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Macrocyclic Diterpenes Isolated from Tobacco. α- and β-3,8,13-Duvatriene-1,5-diols

R. L. Rowland and Donald L. Roberts

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

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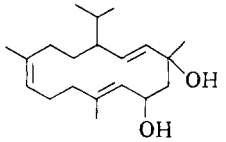
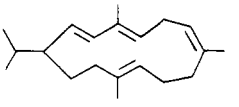
Two macrocyclic diterpenes, α- and β-3,8,13-duvatriene-1,5-diols, isolated from tobacco, are shown to be diastereoisomers of 12-isopropyl-1,5,9-trimethyl-3,8,13-cyclotetradecatriene-1,5-diol (II). These compounds provide two additional examples of the newly characterized naturally occurring diterpene series containing a fourteen-membered ring.

In the preceding paper relating to the constituents of tobacco,[1] we have reported the isolation and characterization of two novel macrocyclic diterpenes. These diterpenes, designated α-4,8,13-duvatriene-1,3-diol (α-I) and β-4,8,13-duvatriene-1,3-diol (β-I), were shown to be diastereoisomers of 12-isopropyl-1,5,9-trimethyl-4,8,13-cyclotetradecatriene-1,3-diol (I). Since this work was completed, cembrene, an unsaturated hydrocarbon isolated from *pinus albicaulis*, has been characterized as 14-isopropyl-3,7,11-trimethyl-1,3,6,10-cyclotetradecatetraene[2] (named as 12-isopropyl-1,5,9-trimethyl-1,4,8,13-cyclotetradecatetraene by the numbering system used in this paper). The structural similarities of cembrene and the diols isolated from tobacco are obvious. Cembrene and the tobacco diols possess the same locations of isopropyl and methyl groups on a cyclotetradecane ring and three double bonds are located in identical positions. Cembrene and the tobacco diols are the first examples of macrocyclic diterpenes and are the first terpenes reported to contain the 14-carbon ring system.

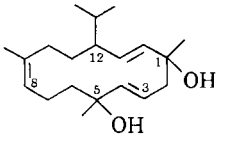


I



Cembrene

At this time we wish to describe the characterization of two additional diterpenes of related structure which we have isolated from tobacco. The new compounds, assigned the names α-3,8,13-duvatriene-1,5-diol[3a] (α-II) and β-3,8,13-duvatriene-1,5-diol[3a] (β-II), are allylic isomers of the compounds of structure I and are demonstrated to be diastereoisomers of 12-isopropyl-1,5,9-trimethyl-3,8,13-cyclotetradecatriene-1,5-diol (II).



II

Because tobacco contains larger quantities of β-II than α-II, characterization studies were initiated upon the β-isomer.

Elemental analyses and active hydrogen determination showed that β-II, m.p. 150–152°, $[\alpha]^{25}D$ + 40°, possesses the formula $C_{20}H_{32}(OH)_2$. The mass spectrum is similar to that of α-I and β-I in showing the fragment of greatest mass at 288, corresponding to the loss of water from the formula $C_{20}H_{34}O_2$. The infrared absorption of β-II indicates that it is an allylic tertiary alcohol (3.0, 9.0 μ) containing a *trans* disubstituted olefinic linkage (10.25 μ). The n.m.r. spectrum[3b] shows the presence of an isopropyl group (6 protons, 9.15 p.p.m.), two CH_3COH groups (6 protons, 8.61 and 8.65 p.p.m.), one $C(CH_3)=C$ group (3 protons, 8.50 p.p.m.), and five olefinic protons. Quantitative hydrogenation proved the presence of three double bonds and one ring. The absence of selective ultraviolet absorption by β-II shows that none of the double bonds are conjugated.

Catalytic hydrogenation of β-II using Adams' catalyst in ethyl alcohol yielded three products: a monohydroxyl compound, alcohol A; and two isomeric diols, alcohols B and C. The major product from hydrogenation, alcohol C, was stable to the oxidizing action of chromic oxide in pyridine or in acetic acid–water. The resulting conclusion that both hydroxyl groups are tertiary is in agreement with the n.m.r. spectra of β-II, alcohol B, and alcohol C, all of which show the presence

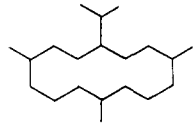
(1) D. L. Roberts and R. L. Rowland, *J. Org. Chem.*, **27**, 3989 (1962).

