Macrocyclic Diterpenes. α- and β-4,8,13-Duvatriene-1,3-diols from Tobacco[1]

DONALD L. ROBERTS AND R. L. ROWLAND

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

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Two macrocyclic diterpenes, α- and β-4,8,13-duvatriene-1,3-diols, isolated from tobacco (*Nicotiana tabacum*), are shown through chemical and physicochemical findings to be diastereoisomers of 12-isopropyl-1,5,9-trimethyl-4,8,13-cyclotetradecatriene-1,3-diol (I). The fourteen-membered ring here represented has not been encountered previously.

The various terpenoids which have been isolated from natural sources present an imposing array of widely different and unique structures. An interesting group of compounds which have been characterized are the macrocyclic terpenes possessing nine-, ten-, and eleven-membered ring systems.[2] We now wish to report the isolation and characterization of two new macrocyclic terpenes for which a fourteen-carbon ring system is indicated.

Hexane extraction of aged burley tobacco (*Nicotiana tabacum*) and chromatography of the extract resulted in the isolation of two isomeric alcohols, to which the names α-4,8,13-duvatriene-1,3-diol, and β-4,8,13-duvatriene-1,3-diol[1b] have been assigned. The α- and β-duvatrienediols constitute 0.01% and 0.005% of the dry burley leaf and also are found in flue-cured, Turkish, and unaged burley tobaccos.

For the sake of clarity, the α-compound (α-I) is discussed separately from the β-compound (β-I) although it is shown in the subsequent discussion that the two compounds are diastereoisomers.

Elemental analyses of α-I, m.p. 65–66°, $[\alpha]^{25}\text{D}$ + 281.6, indicate an empirical formula $(C_{10}H_{17}O)_n$. The mass spectrum shows the largest fragment to have a mass of 288, corresponding to the loss of water from the formula $C_{20}H_{34}O_2$. An active hydrogen determination shows that both oxygens are present in hydroxyl groups. Hydrogenation of α-I gives two saturated diols, $C_{20}H_{40}O_2$; thus, α-I contains three double bonds and one ring.

The infrared spectrum of α-I exhibits a strong hydroxyl band at 3330 cm.$^{-1}$, a weak band at 1665 cm.$^{-1}$ indicative of nonconjugated double bonds, and a strong band at 974 cm.$^{-1}$ characteristic of disubstituted *trans* double bonds. The lack of ultraviolet absorption above 220 mμ establishes the absence of conjugated double bonds. The nuclear magnetic resonance (n.m.r.) spectrum is informative regarding the structure of the diol in that it reveals the presence of four olefinic protons, τ 4.81–5.07[3]; one proton attached to a carbon bearing an oxygen, τ 5.63; two methyl groups attached to ethylenic carbons, τ 8.36 and 8.50; one methyl group attached to an oxygen-bearing carbon, τ 8.69; and an isopropyl group multiplet, τ 9.17. The data thus suggest that α-I contains a secondary hydroxyl group, a tertiary hydroxyl group *alpha* to a methyl group, a disubstituted *trans* double bond, two methyl groups attached to ethylenic carbon atoms, and an isopropyl group as a branching group on a saturated carbon atom.

In the determination of the structure of α-I, consideration was given to its sensitivity to acid and to the slow decomposition of pure α-I at room temperature. For these reasons all chemical transformations of α-I were performed in neutral or basic solutions and at room temperature or below. Due to sensitiveness of α-I and since significant information about its structures can be obtained from the saturated diols, the saturated compounds were investigated initially. These studies and those on the parent compound will be discussed first in order to elucidate the general structural characteristics; subsequently, degradative work which confirms the proposed structure will be described.

Study of the character and relationship of the two hydroxyl groups in α-I provided an early key to the over-all structure. Failure of α-I or the corresponding saturated diols to react with sodium periodate or lead tetraacetate ruled out a vicinal relationship between the two hydroxyl groups. Oxidation of saturated diols α-IIA and α-IIB produced keto alcohols α-IIIA and α-IIIB, respectively. Keto alcohol α-IIIA was cleaved by base, giving diketone IVA, and in like manner keto alcohol α-IIIB gave the corresponding diketone, IVB. In both cases the diketones had the same molecular formulas as the starting keto alcohols, showing that no fragmentation occurred. Hypoiodite oxidation of the diketones produced iodoform and the corresponding dibasic acids, meaning that two methyl keto groups were present in the diketones. One methyl keto group in the

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[1] (a) Presented at the International Symposium of Organic Chemistry of Natural Products, Brussels, Belgium, June 12–15, 1962. Abstract published in *Ind. Chim. Belge*, **27**, 524 (1962). Since the presentation of this work, cembrene, an unsaturated hydrocarbon isolated from *Pinus albicaulis*, has been shown by W. G. Dauben, W. E. Thiessen, and P. R. Resnick, *J. Am. Chem. Soc.*, **84**, 2015 (1962), to be 1-isopropyl-4,8,12-trimethyl-2,4,7,11-cyclotetradecatetraene. This compound, it is noted, contains an identical ring system, and the location of three of the double bonds corresponds to that found in the duvatrienediols. (b) For the purposes of this paper and subsequent papers of this series it will be convenient to introduce nomenclature wherein the compounds are named as derivatives of a parent saturated monocyclic hydrocarbon. We have assigned the name duvane (from *duvan*, Serbian for tobacco) to the structure 1-isopropyl-4,8,12-trimethylcyclotetradecane.

[2] F. Sorm, *Fortschr. Chem. Org. Naturstoffe*, **19**, 1 (1961).

[3] The symbols and presentation of n.m.r. spectra used herein conform to the recommendations set forth in *Proc. Chem. Soc.*, 403 (1960).

