223. Terpenoids Derived from Linalyl Oxide, Part 4. The Oxidation of Davanone. Isolation and Synthesis of the Davana Ethers, Sesquiterpenes of *Artemisia Pallens*

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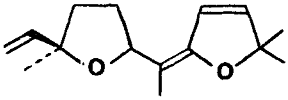
(16. VIII. 74)

Summary. The photosensitized oxygenation of the β,γ-unsaturated ketonic sesquiterpene, davanone, is described. Treatment of davanone epoxide with an acid ion exchange resin yields a stereoisomeric mixture of the davana ethers, sesquiterpenoids containing two reduced furan rings.

We have already described the isolation from *Artemisia pallens* and the synthesis of davana ether (**1**) without experimental detail, [1] and in this publication, we wish to present the details of our synthesis and of another attempted route.



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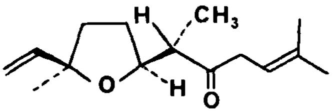

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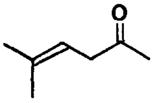

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It was initially believed that since davana ether (**1**) is an oxidized davanone (**2**) [2], it should be possible to place an additional oxygen atom in such a way that cyclization with the carbonyl group would be possible. We first attempted to carry this out by photooxygenation with singlet oxygen. In a previous note [3] it was reported that photoaddition of singlet oxygen to β,γ-unsaturated ketones led *in every case* to the γ-hydroxy-α,β-unsaturated ketone. While this may be true for the rigid steroid cases mentioned therein, we feel that, in view of the results presented here[1], it is most unlikely to be true for 5-methylhex-4-en-2-one (**3**), a ketone corresponding to davanone (**2**), and which the japanese authors claim gives a single photooxidation product [3].

In pyridine solution, the uptake of oxygen by (+)-davanone is complete in less than one hour. We found that the only way to obtain reproducible and consistent results was to reduce the solution from the oxygenation with triphenylphosphine. TLC. indicated that two main new substances had been formed, and, after separation by silica gel chromatography, these were identified as a hemiacetal (**4**) formed by cyclization of the γ-hydroperoxy-α,β-unsaturated ketone (**5**) in the form of its *cis*-isomer, and the alcohols (**6**) formed by addition of oxygen to the other end of the double bond (**7**). While it is difficult to be precise about the amounts of each sub-

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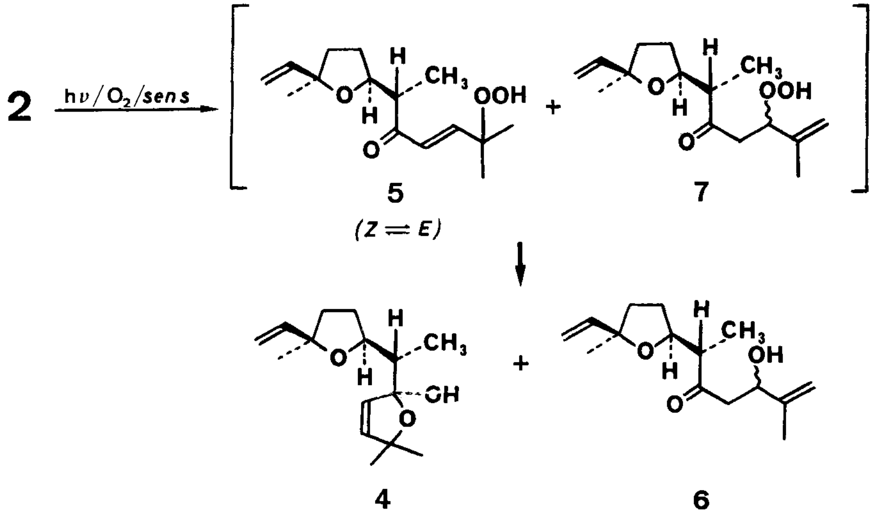
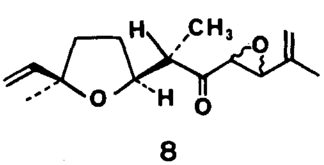
[1] There are several other cases where β,γ-unsaturated ketones react no differently from other trisubstituted olefins, in particular, it has been found that 4-methylhex-3-enal yields products derived from oxygenation at both ends of the double bond [4].