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

(3) (a) The nomenclature used in this series of compounds is based on the name duvane previously assigned to the structure 12-isopropyl-1,5,9-trimethylcyclotetradecane. The α- and β-designations have no absolute stereochemical significance but the α- and β-compounds of the 3,8,13-duvatriene-1,5-diol structure are each related to the correspondingly designated compound of the 4,8,13-duvatriene-1,3-diol structure. (b) N.m.r. values are reported in τ units: G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

of two CH_3COH groupings (six protons at 8.6–8.8 p.p.m.). Moreover, the formation of the monohydric alcohol, alcohol A, from hydrogenation of β-II, indicates that at least one of the hydroxyls of β-II is allylic.

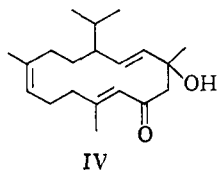
Hydrogenation of β-II using Adams' catalyst in acetic acid gave, in addition to the three alcohols obtained with Adams' catalyst in ethyl acetate, a saturated hydrocarbon III in 7% yield. The same hydrocarbon was obtained in 90% yield by dehydration of the saturated monohydric alcohol A followed by catalytic hydrogenation. Since the product from dehydration of alcohol A should contain only one double bond, it was not susceptible to cyclization reactions and the saturated hydrocarbon III was anticipated to have the same carbon skeleton as that of β-II. Moreover, hydrocarbon III showed infrared absorption identical with that of the saturated hydrocarbon obtained by hydrogenolysis of β-4,8,13-duvatriene-1,3-diol (β-I). Since β-4,8,13-duvatriene-1,3-diol (β-I) has been shown to be 12-isopropyl - 1,5,9 - trimethyl - 4,8,13 - cyclotetradecatriene-1,3-diol (I),[1] hydrocarbon III is 12-isopropyl-1,5,9-trimethylcyclotetradecane, *i.e.*, duvane. Accordingly, β-II must be an unsaturated diol with the carbon skeleton of III, containing a cyclotetradecane ring with isopropyl and methyl substitutions in the same positions as in the 4,8,13-duvatriene-1,3-diols (I).



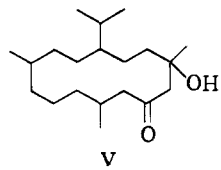
III

To complete the characterization of β-II except for stereochemical assignments, it is then necessary to assign the positions of the two hydroxyl groups and the three double bonds in the cyclotetradecane ring. From the n.m.r. spectrum of β-II and its hydrogenation products and from the absence of reaction of hexahydro-β-II (alcohol C) with oxidizing agents, the hydroxyl groups are located, along with two of the methyl groups, at the 1,5- or 1,9-positions. The n.m.r. spectrum of β-II requires that the third methyl group be attached to an olefinic double bond. The locations of the remaining two double bonds are limited in that at least one double bond is allylic to a hydroxyl and none of the double bonds are conjugated.

Surprisingly, although alcohol C (hexahydro-β-II) was not oxidized by chromic oxide, β-II was oxidized using a large excess of chromic oxide in pyridine. The major product (16–31% yield) was an oil with infrared, ultraviolet, and n.m.r. spectra identical with the spectra of β-4,8,13-duvatrien-1-ol-3-one (β-IV) obtained by oxidation of β-4,8,13-duvatriene-1,3-diol (β-I).[1] Catalytic hydrogenation of the β-4,8,13-duvatrien-1-ol-3-one (β-IV) obtained by oxidation of β-II yielded β-1-duvanol-3-one A and β-1-duvanol-3-one B (β-V), identical on the basis of infrared spectra, melting points, and mixture melting points with the β-1-duvanol-3-ones A and B obtained from β-I by catalytic hydrogenation and subsequent oxidation.[1]



IV



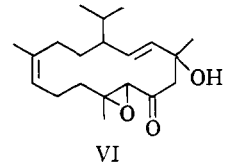
V

The conversion of β-II to β-4,8,13-duvatrien-1-ol-3-one (β-IV) allows structure assignment to β-II. Since β-II is a ditertiary alcohol, oxidation is proposed to have occurred *via* allylic rearrangement. Rearrangement of β-II to a secondary alcohol, either β-I or the alcohol which differs from β-I only in its configuration at the 3-position, and the subsequent oxidation of the secondary alcohol to ketone would account for the formation of β-IV. Accordingly, the structure, 12-isopropyl-1,5,9-trimethyl - 3,8,13 - cyclotetradecatriene - 1,5 - diol (II), is proposed for β-II.

Besides β-4,8,13-duvatrien-1-ol-3-one (β-IV), three other products were obtained from the oxidation of β-II. The structures of the other products, which are in agreement with structure II for β-3,8,13-duvatriene-1,5-diol, are discussed below.