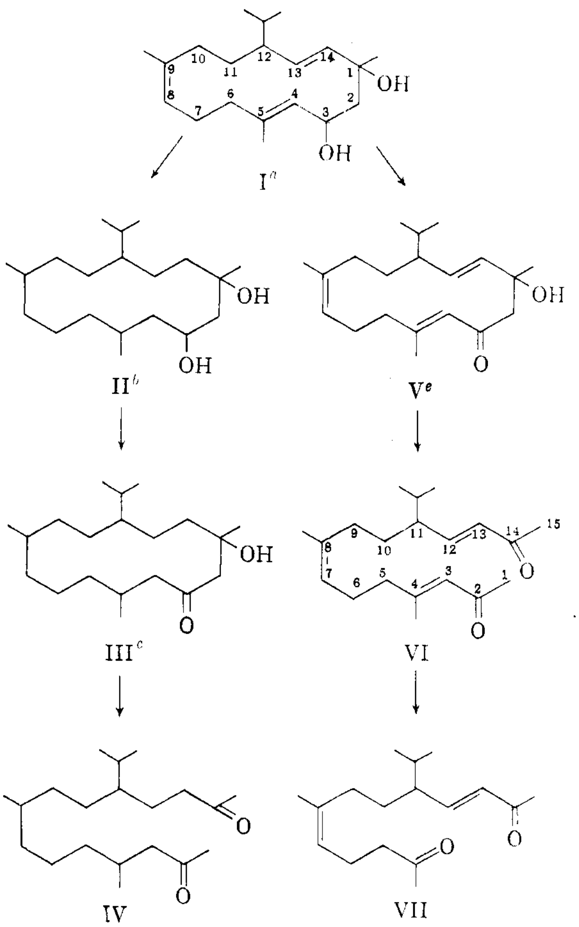
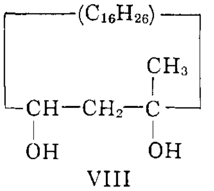


Fig. 1.—Reactions of duvatrienediol

[a] Structure I is used without stereochemical implication to represent α-I and β-I. [b] Represents α-IIA, α-IIB, β-IIA, and β-IIB. [c] Represents α-IIIA, α-IIIB, β-IIIA, and β-IIIB. [d] Represents IVA and IVB. [e] Represents α-V and β-V.

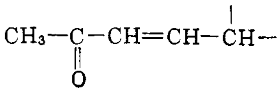
diketones arose from a methylcarbinol unit in the parent keto alcohol (α-IIIA or α-IIIB) and the other must have been formed by cleavage of a ring between the methylcarbinol unit and a methylene group attached to a second oxygen-bearing carbon. Thus the alkaline cleavage of keto alcohols α-IIIA and α-IIIB is recognized as being a retroaldol reaction typical of β-hydroxy ketones. On this basis the partial structure VIII is established for α-I, wherein the secondary and tertiary hydroxyl substituents are placed in a 1,3-relationship on a ring of indeterminate size.



VIII

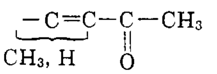
Oxidation of α-I with manganese dioxide[4] (or with chromium trioxide in pyridine) to the α,β-unsaturated keto alcohol (α-V) demonstrates the allylic nature of the secondary hydroxyl group. The significant differences in the n.m.r. spectrum of the keto alcohol (α-V) as compared with the spectrum of the diol (α-I) are the shifts in one olefinic peak from τ 4.81 in α-I to 4.05 in α-V and one methyl peak from τ 8.36 in α-I to 7.88 in α-V. These differences reveal that the carbonyl in α-V is conjugated with a trisubstituted ethylenic bond on which one substituent is a methyl group, a conclusion which is confirmed by the ultraviolet absorption (λ_{max} = 243 mμ, ε 10,000).

Retroaldol reaction of α-V, brought about by aqueous sodium carbonate solution, gave a diketone (VI) having the same molecular formula as α-V; the ring cleavage again demonstrates the β-hydroxy keto group. The strong ultraviolet absorption of diketone VI at 229 mμ (ε 22,000) coupled with its infrared absorption at 1686, 1676, and 1619 cm.$^{-1}$ indicates the presence of two α,β-unsaturated ketone units. The n.m.r. spectrum of VI has methyl resonances at τ 7.84 ($COCH_3$), 7.93 ($COCH_3$), 7.96 (conj. $C{=}CCH_3$), 8.47 ($C{=}CCH_3$), and 9.16 [$CH(CH_3)_2$]. The olefinic region shows four protons, two of which give rise to an ABX pattern typical of a conjugated *trans* double bond adjacent to a methine carbon. This information indicates that diketone VI contains α,β-unsaturated keto units IX and X, where the position of the methyl (in X) is indeterminate.



$CH_3-\underset{\underset{O}{\|}}{C}-CH=CH-\overset{|}{CH}-$

IX



$\underbrace{-C=C-}_{CH_3,\ H}\underset{\underset{O}{\|}}{C}-CH_3$

X

Upon being heated in refluxing sodium hydroxide solution, diketone VI gave one mole of acetone and a new diketone (VII). The infrared spectrum of diketone VII, especially the absorption at 1712, 1672, and 1630 cm.$^{-1}$, suggests little change in structure from VI except for the appearance of a saturated keto group in place of one of the α,β-unsaturated keto groups in VI. This was verified by the n.m.r. (absence of a methyl group at τ 7.96) and ultraviolet spectra (λ_{max} = 224 mμ, ε 15,000). The generation of an unconjugated methyl ketone group in the formation of diketone VII establishes the methyl substituent in partial structure X as *beta* to the carbonyl group.

Diketone VI contains an α,β-unsaturated keto group not present in its precursor (α-V); for such a conjugated system to be formed in the retroaldol reaction, the tertiary hydroxyl group in α-V and hence in α-I must be allylic. This conclusion combined with the data from partial structures VIII, IX, and X leads to partial structure XI for α-I.