stance – in particular because the hemiacetal (**4**) is unstable on GLPC., the proportions isolated corresponded approximately (6:4) with those encountered in singlet



oxygen addition to other 1,1-dimethyl-2-substituted ethylenes [5]. The NMR.-spectra suggest that the hemiacetal (**4**) is at least 90% present in the form of a single isomer, while the allyl alcohols (**6**) are present as two isomers in approximately equal amounts.

If the solution from the photooxygenation is reduced with sodium sulfite, the results are not reproducible, and yields are low, but the major product is always the same hemiacetal (**4**) as obtained in the reduction with triphenylphosphine. The allyl alcohols (**6**) are, however, never detected, the epoxides (**8**) constituting the principal by-products that we could characterize. Unfortunately, while the hemiacetal can not be isolated by GLPC., we were never able to isolate the epoxides by column chromatography on silica gel, so the results given in the experimental section are not quantitative.



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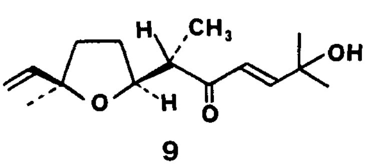

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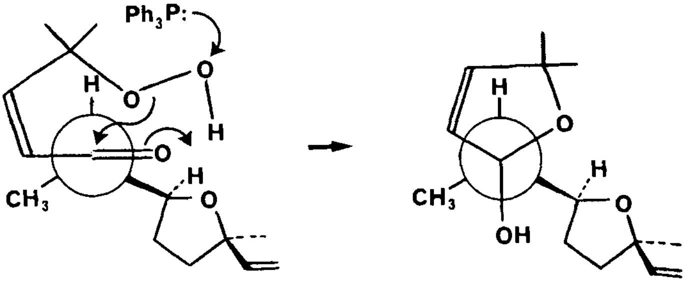
When the hydroperoxide solution was concentrated at room temperature without prior reduction, and the residue chromatographed on silica gel, the only products that could be definitely characterized were small amounts of the hemiacetal (**4**), and the corresponding (*E*)-α,β unsaturated alcohol (**9**), which is probably always present in small amounts (judging from the presence of a spot with the corresponding Rf value on TLC.) after singlet oxygen reactions on davanone. This alcohol can be obtained more conveniently from davanone epoxide (see below).

Despite the fact that small amounts of davana ether (**1**) were frequently encountered in the experiments on photooxygenation of davanone, no conditions were found when it was a major product; moreover, all attempts to dehydrate the hemiacetal (**4**) by pyrolysis or phosphorus oxychloride in pyridine resulted in very complex mixtures.

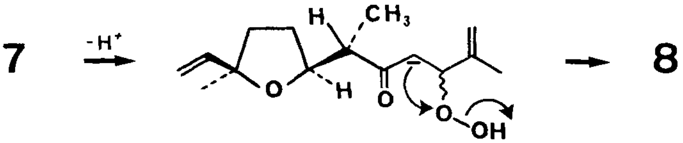
Isomerization about the double bond of the hydroperoxide (**5**) must be easy, and is known to occur during irradiation [6], so that it is not unreasonable that the hemiacetal is isolated after reduction. A possible mechanism for the reaction is shown in *scheme 1*, which accounts for the formation of almost exclusively one isomer as a consequence of the greater ease of approach to the carbonyl group from the least hindered direction. This leads to the hypothesis that the isomer formed is mainly 5*S*,6*S*,7*S*,10*R*, based on the fact that (+)-davanone is the 6*S*,7*S*,10*R*-isomer, and the preferred orientation of carbonyl group [2b].