An α,β-unsaturated ketone, obtained in 4–8% yield from chromic oxide–pyridine oxidation of β-II, is an isomer of β-4,8,13-duvatrien-1-ol-3-one and is designated as iso-β-4,8,13-duvatrien-1-ol-3-one. The infrared spectrum of iso-β-4,8,13-duvatrien-1-ol-3-one shows the presence of an α,β-unsaturated carbonyl group (6.01, 6.24 μ) and a *trans* disubstituted double bond (10.25 μ). The ultraviolet absorption, λ_{max} 242 mμ, log ε 3.97, confirms the α,β-unsaturated ketone structure. The n.m.r. spectrum shows the presence of a hindered isopropyl group (9.17 p.p.m.), one methyl on a carbon bearing a hydroxyl group (8.76 p.p.m.), one methyl on an isolated double bond (8.51 p.p.m.), one methyl on a double bond in a conjugated system (8.24 p.p.m.), and four olefinic protons (5.15–4.0 p.p.m.). The only significant difference in the n.m.r. spectra of β-IV and the iso compound is related to the methyl group on the double bond in the conjugated system. The location of the peak for this methyl group at 8.24 p.p.m. in the iso compound and at 7.92 p.p.m. in β-IV indicates that the 4,5-double bond is *cis* in iso-β-4,8,13-duvatrien-1-ol-3-one and is *trans* in β-4,8,13-duvatrien-1-ol-3-one.[4]

A third product, obtained in 5–15% yield from the chromic oxide–pyridine oxidation of β-II, was shown from its elemental analyses and mass spectrum to correspond to a compound in which one oxygen atom has been added to either β-4,8,13-duvatrien-1-ol-3-one or iso-β-4,8,13-duvatrien-1-ol-3-one. The addition of oxygen to the α,β-unsaturated carbonyl system of IV is reasonable upon consideration of the isolation of α,β-oxido ketones from chromic oxide oxidation of allylic alcohols.[5] The α,β-oxido ketone structure for the third oxidation product is in agreement with its infrared spectrum (carbonyl absorption at 5.92 μ), the absence of selective absorption of ultraviolet light, and its n.m.r. spectrum. Identification of the third oxidation product was completed by its preparation from β-4,8,13-duvatrien-1-ol-3-one (β-IV) by reaction with alkaline



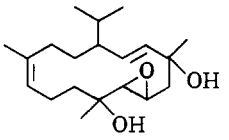
VI

(4) L. M. Jackman and R. H. Wiley, *J. Chem. Soc.*, 2886 (1960).

(5) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd ed., Reinhold Publishing Company, New York, N. Y., 1949, p. 228.

hydrogen peroxide. Accordingly, the third oxidation product is β-4,5-oxido-8,13-duvadien-1-ol-3-one (β-VI).

The fourth oxidation product, isolated in 2–8% yield, was shown by elemental and active hydrogen analyses to be $C_{20}H_{32}O(OH)_2$ and, accordingly, corresponds to β-II to which one oxygen atom has been added. Since the oxidation of β-II has been explained *via* rearrangement to a secondary alcohol, the oxide could be derived from either the tertiary alcohol (II) or secondary alcohol (I) structures. Structure VII, related to the tertiary alcohol II, is favored from consideration of the n.m.r. spectrum. The n.m.r. spectrum of this oxidation product shows two protons at 6.85–7.1 p.p.m.; the protons attached to an epoxide ring are reported to show absorption at 7.0–7.2 p.p.m.[6]



VII

Although oxidative degradation of β-II gave poor yields of oxidation products, levulinic acid and 5-keto-2-isopropylhexanoic acid were identified in the acid fraction from the oxidation. Isolation of these acids is in agreement with structure II.

The α-isomer, α-II, was isolated from tobacco leaf in only trace amounts. α-II, m.p. 118–120°, $[\alpha]^{25}D$ + 100°, was shown from elemental and active hydrogen analyses to be a diol isomeric with β-II. The structural similarity of α-II and β-II is evident from the ultraviolet, mass, and n.m.r. spectra. The mass spectrum of α-II was very similar to that of β-II; however, α-II has the distinction of being the only isomer of this series (I and II) which showed a parent peak at mass 306. The n.m.r. spectrum of α-II is particularly instructive since it shows the presence of five olefinic protons, one methyl group at an olefinic double bond, two methyl groups of the type CH_3C—OH, and a hindered isopropyl group, with all methyl peaks in positions close to the positions observed in β-II.