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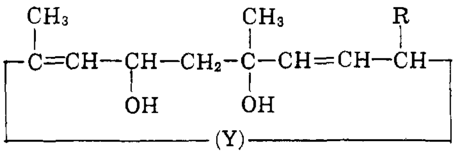
(4) (a) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952); (b) R. J. Gritter and T. J. Wallace, *J. Org. Chem.*, **24**, 1051 (1959).



$$-\overset{\overset{CH_3}{|}}{C}=CH-\underset{\underset{OH}{|}}{CH}-CH_2-\overset{\overset{CH_3}{|}}{\underset{\underset{OH}{|}}{C}}-CH=CH-\overset{\overset{R}{|}}{CH}-\quad (Y)$$

$R + Y = C_{10}H_{19}$

XI

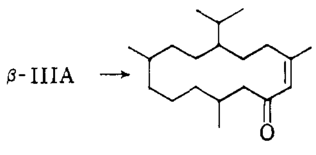
The substituent R and grouping Y of XI are characterized by a study of the n.m.r. spectra of α-I and its unsaturated transformation products. Since these spectra indicate no methyls other than those of the isopropyl group in saturated environments, the branching at the methine carbon must be either an isopropyl group or a chain ending in isopropyl. Secondary splitting associated with the methyls of the isopropyl group suggests that the rotation of the isopropyl group is hindered; hence, the R substituent of the methine carbon must be the isopropyl group since such a group at the end of an extended chain would not be expected to have hindered rotation.

With the assignment of the position of the isopropyl group, only one of the known groupings remains to be located, namely, a trisubstituted ethylenic bond on which one substituent is a methyl group. With all other terminal groups having been accounted for, the methyl-substituted double bond must be part of the ring, and the ring of α-I therefore must contain fourteen carbon atoms.[5] Application of the isoprene rule to the preceding structural data permits the proposal of structure I for α-I.

Confirmation of the size of the carbocyclic ring in α-I (and thus also its carbon skeleton) was obtained by oxidative degradations. Although ozonolysis of the α-diol furnished only levulinaldehyde (40% yield) in isolable amounts, oxidative cleavage using permanganate and periodate provided more significant results. The permanganate–periodate oxidation based on the procedure of Lemieux and von Rudloff[6] produced two acidic products; one was easily identified as levulinic acid, while the other proved to be 5-keto-2-isopropylhexanoic acid.[7] The formation of levulinic acid and 5-keto-2-isopropylhexanoic acid from the oxidative degradation identifies the *alpha*-diol as one of the stereochemical possibilities embraced in structure I. In the nomenclature based on duvane, as suggested earlier, α-I becomes α-4,8,13-duvatriene-1,3-diol.

The isomeric compound, β-I, m.p. 127–127.5°, is likewise a monocyclic, triply unsaturated diol as is shown by the analytical data for the compound and its hexahydro derivatives. The structural similarity with the α-isomer is apparent from the near identity of the ultraviolet and mass spectra, from the observation that differences in the infrared spectra appear only in the fingerprint region, and from the fact that the n.m.r. spectra differ only with respect to small shifts of vinyl and secondary carbinol proton signals. The fact that α-I and β-I are diastereoisomers is proved by the chemical transformations, those of the *beta* series being similar to those performed in the *alpha* series.

As with α-I, β-I was hydrogenated to two hexahydro derivatives (β-IIA and β-IIB); each of these derivatives then was oxidized to a new hydroxy ketone (β-IIIA and β-IIIB). Retroaldol reactions on these hydroxy ketones gave diketones containing two methyl keto groups identical to those obtained from their counterparts in the α-series. A study of the dehydration of compounds β-IIIA and β-IIIB also was made. The hexahydrohydroxy ketone (β-IIIA) on treatment with iodine in benzene was dehydrated to an α,β-unsaturated ketone (XII) (λ_{max} = 243 mμ). Compound β-IIIB failed to react under the same conditions of dehydration. The marked difference in behavior of the two isomers evidently derives from conformational effects that have not been explored adequately in this ring system. Nevertheless, the results of these reactions do provide further evidence for the 1,3-relationship of the hydroxyls.



XII

Oxidation of β-I to β-V was performed in the same manner as the α-I to α-V oxidation. It is noteworthy that both α-I and β-I are difficult to oxidize to keto alcohols as is indicated by the long reaction times (24 to 48 hours) required to complete the reactions.

Retroaldolization of the unsaturated keto alcohol β-V gave a diketone which was found to be identical with diketone VI obtained from α-I *via* α-V. The isolation of diketone VI as a common transformation product from α-V and β-V reveals that these two keto alcohols are epimers[8] at position 1 where the ring opens to give the diketone. Since the asymmetry at position 3 in the original compounds is lost in the oxidation to the keto alcohols, the configuration at position 3 cannot be deduced for the two diols. Hence, the two isomers apparently have the same configuration at position 12 but differ in their stereochemistry at position 1 and possibly at position 3.

The geometrical orientation of two of the double bonds is evident from spectroscopic observations.

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(5) Consistent with the fourteen-member ring structure of α-I is its dehydrogenation to give an aromatic hydrocarbon which, although not identified clearly, had a phenanthrene-like ultraviolet spectrum.

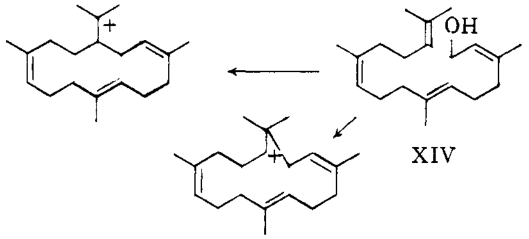
(6) R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1701 (1955).

(7) J. C. Bardhan, N. C. De, and B. B. Datta, *J. Chem. Soc.*, 3195 (1951).

The disubstituted 13,14-double bond was shown to be *trans* by infrared (absorption at 975 cm.$^{-1}$ of α-I and β-I) and n.m.r. spectra (J values of ABX pattern in diketones VI and VII) mentioned previously. The 4,5-double bond is considered to be *trans* as shown in structure I because of the n.m.r. absorption of the 5-methyl group in the diols (τ 8.36) and the keto alcohols (τ 7.88 and 7.92 for α- and β-compounds respectively); these values agree favorably with the values given for *trans* double bonds in related acyclic systems.[9] The configuration of the 8,9-double bond is uncertain; the only information available on the configuration of this bond is obtained from the n.m.r. spectra. These show a broad band for the proton at position 8 and a peak for the 9-methyl group which is broadened but which is not split as is the peak for the 5-methyl group. While the 4- and 13-double bonds are shown correctly in structure I, the 8-double bond whose orientation is not known is shown as *cis* for convenience.

