecular formula $C_{20}H_{32}O_2$. The n.m.r. spectrum of β-V is remarkably similar to that of α-V. The only difference in the spectra of α- and β-V is the position of one of the methyl peaks of the C*H*$_3$COR groupings: in α-V, the C*H*$_3$COR methyl groups appear as a single peak (6 protons) at 8.72; in β-V, the C*H*$_3$COR groups appear as peaks at 8.70 (3 protons) and 8.62 τ (3 protons). The n.m.r. spectra suggest that β-V differs from α-V only in configuration at one of the CH_3COR groupings.

Dehydration of β-V using potassium hydrogen sulfate in dioxane yielded an unsaturated ether, m.p. 70–71°, which showed infrared, mass, and n.m.r. spectra identical with the spectra of the unsaturated ether XIII obtained from dehydration of α-V. Formation of XIII from β-V allows the assignment to β-V of the structure 12-isopropyl-1,5-dimethyl-9-methylen-5,8-oxido-3,13-cyclotetradecadien-1-ol (V) with configurations identical with those of α-V except at the 1-position. Accordingly, β-V is assigned to the β-series relative to configuration at the 1-position.

Isolation from tobacco of seven macrocyclic diterpenes (α- and β-II, α- and β-III, α-IV, and α- and β-V) suggests the tobacco leaf as a source for compounds of the newly characterized diterpene structure containing the cyclotetradecane ring. Unfortunately, the macrocyclic diterpenes have been isolated from tobacco in small quantities, with the total amount of all seven characterized diterpenes constituting less than 0.02% of the dry weight of tobacco.

Of special interest is the isolation of ethereal diterpenes from cigarette smoke. The observation that α-IV and α-V are present in tobacco smoke stands in contrast to the apparent absence of the diterpenediols II and III in cigarette smoke (although α- and β-II are present in tobacco in much larger quantities than α-IV and α-V). The absence of indications for presence of α- and β-II and α- and β-III in smoke is likely related to the previously noted instability of the diols II and III.[2] Relative to II and III, α-IV and α-V are stable compounds.

Experimental[11]

Isolation of α-5,8-Oxido-3,9,13-duvatrien-1-ol (α-IV) and α- and β-5,8-Oxido-3,9(17),13-duvatrien-1-ol (α- and β-V) from Tobacco.—Isolation of α-IV and α- and β-V from tobacco was accomplished by procedures essentially the same as those reported earlier[2,4] for isolation of α- and β-II and α- and β-III. In chromatographic separations, α-IV and α- and β-V were eluted appreciably earlier than α- and β-II and III. From silicic acid, the diterpenes were eluted in the sequence: α-IV, α-V, β-V, α-III, β-III, α-II, and β-II.

α-IV and α-V have been isolated from aged, flue-cured burley, and Turkish tobacco. β-V has been isolated from aged burley and Turkish tobacco. The quantities of pure α-IV and α-V isolated from tobacco amounted to 0.0003% of the tobacco weight. β-V was isolated in only trace amounts.

Isolation of α-5,8-Oxido-3,9,13-duvatrien-1-ol (α-IV) and α-5,8-Oxido-3,9(17),13-duvatrien-1-ol (α-V) from Turkish Tobacco Smoke.—Partition fractions lower layers 2, 3, 2′, 3′, and 4′ from Turkish tobacco smoke after removal of pyrocoll and the homologous indoles and carbazoles,[12] were combined with lower layers 1, 1′, and 5′ to yield 308 g. of material. Repeated chromatography using silicic acid, Florisil, and alumina yielded an alcohol fraction weighing 3.0 g. Rechromatography using Florisil yielded three main fractions. The first, eluted by 1:49 ether–hexane, gave an infrared spectrum identical with that of α-V isolated from tobacco. The third, eluted by 1:24 ether–hexane, gave an infrared spectrum identical with that of α-IV isolated from tobacco. The second fraction contained both α-IV and α-V.

The fraction rich in α-IV, after repeated chromatography on Florisil, was crystallized from hexane at −27° to yield 0.31 g. of α-IV, m.p. 94–95°. A mixture melting point with a sample of α-IV from tobacco gave no depression. The infrared spectra of the smoke- and tobacco-derived samples were identical.

The fraction rich in α-V was treated in the same manner to yield 0.76 g. of α-V, m.p. 109–110°. A mixture melting point with a sample of α-V from tobacco gave no depression. The infrared and n.m.r. spectra of the smoke- and tobacco-derived samples were identical.