The structure of α-II was determined from its oxidation product. The product obtained by chromic oxide–pyridine oxidation of α-II was identical with α-4,8,13-duvatrien-1-ol-3-one (α-IV) obtained by oxidation of α-4,8,13-duvatriene-1,3-diol (α-I).[1] Since α-II exhibits the n.m.r. spectrum of a ditertiary alcohol, the oxidation must have proceeded by allylic rearrangement similar to that postulated in oxidation of β-II. Therefore, α-II must be one of the diastereoisomers of 12-isopropyl-1,5,9-trimethyl-3,8,13-cyclotetradecatriene-1,5-diol (II). Since α-IV and β-IV are epimeric at position 1,[1] α-II and β-II must also differ in configuration at position 1.

The allylic relationship between the 4,8,13-duvatriene-1,3-diols (I) and the 3,8,13-duvatriene-1,5-diols (II) was further demonstrated by the rearrangement of the 1,3-diols to the 1,5-diols. These transformations of I to II were accomplished by slow chromatography on acidic alumina. The isomerizations of α-I to α-II and of β-I to β-II provide verification of the structures of α-II and β-II.

The conversion of α-I to α-II and of β-I to β-II raises the question whether α- and β-II are artifacts produced from α- and β-I during the isolation process. This question is difficult to resolve for α-II since it was isolated from tobacco in minute quantity. However, α-II was isolated using procedures which did not cause isomerization of α-I. The isolation of β-II was accomplished by a variety of procedures involving a minimum of operational steps. Accordingly, we consider that β-II is not an artifact and that the allylic isomers of structures I and II are present in aged tobacco leaf. A similar occurrence of allylic isomers, phytol and isophytol, in jasmine has been noted by Demole and Lederer.[7]

(6) C. Y. Hopkins and H. J. Bernstein, *Can. J. Chem.*, **37**, 775 (1959).

Experimental[8]

Isolation of β-3,8,13-Duvatriene-1,5-diol (β-II).—β-II has been isolated from aged flue-cured and burley tobaccos by several procedures. A simple isolation procedure was as follows: A methanol extract of tobacco was partitioned between 90% methanol and hexane. The material which partitioned into 90% methanol was purified by chromatography using silicic acid or Florisil. From the fractions eluted by hexane–ether mixtures, β-II crystallized after partial concentration and chilling to −27°. The recrystallized material corresponded to 0.0015% of the dry weight of the tobacco.

Physical Properties of β-3,8,13-Duvatriene-1,5-diol (β-II).—β-3,8,13-Duvatriene-1,5-diol melts at 150–152° after recrystallization from ether, $[\alpha]^{25}D$ = +40°. β-II shows no selective absorption of ultraviolet light. Infrared absorption occurs at 3.1, 9.0, and 10.25 μ. The n.m.r. spectrum shows 5 olefinic protons at 4.3–4.6 p.p.m. and methyl peaks at 9.16 (6), 8.61 (3), 8.65 (3), and 8.50 (3).

Anal. Calcd. for $C_{20}H_{34}O_2$: C, 78.39; H, 11.19; active H (2), 0.66; O, 10.42; mol. wt., 306. Found: C, 78.25; H, 11.19; active H, 0.70; O, 10.96; mol. wt. (ebull.), 321; mass, 288 (306–18).

Catalytic Hydrogenation of β-3,8,13-Duvatriene-1,5-diol (β-II).—Quantitative hydrogenation using Adams' catalyst in ethyl acetate gave an equivalent weight of 99, corresponding to three double bonds in a molecular weight of 306. From reduction of 0.8 g. of β-II using Adams' catalyst (24 hr. at 3 atm.), three products were isolated by chromatographic separation followed by crystallization from hexane.

(a) Monohydric alcohol A, 190 mg., m.p. 80–82°, $[\alpha]^{27}D$ 0°.

Anal. Calcd. for $C_{20}H_{40}O$: C, 81.01; H, 13.60; active H (1), 0.34. Found: C, 80.96; H, 13.60; active H, 0.34.

(b) Dihydric alcohol B, 130 mg., m.p. 132–134°, $[\alpha]^{27}D$ +96°. N.m.r. spectrum: 8.78 (6) and 9.11 (9).

Anal. Calcd. for $C_{20}H_{40}O_2$: C, 76.86; H, 12.89; mol. wt., 312. Found: C, 76.42; H, 12.80; mass, 294 (312–18).

(c) Dihydric alcohol C, 310 mg., m.p. 159–161°, $[\alpha]^{30}D$ +13°. N.m.r. spectrum: 8.82 (6) and 9.07–9.15 (9).