Of interest in connection with the configuration and conformation of α- and β-4,8,13-duvatriene-1,3-diols are the results of the hydrogenations. Only two of the four possible hexahydro diastereoisomers were found from the hydrogenations of α-I and β-I; the other isomers could have been formed in no more than trace amounts. This fact shows that one of the trisubstituted double bonds in each of the duvatrienediols hydrogenates stereospecifically.

This first characterization of naturally occurring macrocyclic diterpenes leads to speculation about other new diterpene structures which may exist in nature. In their discussions of biogenesis of sesquiterpenes and diterpenes, Ruzicka[10] and Hendrickson[11] suggested the biogenesis of various sesquiterpenes from farnesol. They formulated the initial cyclizations of farnesol to six-, ten- and eleven-membered ring compounds and subsequent formation of bicyclics containing four-, five-, and nine-membered rings. Although Ruzicka had proposed geranylgeraniol (XIV) as a precursor of fused six-membered ring diterpenes, there has been no evidence to indicate that geranylgeraniol may cyclize to medium or large rings. The present work suggests that XIV is cyclized to the large ring compounds, α- and β-4,8,13-duvatriene-1,3-diols, in a manner comparable to the cyclization of farnesol to the germacrane sesquiterpenes. Similarly, a fifteen-membered ring system (XV), isoprenologous to humulane, would be expected and the characterization of a ring of this structure is anticipated. Furthermore, rearrangements and cyclizations similar to those postulated by Hendrickson for the sesquiterpene macrocycles also may occur with these large ring diterpenes. Accordingly, we propose the existence of a far wider variety of naturally occurring diterpenoid structures than is currently recognized.



XIV

XV

Experimental[12]

Isolation of α- and β-4,8,13-Duvatriene-1,3-diols.—Aged burley tobacco (USDA Grades B3F and C3F from Kentucky's 1954–1955 crops) was extracted with hexane in a column extractor; the hexane was removed *in vacuo* and the residue was chromatographed on silicic acid. The silicic acid columns were eluted with hexane, with 10%, 25%, and 50% ether–hexane mixtures, and with ether. The duvatrienediols were in the fractions eluted with 50% ether–hexane. These fractions were combined and rechromatographed on silicic acid to further purify the mixture of compounds. The diols were separated on basic alumina using ether to elute α-4,8,13-duvatriene-1,3-diol and a 2% methanol–ether mixture to elute β-4,8,13-duvatriene-1,3-diol, successively. The β-duvatrienediol fractions were purified further by recrystallization from hexane to m.p. 127–127.5°. The crude α-duvatrienediol was an oil which was purified by molecular distillation followed by crystallization from pentane. The α-compound crystallized very slowly and the crystals, m.p. 65–66°, were found to de-

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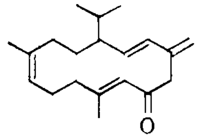
(8) Although the asymmetry at position 12 would be lost in the conversion of α-V and β-V to diketone VI, it is believed that the configuration at position 12 of α-I and β-I is the same. This belief is based on the formation of identical products from the dehydration of α- and β-4,8,13-duvatriene-1-ol-3-ones (α-V and β-V) with anhydrous magnesium sulfate in refluxing benzene. The dehydration products (XIII) have not been characterized completely, but the infrared and ultraviolet spectra of the dehydration product from α-V are identical with corresponding spectra from the β-V product. The optical rotations of the two products are also equal within experimental error.



XIII

(9) (a) R. B. Bates and D. M. Gale, *J. Am. Chem. Soc.*, **82**, 5749 (1960); (b) L. M. Jackman and R. H. Wiley, *J. Chem. Soc.*, 2886 (1960).

(10) L. Ruzicka, *Experientia*, **9**, 357 (1953).

(11) J. B. Hendrickson, *Tetrahedron*, **7**, 82 (1959).

(12) All melting points were determined using a Fisher-Johns melting point apparatus and are uncorrected. Elemental analyses were performed by Huffman Microanalytical Laboratories, Wheatridge, Colo., and by Spang Microanalytical Laboratory, Ann Arbor, Mich. Chromatographic separations were made using Mallinckrodt analytical reagent silicic acid and Merck chromatographic grade aluminum oxide. Silicic acid was used as the adsorbent and hexane–ether mixtures were used as eluents, unless otherwise noted. All nuclear magnetic resonance spectra were run in deuteriochloroform (approx. 5% solutions) on a Varian Associates' HR-60 instrument. Mass spectroscopy was used to determine all molecular weights and to check compound purities. The authors are indebted to the members of the Analytical Research Division for physical measurements and in particular they wish to thank John J. Whalen and Johnnie L. Stewart for infrared spectra, George W. Young for mass spectra, and Dr. A. H. Laurene for the n.m.r. data.

compose on standing unless kept cold (−10°). The minimum concentrations of α- and β-4,8,13-duvatriene-1,3-diols found in burley tobacco were 0.01% and 0.005% by weight of dry tobacco. The compounds were isolated from flue-cured, Turkish, and unaged burley tobaccos using very similar procedures.

Physical Data on α-4,8,13-Duvatriene-1,3-diol (α-I).—Melting point: 65–66°. Optical activity: $[\alpha]^{25}\text{D}$ +281.6° (chloroform). Infrared spectrum (Nujol): 3330 (s), 1665 (w), 1345, 1190, 1160, 1118, 1024, 995, 974 (s), 954, and 818 cm.$^{-1}$. Ultraviolet spectrum: $\lambda_{\max}^{\text{EtOH}}$ = end absorption below 220 mμ. N.m.r. spectrum[13]: 4.81 (3), 5.07 (1), 5.63 (1) (broad), 8.36 (3) (doublet, J = 1.2 c.p.s.), 8.50 (3) (half peak width = 3.2 c.p.s.), 8.69 (3), 9.17 (6) (doublet with secondary splitting).