Physical Properties of α-5,8-Oxido-3,9,13-duvatrien-1-ol (α-IV).—α-IV crystallized from hexane in needles melting at 95–96°; $[\alpha]^{27}\text{D}$ +86°. α-IV shows no selective absorption of ultraviolet light. Infrared absorption occurs at 2.9, 9.6, 10.3, and 13.1 μ; n.m.r. spectrum, 9.13 (6), 8.70 (6), 8.50 (3), 5.5 (1), and 4.3–4.65 τ (5).

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.60; active H (1), 0.33; mol. wt., 304. Found: C, 78.99; H, 10.54; active H (Grignard), 0.3; active H (tritium exchange), 0.33; mass, 304.

α-IV was recovered in quantitative yield from attempted reduction using a large excess of lithium aluminum hydride in ether.

Catalytic Hydrogenation of α-5,8-Oxido-3,9,13-duvatrien-1-ol (α-IV).—From the hydrogenation of 223 mg. of α-IV using Adams' catalyst in ethyl acetate (24 hr. at 3 atm.), chromatography using silicic acid allowed the isolation of 190 mg. of hydrogenation product, m.p. 116–118°. Recrystallization from hexane at −27° raised the melting point to 118–120°.

Anal. Calcd. for $C_{20}H_{38}O_2$: C, 77.37; H, 12.33; active H (1), 0.32; mol. wt., 310. Found: C, 77.70; H, 12.43; active H (Grignard), 0.35; active H (tritium exchange), 0.28; mass, 310.

Hexahydro α-IV was recovered from attempted reaction with chromic oxide–pyridine at 25° for 22 hr.

Chromic Oxide–Pyridine Oxidation of α-5,8-Oxido-3,9,13-duvatrien-1-ol (α-IV).—To a slurry of 1.2 g. of chromic oxide in 10 ml. of pyridine was added α-IV (300 mg.). After 2 days at room temperature, the reaction mixture was processed by the standard procedure followed by chromatography using silicic acid to yield 220 mg. of material showing infrared absorption at 3.0 and 6.05 μ. The oxidation product, after recrystallization from an ether–hexane solution, melted at 144.5–146.5°; $[\alpha]^{26}\text{D}$ +63°; $\lambda_{\text{max}}^{\text{EtOH}}$ 235 mμ (log ε 4.0); n.m.r. spectrum, 9.07 (6), 8.73 (3), 8.65 (3), 8.27 (3), 4.4–4.6 (4), and 3.4 τ (1).

Anal. Calcd. for $C_{20}H_{32}O_3$: C, 74.96; H, 10.46; active H (2), 0.63; mol. wt., 320. Found: C, 74.92; H, 10.14; active H (tritium exchange), 0.59; mass, 302 (320–18).

The ketone obtained from oxidation of α-IV was recovered unchanged from refluxing with 1:1 ethanol–10% sodium hydroxide solution for 5 hr.

Dehydration of α-5,8-Oxido-3,9,13-duvatrien-1-ol (α-IV).—A mixture of 100 mg. of α-IV, 200 mg. of potassium hydrogen sulfate, and 10 ml. of anhydrous, peroxide-free dioxane was refluxed for 3 hr. The dioxane solution was decanted from the potassium hydrogen sulfate and concentrated to yield a pale yellow oil (93 mg.). Chromatography of this oil on Florisil yielded 49 mg. of a colorless solid, m.p. 41–42°; $\lambda_{\text{max}}^{\text{cyclohexane}}$ 236 mμ (log ε 4.4). Infrared absorption occurred at 6.10, 6.23, 10.35, 11.3, and 11.7 μ; n.m.r. spectrum, 9.13 (6), 8.70 (3), 8.50 (3), 7.08 (2), 5.50 (1), 5.04 (2), and 3.9–4.9 τ (5).

Anal. Calcd. for $C_{20}H_{30}O$: C, 83.85; H, 10.56; mol. wt., 286. Found: C, 83.77; H, 10.68; mass, 286.

The same product was obtained in 40% yield when a mixture of α-IV (100 mg.), *p*-toluenesulfonic acid (60 mg.), and benzene (10 ml.) was refluxed for 3 min.