Anal. Calcd. for $C_{20}H_{40}O_2$: C, 76.86; H, 12.89; mol. wt., 312. Found: C, 76.93; H, 12.88; mol. wt. (ebull.), 354; mass, 294 (312–18).

From the attempted reactions of alcohol C with chromium trioxide in pyridine or in acetic acid–water, alcohol C was recovered unchanged.

Hydrogenolysis of β-3,8,13-Duvatriene-1,5-diol (β-II).—Hydrogenolysis of 300 mg. of β-II, using Adams' catalyst in 50 ml. of ethyl acetate containing four drops of 70% perchloric acid, gave a 50% yield of a saturated hydrocarbon, $n^{26}D$ 1.4955, which appeared from its elemental analysis to be tricyclic.

Anal. Calcd. for $C_{20}H_{36}$: C, 86.87; H, 13.13. Found: C, 86.86; H, 13.03.

(7) E. Demole and E. Lederer, *Bull. soc. chim. France*, 1128 (1958).

(8) All melting points were determined using a Fisher–Johns melting point apparatus and are uncorrected. Elemental analyses were performed by the Huffman Microanalytical Laboratories, Wheatridge, Colorado, and by the Spang Microanalytical Laboratory, Ann Arbor, Michigan. Active hydrogen was determined by the procedure of J. A. Giles, *Anal. Chem.*, **32**, 1716 (1960). Nuclear magnetic resonance (n.m.r.) spectra were run in deuterated chloroform solution using Varian Associates HR-60 instrument. The n.m.r. spectra are reported by τ value [G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958)], with the number of hydrogens in parentheses. We are indebted to John J. Whalen and Johnnie L. Stewart for infrared spectra, to George W. Young for mass spectra, to Dr. A. H. Laurene for n.m.r. data, and to J. A. Giles and P. H. Ayers for the active hydrogen determinations.

The product from hydrogenation of 200 mg. of β-II using Adams' catalyst in glacial acetic acid (24 hr. at 3 atm.) was chromatographed with acid-washed alumina (Merck), giving 14 mg. of hydrocarbon III (with infrared absorption identical with that obtained by catalytic hydrogenation of dehydrated monohydric alcohol A), 60 mg. of monohydric alcohol A, and 130 mg. of a mixture of dihydric alcohols B and C.

Conversion of Monohydric Alcohol A to 12-Isopropyl-1,5,9-trimethylcyclotetradecane (III).—Alcohol A (60 mg.) and fused potassium acid sulfate (200 mg.) were heated under nitrogen at 180° for 10 min. The residue was extracted with three 10-ml. portions of ethyl acetate, and the ethyl acetate extracts were hydrogenated using Adams' catalyst. The hydrogenation product, 52 mg., showed infrared absorption identical with that of hydrocarbon III obtained in 7% yield by hydrogenation of β-II in acetic acid.

Anal. Calcd. for $C_{20}H_{40}$: C, 85.63; H, 14.37; mol. wt., 280. Found: C, 85.82; H, 14.29; mass, 280.

Hydrogenolysis of β-4,8,13-Duvatriene-1,3-diol (β-I).—The product from hydrogenation of 500 mg. of β-I using Adams' catalyst in glacial acetic acid (18 hr. at 3 atm.) was chromatographed using alumina (Merck). Besides the β-1,3-duvanediols A and B,[1] a saturated hydrocarbon (20 mg.) was isolated. The hydrocarbon showed infrared absorption identical with that of hydrocarbon III obtained from hydrogenolysis of β-II.

Conversion of β-3,8,13-Duvatriene-1,5-diol (β-II) to β-1-Duvanol-3-ones A and B (β-V).—The oxidation of 290 mg. of β-II with 1 g. of chromic oxide in 8 ml. of pyridine at room temperature for 40 hr., followed by chromatography on silicic acid, yielded 86 mg. of an oil, identified as β-4,8,13-duvatrien-1-ol-3-one (β-IV) by infrared absorption. Hydrogenation using Adams' catalyst in ethanol (24 hr. at 3 atm.) followed by chromatographic separation on silicic acid and crystallization from pentane gave 11 mg. of solid, m.p. 126–127.5°, no depression of melting point with β-1-duvanol-3-one A (β-V), and 41 mg. of solid, m.p. 99–100°, no depression of melting point with β-1-duvanol-3-one B (β-V). The infrared spectra were identical with those of the corresponding β-1-duvanol-3-ones prepared by chromic oxide–pyridine oxidation of β-1,3-duvanediols A and B.[1]

Chromic Oxide–Pyridine Oxidation of β-3,8,13-Duvatriene-1,5-diol (β-II).—For the oxidation of β-II using chromic oxide in pyridine, the reaction time was varied from 20 to 140 hr. In each case, four reaction products were isolated and β-II was recovered. The results from a typical run are as follows.