Scheme 1



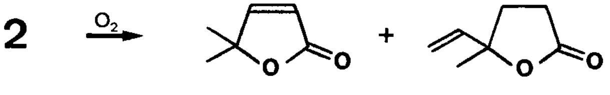
The behavior of the hydroperoxide **7** is probably conditioned by the ease with which it forms an anion, such anions (*scheme 2*) being known to be intermediates in the *Weitz-Scheffer* epoxidation of unsaturated ketones [7]. It is thus not surprising that we isolated the epoxides (**8**) after reduction of the hydroperoxides with the basic sodium sulfite. Possibly the lability of such β-hydroperoxyketones is the reason that alcohols corresponding to **6** were not observed in the Japanese work, indeed, some of their reported yields are significantly low [3].

Scheme 2



It was observed that if davanone is left open to the air it is slowly oxidized. The main products of this autoxidation are apparently polymeric, and do not exit from a gas chromatography column, but there is a small amount of volatile material, mostly consisting of fission products. In particular, the lactones **10** and **11** were characterized as the major compounds present, and it is not surprising that both of these are present in the natural oil. Lactone **11** is a constituent of tobacco [8] and black tea [9].

Confirmation of the structure assigned to the alcohol **9** was obtained when davanone epoxide (**12**), obtained smoothly by treatment of davanone with buffered peracetic acid, was treated with an acid ion exchange resin. The main product in this case was the desired davana ether isomeric mixture, the spectra of which were identical with the davana ethers isolated from *Artemisia pallens* [1], but approximately 20% of the product after distillation consisted of the (E)-α,β-unsaturated alcohol **9**. We were unable to find a satisfactory method for converting the latter cleanly to the davana ethers.



10 **11**

Experimental Part

Photooxidation of davanone. A solution of 10 g of davanone and a spatula point of bengal red in 400 ml of pyridine was irradiated in a current of oxygen. After absorbing 990 ml of oxygen in less than 1 h (corr. for 0° and 760 mm, calc. for 1 equiv. 960 ml), the reaction practically stopped. The mixture was stirred overnight with 10 g of triphenylphosphine, then concentrated and the residue taken up in hexane and filtered. The solution was chromatographed on silica gel in hexane/ether 9:1, and two main products were eluted, both of which were very difficult to dry completely. In order, these were:

2,6,10-trimethyl-2,5:7,10-dioxido-dodeca-3,11-dien-5-ol (**4**), 2.2 g. NMR. ($CDCl_3$): 0.89 (3 H, *d*, $J = 7$ Hz, $CH_3CH{<}$); 1.28; 1.36; 1.41 (each 3 H, *s*, $CH_3{-}C{\leqslant}$); 1.4–2.3 (5 H, *m*, CH_2); 4.25 (1 H, *m*, $CH_2{-}CH{-}CH$); 5.02 (1 H, $d \times d$, $J = 2$ and 10 Hz) and 5.21 (1 H, $d \times d$, $J = 2$ and 17 Hz, $CH{=}CH_2$); 5.66 and 5.96 (1H each, *d*, $J = 10.5$ Hz, $CH{=}CH$ (*cis*)); 5.93 (1H, $d \times d$, $J = 10$ and 17 Hz, $CH{=}CH_2$). – MS.: 43 (100), 55 (51), 41 and 69 (43), 97 (34), 111 (30), 67 and 27 (27), 39 and 81 (24)... 234 (M-18^+, 1.5). – IR. (CCl_4): 3420 (OH), practically no absorption 1500–1800. – No UV. absorption above 210 nm.