Perbenzoic Acid Oxidation of α-4,8,13-Duvatriene-1,3-diol (α-II).—To a chilled solution of α-4,8,13-duvatriene-1,3-diol (α-II, 4.8 g.) in 30 ml. of chloroform was added 27 ml. of cold chloroform solution containing 1.0 g. of perbenzoic acid. After the reaction mixture remained at 25° for 18 hr., it was diluted with 200 ml. of pentane and was washed with two 100-ml. portions of 10% sodium hydroxide solution. Concentration of the organic phase and chromatography using silicic acid yielded 2.5 g. of unchanged α-II and 2.0 g. of oxidation product. The oxidation product (α-VI), after two recrystallizations from ether–hexane solutions, melted at 103–105°. Infrared absorption occurred at 2.95, 8.45, 9.40, 9.9, and 10.20 μ; n.m.r. spectrum, 9.15 (6), 8.80 (3), 8.62 (3), 8.20 (3), 7.06 (1), 5.50 (1), and 4.47–4.60 (3).

Anal. Calcd. for $C_{20}H_{34}O_3$: C, 74.49; H, 10.62; mol. wt., 322. Found: C, 74.11; H, 10.46; mass, 304 (322–18).

Conversion of α-8,9-Oxido-4,13-duvadiene-1,3-diol (α-VI) to α-5,8-Oxido-3,9,13-duvatrien-1-ol (α-IV). Method A.—A solution of 0.967 g. of α-VI in 40 ml. of chloroform was allowed to stand with occasional shaking at 25° for 20 hr. with 1 ml. of 2 *N* sulfuric acid. The reaction mixture was diluted with 120 ml. of hexane and was washed successively with 30 ml. of water, with 50 ml. of 10% sodium hydroxide solution, and with three 30-ml. portions of saturated salt solution. The residue from concentration of the organic phase was separated by chromatography on silicic acid to yield 0.324 g. (30%) of α-IV and 0.620 g. of material showing the infrared absorption of α-VI. α-IV synthesized by this reaction showed infrared absorption identical with that of naturally occurring α-IV, melted at 95–97° after recrystallization from pentane, and showed no depression of melting point when mixed with authentic α-IV. Treatment of 0.402 g. of recovered α-VI with 15 ml. of chloroform and 12 drops of 2 *N* sulfuric acid for 40 hr. resulted in formation of an additional 0.200 g. of α-IV.

Method B.—A mixture of 0.130 g. of α-VI, 1.5 g. of anhydrous magnesium sulfate, and 15 ml. of toluene was heated under reflux for 2.5 hr. The residue from concentration of the solution was chromatographed twice on silicic acid to yield 30 mg. of material showing the infrared spectrum of α-IV.

Method C.—A mixture of 0.227 g. of α-VI, a catalytic amount of iodine, and 30 ml. of benzene was heated under reflux for 2.5 hr. The reaction mixture was diluted with 40 ml. of ether and was washed with two 25-ml. portions of sodium metabisulfite solution. The residue from concentration of the organic phase was chromatographed twice on silicic acid to yield 110 mg. of material with the infrared spectrum of α-IV.

---

(11) All melting points were determined using a Fisher-Johns melting point apparatus and are uncorrected. All rotations were measured in chloroform solutions. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich., and Huffman Microanalytical Laboratories, Wheatridge, Colo. Active hydrogen determinations designated "tritium exchange" were made by the procedure of Giles, *Anal. Chem.*, **32**, 1716 (1960). Nuclear magnetic resonance (n.m.r.) spectra were run in deuterated chloroform solution using a Varian Associates HR-60 instrument and are reported by τ-values[5] with the number of protons in parentheses. We are indebted to John J. Whalen and Johnnie L. Stewart for infrared spectra, to George W. Young for mass spectra, to J. A. Giles and P. H. Ayers for active hydrogen determinations, to Bruce W. Woosley, Max A. Wagoner, Richard F. Walsh, Anthony Angel, and Earl Hester for technical assistance, and to Dr. M. Senkus and Dr. C. E. Teague, Jr., for helpful discussions

(12) A. Rodgman and L. C. Cook, *Tobacco Sci.*, **6**, 174 (1962).

Physical Properties of α-5,8-Oxido-3,9(17),13-duvatrien-1-ol (α-V).—α-V, recrystallized from hexane or pentane, melts at 109–110°, and shows no selective absorption of ultraviolet light; $[\alpha]^{25}\text{D}$ +77.4°. Infrared absorption occurred at 2.95, 6.05, 9.3, 10.2, 11.1, and 11.6 μ; n.m.r. spectrum, 9.13 (6), 8.72 (6), 5.2 (2), and 4.55–4.9 τ (4).