To a mixture prepared by addition of 6.0 g. of chromic oxide to 50 ml. of pyridine was added 1.9 g. of β-II. After 6 days, the mixture was diluted with 300 ml. of water and was extracted with 200 ml. of ether. The ethereal extract was washed with 100 ml. of water and with two 150-ml. portions of 2 *N* hydrochloric acid. The residue from concentration of the ethereal extract was separated by chromatography into five components, described in the order of elution from silicic acid.

(a) Iso-β-4,8,13-duvatrien-1-ol-3-one, 120 mg. Infrared absorption: 2.95, 6.01, 6.24, and 10.25 μ. Ultraviolet absorption: λ_{max}^{EtOH} 242–243 mμ, log ε 3.97. N.m.r. spectrum: 9.17 (6), 8.76 (3), 8.51 (3), 8.24 (3), and 5.15–4.0 (4).

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.90; H, 10.60; mol. wt., 304. Found: C, 79.04; H, 10.63; mass, 304.

(b) β-4,8,13-Duvatrien-1-ol-3-one (β-IV), 310 mg. Infrared absorption identical with β-4,8,13-duvatrien-1-ol-3-one obtained by chromic oxide–pyridine oxidation of β-4,8,13-duvatriene-1,3-diol (β-I)[1]: 2.95, 6.04, 6.22, and 10.25 μ. Ultraviolet absorption: λ_{max}^{EtOH} 244 mμ, log ε 4.27. The n.m.r. spectrum was identical with that of β-4,8,13-duvatrien-1-ol-3-one obtained by oxidation of β-I.[1]

(c) β-4,5-Oxido-8,13-duvadien-1-ol-3-one (β-VI), 100 mg., melting point after recrystallization from pentane at −27°, 122–124°. Infrared absorption: 2.90, 5.92, and 10.28 μ. Ultraviolet absorption: no selective absorption above 220 mμ. N.m.r. spectrum: 9.15 (6), 8.67 (3), 8.56 (3), 8.43 (3), 7.17 (2), 6.42 (1), and 5.45–4.7 (3).

Anal. Calcd. for $C_{20}H_{32}O_3$: C, 75.00; H, 10.06; mol. wt., 320. Found: C, 75.36; H, 9.95; mass, 320.

(d) β-3,8,13-Duvatriene-1,5-diol (β-II), 50 mg., identified by its infrared spectrum and m.p., 150–152°.

(e) β-3,4-Oxido-8,13-duvadiene-1,5-diol (β-VII), 50 mg., melting point after recrystallization from pentane at −27°, 117–119°. Infrared absorption: 2.90, 6.0, 9.0, and 10.25 μ. Ultraviolet absorption: no selective absorption above 220 mμ. N.m.r. spectrum: 9.14 (6), 8.93 (3), 8.60 (3), 8.50 (3), 7.0 (2), and 4.7 (3).

Anal. Calcd. for $C_{20}H_{34}O_3$: C, 74.48; H, 10.62; active H (2), 0.62; mol. wt., 322. Found: C, 74.49; H, 10.44; active H, 0.60; mass, 304 (322–18).

Peroxide Oxidation of β-4,8,13-Duvatrien-1-ol-3-one (β-IV) to β-4,5-Oxido-8,13-duvadien-1-ol-3-one (β-VI).—To a solution of 103 mg. of β-4,8,13-duvatrien-1-ol-3-one (β-IV) in 6 ml. of ethyl alcohol was added a solution prepared from 0.2 g. of hydrated sodium carbonate, 5 ml. of water, and 1 ml. of 30% hydrogen peroxide. After 10 min., 60 ml. of water was added. The mixture was extracted with two 100-ml. portions of ether. The ethereal extracts were washed with four 30-ml. portions of water. Chromatography of the residue from concentration of the ethereal extract gave 20 mg. of β-4,8,13-duvatrien-1-ol-3-one and 50 mg. of material showing the infrared absorption of crude β-4,5-oxido-8,13-duvadien-1-ol-3-one. Crystallization of the latter fraction from pentane at −27° yielded 14 mg. of solid, m.p. 120–122°, with infrared absorption identical with that of β-4,5-oxido-8,13-duvadien-1-ol-3-one isolated directly from chromic oxide–pyridine oxidation of β-3,8,13-duvatriene-1,5-diol.