Anal. Calcd. for $C_{20}H_{34}O_2$: C, 78.39; H, 11.19; act. H × 2, 0.64; mol. wt., 306. Found: C, 78.03; H, 11.07; act. H,[14] 0.62; mol. wt., 288[15] (306 minus 18).

α-1,3-Duvanediols A and B (α-II).—A solution of 2.1 g. of α-4,8,13-duvatriene-1,3-diol in absolute ethanol containing platinum oxide catalyst was hydrogenated at room temperature for 48 hr. under a pressure of 3 atm. On chromatography, two glycols, α-1,3-duvanediol A (30 mg.), m.p. 195–196°, and α-1,3-duvanediol B (50 mg.), m.p. 113–114°, were isolated. The compounds gave negative permanganate and tetranitromethane tests for unsaturation.

Anal. Calcd. for $C_{20}H_{40}O_2$: C, 76.86; H, 12.90; mol. wt., 312. Found for A: C, 76.51; H, 12.80; mol. wt., 312. Found for B: C, 76.82; H, 13.02; mol. wt., 312.

A sizable amount (1.5 g.) of a mixture of tetrahydrodiols also was obtained from the reduction. This mixture of isomers melted over a range of 110–114°. The mixture showed n.m.r. absorption at τ 4.45 for the olefinic protons and could be hydrogenated further to the duvanediols.

Anal. Calcd. for $C_{20}H_{38}O_2$: C, 77.36; H, 12.34; mol. wt., 310. Found: C, 77.16; H, 12.35; mol. wt., 310.

When the hydrogenation was done in glacial acetic acid, a 6% yield of saturated monohydric alcohol, m.p. 117–118°, was obtained, along with the tetrahydrodiols and the duvanediols.

Anal. Calcd. for $C_{20}H_{40}O$: C, 81.00; H, 13.60; mol. wt., 296. Found: C, 80.91; H, 13.50; mol. wt., 296.

α-1-Duvanol-3-ones A and B (α-III).—α-1,3-Duvanediols A and B were oxidized separately with chromium trioxide and pyridine according to Poos, *et al.*[16] Isomer A gave α-1-duvanol-3-one A, m.p. 73–75°, and isomer B gave α-1-duvanol-3-one B, m.p. 125–126°.

Anal. Calcd. for $C_{20}H_{38}O_2$: C, 77.36; H, 12.34; mol. wt., 310. Found for A: C, 77.48; H, 12.41; mol. wt., 310. Found for B: C, 77.14; H, 12.15; mol. wt., 310.

Retroaldol Reaction on α-1-Duvanol-3-ones A and B.—An alcoholic solution of α-1-duvanol-3-one B (55 mg.) was converted to a diketone (IVB) by refluxing with 10 ml. of 10% aqueous sodium hydroxide. The diketone, molecular weight 310, gave iodoform and a dibasic acid on treatment with hypoiodite. The 2,4-dinitrophenylhydrazone, m.p. 56°, was recrystallized from aqueous methanol.

Anal. Calcd. for $C_{32}H_{46}O_8N_8$: C, 57.30; H, 6.91; N, 16.71. Found: C, 57.43; H, 6.99; N, 16.55.

The "A" isomer gave a similar product on treatment with alkali; it was identical in its infrared spectrum with the diketone from α-duvanolone B.

α-4,8,13-Duvatriene-1-ol-3-one (α-V).—A solution of 1 g. of α-4,8,13-duvatriene-1,3-diol in 5 ml. of pyridine was added to a stirred mixture of 1 g. of chromium trioxide in 10 ml. of pyridine.[16] After 48 hr. at room temperature, water (125 ml.) was added and the mixture was extracted with ether. After washing the ether layer with water, the solution was dried and concentrated on a rotary evaporator. The product (0.82 g.) was chromatographed and then crystallized from pentane. The α-4,8,13-duvatriene-1-ol-3-one melted at 77–78°, $[\alpha]^{25}\text{D}$ +112 (chloroform); $\lambda_{\max}^{\text{EtOH}}$ = 243 mμ (ε 10,000); infrared spectrum (Nujol): 3400, 1665, 1605, and 980 cm.$^{-1}$; n.m.r. spectrum: 4.05 (1), 4.61 (2), 5.13 (1), 7.88 (3) (doublet, J = 1.3 c.p.s.), 8.40 (3) (half peak width = 2.9 c.p.s.), 8.63 (3), and 9.13 (6) (doublet with secondary splitting).

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59; mol. wt., 304. Found: C, 78.93; H, 10.41; mol. wt., 304.

The same α-duvatrienolone was obtained in 20% yield by oxidation of α-duvatrienediol with activated manganese dioxide.[4]

Dehydration of α-4,8,13-Duvatriene-1-ol-3-one.—To a solution of 204.8 mg. of α-4,8,13-duvatriene-1-ol-3-one in 50 ml. of benzene, 200 mg. of anhydrous magnesium sulfate was added. The mixture then was refluxed for 4 hr., was filtered, and the solvent was evaporated. After chromatography, 40 mg. of liquid dehydration product (XIII), $[\alpha]^{25}\text{D}$ +60 ± 8°, was obtained along with 141.5 mg. of starting keto alcohol. Ultraviolet spectrum: $\lambda_{\max}^{\text{EtOH}}$ = 232 mμ (ε 14,000); infrared spectrum: 1672, 1613, 1212, 972 and 886 cm.$^{-1}$.

No analyses were obtained because the material could not be crystallized and only a small amount was available.

Retroaldol Reaction of α-4,8,13-Duvatriene-1-ol-3-one.—A 550-mg. sample of α-4,8,13-duvatriene-1-ol-3-one was shaken with 10 ml. of 10% aqueous sodium carbonate and 3 ml. of ethanol for 24 hr. The solution was extracted with ether and the ether solution was washed with water, dried, and concentrated. After purification by chromatography, the product (534 mg.), 11-isopropyl-4,8-dimethyl-3,7,12-pentadecatriene-2,14-dione (VI), was an oil, $[\alpha]^{25}\text{D}$ 0° (chloroform), with an ultraviolet absorption at 229 mμ, (ε 22,000, ethanol); infrared spectrum: 1686, 1676, 1619, 1252, 1213, 1168, and 988 cm.$^{-1}$; n.m.r. spectrum: 3.58 (1) (J for quartet = 8.3 c.p.s.), 4.10 (1) (J for doublet = 15.9 c.p.s.), 4.32 (1), 5.19 (1), 7.84 (3), 7.93 (3), 7.96 (3) (doublet, J = 1.1 c.p.s.), 8.47 (3) (half peak width = 2.7 c.p.s.), 9.16 (6) (doublet with secondary splitting).