$C_{15}H_{24}O_3 \cdot H_2O$ (270.4) Calc. C 66.63 H 9.69% Found C 66.92 H 9.04%

2,6,10-trimethyl-2,5:7,10-dioxido-dodeca-1,11-dien-3-ol-5-one (**6**), 1.7 g. NMR. ($CDCl_3$): 1.03 (3 H, *d*, $J = 6.5$ Hz, $CH_3CH{<}$); 1.29 (3 H, *s*, $CH_3{-}C{\leqslant}$); 1.62 (3 H, *s*, $CH_3{-}\overset{|}{C}{=}$), superimposed on signals for CH_2CH_2; 2.5–3.0 (3 H, *m*, $CH{-}CO{-}CH_2$, two isomers); 4.13 (1 H, *m*, $CH_2{-}\underset{\underset{O}{|}}{CH}{-}CH$); 4.57 (1 H, *m*, $C{=}C{-}\underset{\underset{OH}{|}}{CH}{-}CH_2$); 4.8–5.4 (4 H, *m*, $C{=}CH_2$); 5.93 (1 H, 2 groups of 4 lines, separated by about 0.5 Hz, $J = 10$ and 17, $CH{=}CH_2$). – MS.: 43 (100), 41 (61), 55 (54), 111 (44), 71 (33), 41, 57, 93 (30), 69 (26), 70 (25)... 167 (M-85^+, 2). – IR.: 3470 (OH), 1705 (C=O).

$C_{15}H_{24}O_3$ (252.3) Calc. C 71.39 H 9.59% Found C 70.19 H 9.04%

When the solution from the photooxygenation step was reduced by stirring with a saturated solution of sodium sulfite, the results were less reproducible. In a typical experiment, the mixture, after reduction, was extracted with pentane, the pentane solution rapidly washed with ice-cold 10% hydrochloric acid, followed by water, then concentrated. The products were purified by either chromatography on silica gel, when the principal substance (90% of the eluted material) was 2,6,10-trimethyl-2,5:7,10-dioxido-dodeca-3,11-dien-5-ol, identical with the material described above, or by GLPC., when the only substances eluted were two isomers of *2,6-10-trimethyl-3,4:7,10-dioxido-dodeca-1,11-dien-5-one* (**8**) in almost equal amounts. The less polar isomer, eluted first, had NMR. (CCl_4): 0.97 (3 H, *d*, $J = 7$ Hz, $CH_3CH{<}$); 1.35 (3 H, *s*, $CH_3C{\leqslant}$); 1.65 (3 H, *d*, $J = 1.5$ Hz, $CH_3{-}\overset{|}{C}{=}$); 2.5–3.0 (1 H, *m*, $CO{-}\underset{\underset{CH}{|}}{CH}{-}CH_3$); 3.3–3.6 (2 H, *m*, $CO{-}\underbrace{CH{-}CH}_{O}{-}\overset{|}{C}{=}$);

3.8–4.2 (1 H, *m*, $CH_2-\underset{\substack{|\\ O}}{CH}-CH$); 4.9–5.3 (4 H, *m*, $C{=}CH$); 5.95 (1 H, *d* × *d*, *J* = 10 and 17, $CH{=}CH_2$).

The NMR.-spectrum of the other isomer was very similar, except for a clearly defined pair of doublets, 3.39 and 3.49 (2 H, *d*, *J* = 2.5 Hz, $\underset{\diagdown O \diagup}{CH-CH}$). The MS. of the two epoxides were virtually identical: 55 (100), 111 (82), 43 (73), 41 (66), 93 (56), 83 (43), 39 (40), 29 (37), 27 and 67 (35)... 235 (M-15$^+$, 2). – No OH band was visible in the IR.-spectrum.

$C_{15}H_{22}O_3$ (250.3) Calc. C 71.97 H 8.86% Found C 71.69 H 8.81%

In another experiment using 1 g of davanone, in which the photo-oxygenation step was carried out in the same way, the pyridine solution was concentrated in high vacuum at room temperature, then the residue was chromatographed directly on a column of silica gel. With hexane/ether 8:2, a small amount of the hemiactal (**4**) was isolated, followed immediately by 0.1 g of E-2,6,10-trimethyl-7,10-oxido-dodeca-3,11-dien-2-ol-5-one (**9**), the spectra of which were identical with those of the product prepared from davanone epoxide (see below).