Oxidative Degradation of β-3,8,13-Duvatriene-1,5-diol (β-II).—A solution of 2 g. of β-II in 200 ml. of pyridine was added with stirring to a mixture of 19 g. of sodium periodate, 0.2 g. of potassium permanganate, and 2 g. of potassium carbonate in 600 ml. of water. The permanganate color was dissipated rapidly. Potassium permanganate was added portionwise over a period of 4.5 days. After addition of 5.7 g. of potassium permanganate the permanganate color persisted for a period of 2.5 hr. The reaction mixture was filtered through Celite. The alkaline filtrate was extracted with two 350-ml. portions of ether. The aqueous solution was acidified with sulfuric acid to a pH of < 2 and the acidified solution was extracted with three 200-ml. portions of ether. Of the ethereal extracts from the acidified solution, 60% was allowed to react with diazomethane, yielding 560 mg. of mixed methyl esters. Chromatography on silicic acid gave 106 mg. of an oil showing infrared absorption indicative of methyl 5-keto-2-isopropylhexanoate and 91 mg. of an oil showing the infrared absorption of methyl levulinate.

Of the crude methyl 5-keto-2-isopropylhexanoate, 43 mg. was converted to the semicarbazone. After crystallization from pentane, 7 mg. of solid was obtained which showed infrared absorption similar to that of authentic methyl 5-keto-2-isopropylhexanoate semicarbazone. The product melted at 123–125° and a mixture with authentic semicarbazone melted at 124–127°.

The crude methyl levulinate isolated from the oxidation reaction was converted to the 2,4-dinitrophenylhydrazone derivative. After chromatography on silicic acid and crystallization from ethanol, 15 mg. of solid, m.p. 137–139°, with infrared absorption of methyl levulinate dinitrophenylhydrazone, was obtained.

Isolation of α-3,8,13-Duvatriene-1,5-diol (α-II).—The isolation of α-3,8,13-duvatriene-1,5-diol was accomplished by the procedure reported for isolation of the α- and β-4,8,13-duvatriene-1,3-diols (α- and β-I).[1] In the chromatographic separation using alumina, α-II was eluted after β-II but before α- and β-I.

Physical Properties of α-3,8,13-Duvatriene-1,5-diol (α-II).—α-II melts at 118–120° after recrystallization from hexane, $[\alpha]^{25}D$ +100°. α-II shows no ultraviolet absorption other than end absorption below 220 mμ. Infrared absorption occurs at 3.05, 8.8, 9.0, 9.25, and 10.2 μ. The n.m.r. spectrum shows peaks at 9.18 (6), 8.67 (6), 8.49 (3), 4.62 (3), and 4.37 (2).

Anal. Calcd. for $C_{20}H_{34}O_2$: C, 78.39; H, 11.19; active H (2), 0.66; mol. wt., 306. Found: C, 78.40; H, 11.12; active H, 0.60; mass, 306.

Chromic Oxide–Pyridine Oxidation of α-3,8,13-Duvatriene-1,5-diol (α-II).—A mixture prepared by addition of 300 mg. of α-II to a suspension of 1.0 g. of chromic oxide in 15 ml. of pyridine was allowed to stand at room temperature for 4 days. After addition of 125 ml. of water, the mixture was extracted with ether. The residue from concentration of the dried ethereal extract was separated by chromatography using silicic acid into three fractions: (1) 54 mg. of α-4,8,13-duvatrien-1-ol-3-one (α-IV), m.p. 74–75°, mixture melting point with α-IV prepared by oxidation of α-I,[1] 73–74°, infrared absorption identical with that of α-IV prepared by oxidation of α-I; (2) 49 mg. of material which showed infrared absorption indicating a mixture of α-IV and another α,β-unsaturated keto alcohol; (3) 51 mg. of unreacted α-II.

Isomerization of 4,8,13-Duvatriene-1,3-diols (I) to 3,8,13-Duvatriene-1,5-diols (II).—A hexane solution of 216 mg. of α-I was added to a 20 × 75 mm. chromatographic column of acid-washed alumina (Merck). After α-I had been allowed to contact the adsorbent for 40 hr., elution was attempted using hexane–ether mixtures. Elution with ether yielded 20 mg. (9%) of material with infrared absorption identical with that of α-II. Starting material, α-I, 170 mg., was recovered by elution with ether containing 2% methanol.

Using the same procedure, β-I was converted to β-II in 20% yield.