The compound was also obtained in 10% yield by passing an ether–hexane solution of α-4,8,13-duvatriene-1-ol-3-one through acid-washed alumina.

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59; mol. wt., 304. Found: C, 78.33; H, 10.59; mol. wt., 304.

The mono-2,4-dinitrophenylhydrazone from 11-isopropyl-4,8-dimethyl-3,7,12-pentadecatriene-2,14-dione was an oil.

Anal. Calcd. for $C_{26}H_{36}O_5N_4$: C, 64.44; H, 7.49; N, 11.56. Found: C, 64.35; H, 7.60; N, 11.12.

5-Isopropyl-8-methyl-3,8-tridecadiene-2,12-dione (VII).—11 - Isopropyl - 4,8 - dimethyl - 3,7,12 - pentadecatriene-2,14-dione (526 mg.), obtained from α-duvatrienolone, was dissolved in 20 ml. of 2% sodium hydroxide solution and 20 ml. of ethanol. Volatile products were obtained by distillation and collected in a saturated solution of 2,4-dinitrophenylhydrazine in 2 *N* hydrochloric acid, the distillation being continued until no further precipitation occurred. The precipitate was filtered, dried, and weighed; the precipitate, identified as acetone 2,4-dinitrophenylhydrazone *via* infrared spectrum and mixed melting point, represented a 74% yield of acetone based on a mole for mole formation. The residue from the distillation was extracted with ether and gave 354 mg. of a crude diketone. Purification by chromatography gave 5-isopropyl-8-methyl-3,8-tridecadiene-2,12-dione (VII), which had ultraviolet absorption at 224 mμ (ε 15,000, ethanol) and a molecular weight of 264; infrared spectrum: 1712, 1672, 1630, 1250, 1163, and 987 cm.$^{-1}$; n.m.r. spectrum: 3.46 (1) (J for quartet = 8.3 c.p.s.), 4.11 (1) (J for doublet = 15.9 c.p.s.), 5.00 (1), 7.77 (3), 7.89 (3), 8.41 (3), and 9.12 (6) (doublet with secondary splitting).

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[13] All chemical shifts are given by τ-value, with the number of hydrogens in parentheses.

[14] J. A. Giles, *Anal. Chem.*, **32**, 1716 (1960).

[15] A careful examination of the mass spectra failed to show a peak at mass 306.

[16] G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

The 2,4-dinitrophenylhydrazone of diketone VII melts at 89–91°.

Anal. Calcd. for $C_{29}H_{36}O_8N_8$: C, 56.67; H, 5.80; N, 17.91; neut. equiv., 312. Found: C, 56.38; H, 5.78; N, 17.75; neut. equiv.,[17] 326.

Ozonolysis of α-4,8,13-Duvatriene-1,3-diol.—A sample of α-4,8,13-duvatriene-1,3-diol was dissolved in ethyl acetate and was ozonized at −10° for 1 hr. The solvent was evaporated *in vacuo*, zinc dust was added, and the mixture was steam distilled into a saturated solution of 2,4-dinitrophenylhydrazine in 2 *N* hydrochloric acid. After filtration, the 2,4-dinitrophenylhydrazones were separated by chromatography. The major product was identified as levulinaldehyde 2,4-dinitrophenylhydrazone (40% yield of theoretical on a one mole basis), m.p. 232–233°, by its infrared spectrum and mixed melting point. The material not volatile with steam furnished, after oxidation with 10% hydrogen peroxide, no readily identifiable products.

Periodate–Permanganate Oxidation[6] of α-4,8,13-Duvatriene-1,3-diol.—α-4,8,13-Duvatriene-1,3-diol (2 g.) was mixed with 200 ml. of water and 1.40 g. of potassium carbonate. To this mixture were added 27.9 g. of sodium metaperiodate and 1 g. of potassium permanganate in 200 ml. of water. The solution was stirred for 18 hr., washed once with ether, then acidified with 1 *N* sulfuric acid, and treated with excess sodium bisulfite. The aqueous solution was extracted with ether. The ether extractables (1.1 g.) then were esterified with diazomethane. Vapor phase chromatography of the methyl esters indicated that the mixture contained three main constituents; these were isolated in fair purity by chromatography on silicic acid.

Component A.—The first material eluted was identified as methyl 5-keto-2-isopropylhexanoate by comparison with an authentic sample prepared by the method of Bardhan, De, and Datta.[7] The infrared spectra of the methyl esters were identical as were the spectra of the semicarbazones, m.p. 124° and m.m.p. 123–124°. The two methyl esters also were shown to have identical retention times on vapor phase chromatography. They were chromatographed on an F&M vapor fractometer, using a 4-ft. silicone oil 710 column. The retention time for methyl 5-keto-2-isopropylhexanoate was 15 min. at a programming rate of 4.3°/min., starting at 75° with a helium flow of 60 ml./min.

Component B.—This material was methyl levulinate, identified by its infrared spectrum and the infrared spectrum of its 2,4-dinitrophenylhydrazone, m.p. 139–140°. The retention time on vapor phase chromatography of methyl levulinate was 7 min., using the same conditions as with the methyl 5-keto-2-isopropylhexanoate.

Component C.—Component C was recovered from the liquid chromatography in a relatively small amount and was characterized by its infrared spectrum (1778 and 1733 cm.$^{-1}$) as a γ-lactone, but the small amount prohibited complete identification.