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.60; active H (1), 0.33; mol. wt., 304. Found: C, 78.86; H, 10.69; active H (tritium exchange), 0.29; mass, 304.

Catalytic Hydrogenation of α-5,8-Oxido-3,9(17),13-duvatrien-1-ol (α-V).—Catalytic hydrogenation of 267 mg. of α-V using Adams' catalyst in ethyl acetate (24 hr. at 3 atm.), followed by chromatography of the product on silicic acid, allowed isolation of 250 mg. of hexahydro α-V, m.p. 117–119°. The infrared absorption of hexahydro α-V was identical with that of hexahydro α-IV and a mixture of hexahydro α-V and hexahydro α-IV melted at 118–119°.

Anal. Calcd. for $C_{20}H_{38}O_2$: C, 77.37; H, 12.33; mol. wt., 310. Found: C, 77.53; H, 12.18; mass, 310.

Dehydration of α-5,8-Oxido-3,9(17),13-duvatrien-1-ol (α-V) to 5,8-Oxido-1(15),3,9(17),13-duvatetraene (XIII).—A mixture of 0.20 g. of α-V, 0.40 g. of potassium hydrogen sulfate, and 20 ml. of anhydrous, peroxide-free dioxane was refluxed for 3 hr. The cooled solution was decanted from the potassium hydrogen sulfate, concentrated, and the residue (190 mg.) chromatographed on Florisil. The fractions eluted by 1:99 ether-hexane yielded a colorless oil (90 mg.) which slowly solidified. The solid, XIII, melted at 66–67°. Crystallization from methyl alcohol raised the melting point to 70–71°. XIII showed infrared absorption at 6.08, 6.25, 10.3, 11.3, and 11.6 μ; $\lambda_{\max}^{\text{cyclohexane}}$ 237 mμ (log ϵ 4.28); n.m.r. spectrum, 9.12 (6), 8.70 (3), 7.07 (2), 5.55 (1), 5.06 (4), and 3.9–4.6 τ (4).

Anal. Calcd. for $C_{20}H_{30}O$: C, 83.85; H, 10.56; mol. wt., 286. Found: C, 83.03; H, 10.46; mass, 286.

Dehydration and Cyclization of α-5,8-Oxido-3,9(17),13-duvatrien-1-ol (α-V).—A solution of α-V (200 mg.) and p-toluenesulfonic acid (120 mg.) in benzene (10 ml.) was refluxed for 30 min., cooled to 25°, diluted with ether (50 ml.), and washed with a total of 25 ml. of 5% sodium carbonate solution. The organic phase, after treatment with anhydrous sodium sulfate, was concentrated to yield 190 mg. of a pale yellow, viscous oil. Chromatography on Florisil yielded a colorless oil which readily solidified. The solid (XIV, 90 mg.) melted at 49–50°. Crystallization from hexane at −27° raised the melting point to 50–51°; $\lambda_{\max}^{\text{cyclohexane}}$ 251 mμ (log ϵ 3.99). Infrared absorption occurred at 6.15, 9.75, and 12.0 μ; n.m.r. spectrum, 9.25 (3), 9.06 (6), 8.77 (3), 8.22 (3), 6.28 (1), and 3.98 τ (1).

Anal. Calcd. for $C_{20}H_{30}O$: C, 83.85; H, 10.56; mol. wt., 286. Found: C, 83.11; H, 10.44; mass, 286.

Cyclization of 5,8-Oxido-1(15),3,9(17),13-duvatetraene.—A mixture of XIII (25 mg.) and p-toluenesulfonic acid (10 mg.) in benzene (5 ml.) was refluxed for 30 min. The reaction mixture was processed as in the preceding section to yield 22 mg. of pale yellow oil. Chromatography on Florisil yielded 13 mg. of a colorless solid, m.p. 46–48°, whose infrared and ultraviolet absorption spectra were identical with those previously recorded for the sample of XIV.

Physical Properties of β-5,8-Oxido-3,9(17),13-duvatrien-1-ol (β-V).—β-V, after recrystallization from hexane, melted at 108–109°, $[\alpha]^{25}\text{D}$ +72.5°. β-V shows no selective ultraviolet absorption other than end absorption; infrared spectrum, 3.10, 6.10, 8.95, 9.30, 10.25, 10.82, 11.30, and 11.60 μ; n.m.r. spectrum, 9.12 (6), 8.70 (3), 8.62 (3), 4.50–5.52 (6).