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The Mitomycin Antibiotics. Synthetic Studies. I. Synthesis of Model Quinones

WILLIAM A. REMERS, PHILIP N. JAMES, AND MARTIN J. WEISS

Organic Chemical Research Section, Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York

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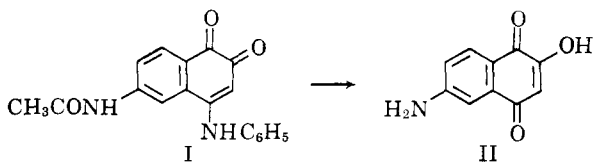
Certain Bz(benz)-amino-substituted 2-hydroxy-1,4-naphthoquinones and 5-hydroxy-6-methyl-substituted indoloquinones, including a pyrrolo[1,2-*a*]indoloquinone, have been prepared. Their pertinence as ultraviolet models for mitomycin degradation products is discussed.

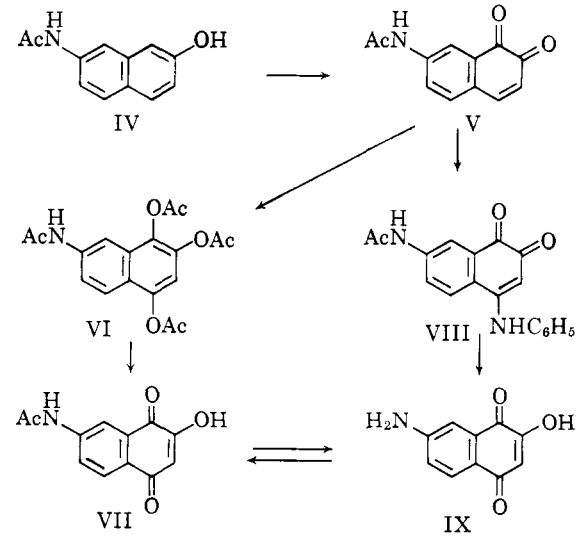
In the course of an investigation concerning the structure of the mitomycin group of antibiotics, Webb and collaborators isolated degradation products which were apparently amino-substituted 2-hydroxy-3-methyl-1,4-quinones.[1] In this paper we wish to report the synthesis of several naphtho- and indoloquinones prepared as ultraviolet models of these degradation products. One of the partial structures originally suggested for these products contained a 1,4-naphthoquinone nucleus and, therefore, we undertook the synthesis of the four possible Bz-amino-2-hydroxy-1,4-naphthoquinones. Although three of these compounds and a potential close precursor to the fourth had already been reported by Kehrmann and his collaborators,[2] it was desirable to devise more convenient pathways for the preparation of three of the compounds in view of the difficult and tedious procedures which the Kehrmann group had utilized. In particular, it appeared that the use of the Fremy's salt (potassium nitrosodisulfonate) procedure[3] for the conversion of phenolic compounds to quinones might lead to considerably shortened sequences.

The unknown 6-amino-2-hydroxy-1,4-naphthoquinone (II) was prepared by hydrolysis, according to the procedure of Thomson,[4] of the known[2a] 6-acetamido-4-anilino-1,2-naphthoquinone (I).



I II

7-Amino-2-hydroxy-1,4-naphthoquinone (IX)[2b] was prepared as follows. 7-Amino-2-naphthol (III)[5] was converted to the *N*-acetyl derivative IV *via* *O*,*N*-diacetylation of the hydrochloride in aqueous solution, followed by de-*O*-acetylation in dilute alkali. The previously reported[5] acetylation in pyridine was found difficult to repeat. Oxidation of IV with Fremy's salt afforded an 89% yield of 7-acetamido-1,2-naphthoquinone (V). This conversion previously required three steps.[2d] Attempts to elaborate the 2-hydroxy-1,4-quinone system *via* Thiele acetylation of V followed by hydrolysis and oxidation of the tetraacetate VI were unpromising. The Thiele acetylation gave erratic results and the yield of VI was never better than 18%, although subsequent alkaline hydrolysis of VI followed by ferric chloride oxidation gave a 96% yield of the 7-acetamido derivative VII. A superior route was provided by the addition of aniline to V. The resulting 7-acetamido-4-anilino-1,2-naphthoquinone (VIII), formed in 40% yield by the procedure of Kehrmann and Wolff,[2d] then was hydrolyzed in sulfuric acid directly to the desired IX, obtained in 76% yield after partition chromatography. Compound IX could be *N*-acetylated to VII; VII could be hydrolyzed to IX.



Preparation of 8-amino-2-hydroxy-1,4-naphthoquinone (XIII)[2e] was accomplished by similar procedures: Fremy's salt oxidation of 8-acetamido-2-naphthol (X), addition of aniline to the resulting 8-acetamido-1,2-

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