Dehydrogenation of α-4,8,13-Duvatriene-1,3-diol.—A mixture of α-4,8,13-duvatriene-1,3-diol (200 mg.), high boiling kerosene (10 ml.), and 10% palladium on charcoal (200 mg.) was heated at 230° for 5 hr. under nitrogen. After cooling, the mixture was chromatographed on alumina, using hexane and benzene–hexane mixtures as eluents. The fractions eluted with benzene–hexane mixtures contained 35 mg. of aromatic hydrocarbon; ultraviolet spectrum: $\lambda_{\max}^{\text{cyclohexane}}$ = 257, 273, 281, 287, and 300 mμ. The 2,4,7-trinitrofluorenone complex melted at 145°.

Physical Data on β-4,8,13-Duvatriene-1,3-diol (β-I).—Melting point: 127–127.5°. Optical activity: $[\alpha]^{25}\text{D}$ +162° (chloroform). Infrared spectrum (Nujol): 3280 (s), 1667 (w), 1166, 1142, 1117, 1095, 1083, 1035, 975 (s), 946, 923, 889 and 875 cm.$^{-1}$. Ultraviolet spectrum: $\lambda_{\max}^{\text{EtOH}}$ = end absorption below 220 mμ. N.m.r. spectrum: 4.82 (2), 4.96 (2), 5.36 (1) (broad), 8.36 (3) (doublet, J = 1.2 c.p.s.), 8.53 (3) (half peak width = 3.1 c.p.s.), 8.65 (3), 9.18 (6) (doublet with secondary splitting).

Anal. Calcd. for $C_{20}H_{34}O_2$: C, 78.39; H, 11.19; act. H × 2, 0.64; mol. wt., 306. Found: C, 78.37; H, 11.09; act. H, 0.61; mol. wt., 288[15] (306 minus 18).

β-1,3-Duvanediol (β-II).—A solution of β-4,8,13-duvatriene-1,3-diol (187 mg.) in 50 ml. of absolute ethanol containing 10 mg. of platinum oxide catalyst was hydrogenated for 18 hr. at room temperature under a pressure of 3 atm. Chromatography of the products gave β-1,3-duvanediol A, m.p. 122–123°, and β-1,3-duvanediol B, m.p. 139–139.5°.

Anal. Calcd. for $C_{20}H_{40}O_2$: C, 76.86; H, 12.90; mol. wt., 312. Found for A: C, 76.61; H, 13.14; mol. wt., 312. Found for B: C, 76.94; H, 12.81; mol. wt., 312.

Also isolated from the hydrogenation of β-4,8,13-duvatriene-1,3-diol was a small amount of two tetrahydro derivatives A and B, m.p. A, 112–113°, and B, 131–132°.

Anal. Calcd. for $C_{20}H_{38}O_2$: C, 77.36; H, 12.34; mol. wt., 310. Found for A: C, 77.37; H, 12.17; mol. wt., 310. Found for B: C, 77.28; H, 12.34; mol. wt., 310.

β-1-Duvanol-3-ones A and B (β-III).—The β-duvanediols, A and B, were oxidized separately with chromium trioxide and pyridine, using the procedure described by Poos, *et al.*[16] Each duvanediol isomer gave a different keto alcohol. The β-1-duvanol-3-one A from diol A melted at 127–128°, $[\alpha]^{27}\text{D}$ −113° (chloroform), and β-1-duvanol-3-one B from diol B melted at 98–99°, $[\alpha]^{27}\text{D}$ −38° (chloroform). The infrared spectra showed a sharp hydroxy peak at 3450 cm.$^{-1}$ and a carbonyl peak at 1700 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{38}O_2$: C, 77.36; H, 12.34; mol. wt., 310. Found for A: C, 76.57; H, 11.93; mol. wt., 310. Found for B: C, 77.26; H, 12.24; mol. wt., 310.

A solution of 15 mg. of β-1-duvanol-3-one A, m.p. 127°, and a catalytic amount of iodine in 10 ml. of benzene was refluxed for 2 hr. The mixture was extracted with sodium bisulfite solution and with water. After evaporation of the solvent, the product was chromatographed and 8 mg. of an α,β-unsaturated ketone, m.p. 84–85°, was obtained. The compound had infrared absorption at 1680 and 1615 cm.$^{-1}$, ultraviolet absorption at 243 mμ (ethanol, $\epsilon < 5000$), and a molecular weight of 292. Treatment of β-1-duvanol-3-one B with iodine and benzene in the same manner as the A isomer resulted in β-duvanolone B being recovered unchanged.

Retroaldol Reaction of β-1-Duvanol-3-one.—The same retroaldol procedure was used for β-1-duvanol-3-one B as for the α-1-duvanol-3-ones. A diketone (IVB) was obtained having the same infrared spectrum and molecular weight as the diketone from α-1-duvanol-3-one. The 2,4-dinitrophenylhydrazone, m.p. 56–58°, was prepared and was identical, as shown by infrared spectrum and mixed melting point, with the derivative from the diketone (IV) obtained from α-1-duvanol-3-one B.

β-4,8,13-Duvatriene-1-ol-3-one (β-V).—A solution of β-4,8,13-duvatriene-1,3-diol (212 mg.) in pyridine (5 ml.) was oxidized 24 hr. with the chromic anhydride–pyridine complex.[16] After addition of water, the solution was extracted with ether and the ether-extractable material (194 mg.) was chromatographed. The infrared spectrum of the main product, 112 mg. of an oil (3460, 1675, and 1615 cm.$^{-1}$), showed it to be an α,β-unsaturated keto alcohol, *β-4,8,13-duvatriene-1-ol-3-one*, $[\alpha]^{25}\text{D}$ +203° (*chloroform*); $\lambda_{\max}^{\text{EtOH}}$ 244 mμ (ε 10,000); n.m.r. spectrum: 3.93 (1), 4.63 (2), 5.03 (1), 7.92 (3) (doublet, J = 1.4 c.p.s.), 8.41 (3) (half peak width = 3.1 c.p.s.), 8.61 (3), and 9.13 (6) (doublet with secondary splitting).