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.60; mol. wt., 304. Found: C, 78.77; H, 10.64; mass, 304.

A mixture of β-V and α-V melted at 70–95°.

Dehydration of β-5,8-Oxido-3,9(17),13-duvatrien-1-ol (β-V).—A mixture of β-V (188 mg.), potassium hydrogen sulfate (400 mg.), and 20 ml. of dioxane was heated under reflux for 3 hr. The residue from concentration of the dioxane solution was chromatographed on Florisil; the dehydration product was eluted with 1% ether in pentane. The infrared, mass, and n.m.r. spectra of the unsaturated ether (61 mg.), m.p. 70–71° after recrystallization from methyl alcohol, were identical with the spectra of the product obtained by potassium hydrogen sulfate dehydration of α-V.

Anal. Calcd. for $C_{20}H_{30}O$: C, 83.85; H, 10.56; mol. wt., 286. Found: C, 84.14; H, 10.25; mass, 286.

Ion Radicals. IV.[1] The Electron Spin Resonance Spectra of Substituted Thianthrenes in Sulfuric Acid Solution

H. J. SHINE, C. F. DAIS, AND R. J. SMALL

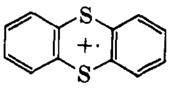
The Department of Chemistry, Texas Technological College, Lubbock, Texas

Received May 20, 1963

Fifteen thianthrenes with substituents in the 1-, 2-, and 2,7-positions have been prepared. Each of the thianthrenes dissolves in 96% sulfuric acid to give a colored, paramagnetic solution. The e.s.r., ultraviolet, and visible spectra of these solutions have been recorded. The hyperfine structures of the e.s.r. spectra are in accord with the recent proposals[1] for the structure of the thianthrene positive ion radical and the major coupling of the 2,3,7,8-protons. The g-values of all but one of the thianthrenes were close to 2.008–2.009. The exception was 2,7-dibromothianthrene with a g-value of 2.0101. Line widths and hyperfine splittings are reported.

Solutions of thianthrene in concentrated sulfuric acid are purple in color[2,3] and are paramagnetic.[1,4-10] Solutions of thianthrene in solvents containing Lewis acids such as aluminum chloride[1b,8,9] and antimony pentachloride[8,9] exhibit paramagnetic resonance.

The formation of a paramagnetic species in these systems has been interpreted[1,7,9,10] as a one-electron oxidation to give the ion radical I.



I

---

[1] (a) Presented at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963; (b) part I, H. J. Shine and L. Piette, *J. Am. Chem. Soc.*, **84**, 4798 (1962); (c) part II, H. J. Shine, C. F. Dais, and R. J. Small, *J. Chem. Phys.*, **38**, 569 (1963); (d) supported by the Directorate of Chemical Sciences, Air Force Office of Scientific Research, grants AF-AFOSR-61-48 and AF-AFOSR-23-63, to whom we express our thanks.

[2] K. Fries and W. Vogt, *Ber.*, **44**, 756 (1911).

[3] K. Fries and W. Vogt, *Ann.*, **381**, 312 (1911).

[4] J. M. Hirshon, D. M. Gardner, and C. R. Fraenkel, *J. Am. Chem. Soc.*, **75**, 4115 (1953).

[5] J. E. Wertz and J. Vivo, *J. Chem. Phys.*, **23**, 2193 (1955).

[6] A. Fava, P. B. Sogo, and M. Calvin, *J. Am. Chem. Soc.*, **79**, 1078 (1957).

[7] W. C. Needler, Ph.D. thesis, University of Minnesota, August, 1961 [*Dissertation Abstr.*, **22**, 3873 (May, 1962)]. At the time of submission of our first papers in this series we were not aware of the work of Professor J. E. Werz and Dr. Needler. We wish to thank Dr. E. T. Kaiser, Washington University, for calling our attention to this thesis.

[8] M. Kinoshita and H. Akamatu, *Bull. Chem. Soc. Japan*, **35**, 1040 (1962).

[9] M. Kinoshita, *ibid.*, **35**, 1137 (1962).

[10] E. A. C. Lucken, *J. Chem. Soc.*, 4963 (1962).