The same keto alcohol was obtained in 20% yield by oxidation of β-4,8,13-duvatriene-1,3-diol with activated manganese dioxide.[4]

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59; mol. wt., 304. Found: C, 78.48; H, 9.75; mol. wt., 304.

Dehydration of β-4,8,13-Duvatriene-1-ol-3-one.—A solution of 100 mg of β-4,8,13-duvatriene-1-ol-3-one in 25 ml.

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[17] A. J. Sensabaugh, R. H. Cundiff, and P. C. Markunas, *Anal. Chem.*, **30**, 1445 (1958).

of benzene was mixed with 1 g. of anhydrous magnesium sulfate and the mixture was refluxed for 3 hr. After filtering and evaporating the solvent, the product was chromatographed. Two products were obtained. The first one (30 mg.), $[\alpha]^{25}D$ +71 ± 7°, was a material having the same ultraviolet and infrared spectra as the dehydration product (XIII) from α-4,8,13-duvatriene-1-ol-3-one. The second product (40 mg.) had ultraviolet (λ_{max}^{EtOH} = 289 mμ, ε 11,000) and infrared absorption (1659, 1620, 1226, 1140, 968 cm.$^{-1}$) consistent with the structure 1,4,8,13-duvatetraene-3-one. No analyses were obtained due to limited amounts of compounds.

Retroaldol Reaction of β-4,8,13-Duvatriene-1-ol-3-one.—A solution of β-4,8,13-duvatriene-1-ol-3-one in 10% sodium carbonate solution containing a small amount of alcohol was refluxed for 0.5 hr. The solution was extracted with ether and the ether solution was washed, dried, and evaporated. The product was an oil which was further purified by chromatography. The compound had the same infrared, ultraviolet, and nuclear magnetic resonance spectra and molecular weight as 11-isopropyl-4,8-dimethyl-3,7,12-pentadecatriene-2,14-dione (VI), obtained previously from α-4,8,13-duvatriene-1-ol-3-one.

Ozonolysis of β-4,8,13-Duvatriene-1,3-diol.—β-4,8,13-Duvatriene-1,3-diol (665 mg.) in 75 ml. of methylene chloride was ozonized for 30 min. at −78°. The solution was allowed to warm to room temperature and the solvent was evaporated *in vacuo*. Zinc dust was added and the mixture was steam distilled into a saturated solution of 2,4-dinitrophenylhydrazine in 2 *N* hydrochloric acid. The precipitate was filtered and chromatographed on silicic acid to give 311 mg. (35% yield of theoretical on a one mole basis) of levulinaldehyde 2,4-dinitrophenylhydrazone identified *via* infrared and mixed melting point. On the same basis a 55% yield of levulinaldehyde was obtained from a second ozonization of β-duvatrienediol.

Permanganate Oxidation of β-4,8,13-Duvatriene-1,3-diol.—Potassium permanganate (7.75 g., 49 mmoles) in 100 ml. of water was added to 1 g. of β-4,8,13-duvatriene-1,3-diol (3.26 mmoles) mixed with 300 ml. of water. The solution was stirred for 24 hr., then was treated with sulfur dioxide, and extracted with ether. The oil (300 mg.) obtained after evaporation of the ether was treated with diazomethane and the resulting mixture was analyzed by vapor phase chromatography. It was found to contain two major components, along with several minor ones; the two major components were determined to be methyl levulinate and methyl 5-keto-2-isopropylhexanoate by comparison of vapor phase chromatograms of samples enriched by the addition of authentic specimens. The vapor phase chromatograms were done using the same conditions as described previously for the products from the periodate–permanganate oxidation of α-4,8,13-duvatriene-1,3-diol.

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Fluorinated Cyclic Polysulfides and Their Polymers

C. G. KRESPAN AND W. R. BRASEN

Contribution No. 778 from the Central Research Department, Experimental Station,
E. I. du Pont de Nemours and Company, Wilmington 98, Delaware

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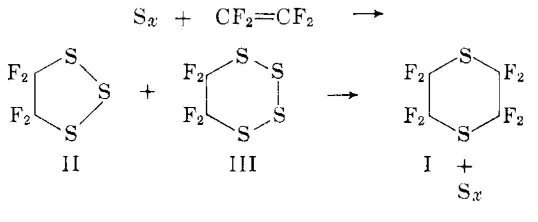
A unique cyclic tetrasulfide, tetrafluoro-1,2,3,4-tetrathiane, has been prepared in good yield directly from sulfur and tetrafluoroethylene. The new cyclic polysulfides, tetrafluoro-1,2,3-trithiolane and octafluoro-1,2,5-trithiepane, have also been isolated. The polymerization of these compounds and their role in the preparation of the thermally stable octafluoro-1,4-dithiane are described.

During earlier studies[1] of the interaction of sulfur with tetrafluoroethylene to produce octafluoro-1,4-dithiane (I), it was observed that polysulfides were also formed, apparently as intermediates to the dithiane. Further investigation of this reaction has now resulted in the characterization of several unusual cyclic and linear polysulfides of tetrafluoroethylene. Unlike reactions of sulfur with hydrocarbons, the number and amount of by-products are small, and individual polysulfides of tetrafluoroethylene are easily obtained.

Fluorinated Cyclic Polysulfides.—In order to obtain the primary products formed from tetrafluoroethylene and sulfur, the reaction was conducted at atmospheric pressure in a flow system with a large excess of sulfur. These conditions were attained by passing tetrafluoroethylene through vapors of refluxing sulfur (b.p. *ca.* 445°) and continuously withdrawing volatile product. High yields of polysulfides were obtained by this procedure, and it was possible to isolate 10% of the yellow tetrafluoro-1,2,3-trithiolane (II) and 60% of the pale yellow tetrafluoro-1,2,3,4-tetrathiane (III) with little of the dithiane I having been formed. Both II and III are malodorous oils with b.p. 38–39° (30 mm.) and 59–61° (15 mm.), respectively.



At the high temperature of 445°, some tetrafluoroethylene is lost in cracking reactions in which

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[1] C. G. Krespan and C. M. Langkammerer, *J. Org. Chem.*, **27**, 3584 (1962).