Autoxidation of davanone. Small samples of davanone were left open to the air for several weeks. The products were isolated by direct GLPC.:

a) *4-Methylpent-2-enolide* (**10**). NMR. ($CDCl_3$): 1.49 (6 H, *s*, $CH_3{-}C$); 5.99, 7.40 (each 1 H, *d*, *J* = 6 Hz, $CH{=}CH{-}C{=}O$). – MS.: 97 (100), 43 (96), 69 (88), 41 (18), 26, 39, and 54 (14), 112 (M^{+}, 11), 27 and 59 (9).

This material was identical in all respects with authentic synthetic methylpentenolide [10] and also with a substance isolated from the first fraction (b.p. less than 35°/0.01 Torr) of the commercial oil of *Artemisia pallens* (davana).

b) *4-Methylhex-5-enolide* (**11**). NMR. ($CDCl_3$): 1.5 (3 H, *s*, CH_3C); 2.0–2.25 (2 H), and 2.4–2.7 (2 H, *m*, $CH_2{-}CH_2{-}CO$); 5.14 and 5.27 (2 H, *d* × *q*, *J* = 1.5, 10 and 17 Hz, $CH{=}CH_2$); 5.92 (1 H, *d* × *d*, *J* = 10 and 17 Hz, $CH{=}CH_2$). – MS.: 111 (100), 43 and 55 (82), 71 (49), 27 and 67 (47), 56 (38), 99 (32), 41 (30), 39 and 98 (25)... 126 (M^{+}, 17).

This material was identical in all respects with authentic synthetic methylhex-5-enolide [11] and with a substance isolated from the most volatile fraction of the commercial davana oil.

Davanone epoxide (**12**). A solution of 7 g of davanone and 2.3 g of sodium acetate in 70 ml of methylene chloride was stirred at 0–2° while 6.3 g of peracetic acid (30% in acetic acid) were added dropwise. After the addition was ended, the mixture was stirred for 3 h at room temperature, then poured into 200 ml water. The aqueous layer was extracted once with methylene chloride, and the combined organic part was washed to neutrality, first with a solution of sodium hydrogen carbonate, then with water. After drying and concentrating, the solution yielded almost pure davanone epoxide (7 g). For analysis, this was purified by chromatography on silica gel (eluted with toluene/ether 4:1), and GLPC. – NMR.: 0.98 (3 H, *d*, *J* = 7 Hz, CH_3CH); 1.19; 1.23; 1.29 (3 H each, *s*, $CH_3C\lesssim$); 1.6–2.0 (4 H, $CH_2{-}CH_2$); 2.4–3.1 (4 H, $CH-CO-CH_2-\underset{\diagdown O \diagup}{CH-\overset{|}{C}}-$); 4.00 (1 H, *m*, $CH_2-\underset{\substack{|\\ O}}{CH}-CH\langle$); 4.8–5.3 (2 H, *m*, $CH{=}CH_2$); 5.92 (1 H, *d* × *d*, *J* = 10 and 17 Hz, $CH{=}CH_2$). – MS.: 43 (100), 55 (42), 41, 69, 111 (36), 97 and 109 (33), 93 (23), 67 (22), 124 (19)... 234 (M-18$^+$, 10).

$C_{15}H_{24}O_3$ (252.3) Calc. C 71.39 H 9.59% Found C 71.16 H 9.55%

Treatment of davanone epoxide with acid. A solution of 4 g of davanone epoxide in 15 ml of dry ether was heated at reflux while being stirred with 0.1 g of Dowex 50 resin (acid form) that had previously been dried in high vacuum over P_2O_5 for 48 h. After 38 h, the solution was concentrated and the residue distilled in a short-path distillation apparatus (bath temp. 80°/0.01 Torr). GLPC. of the product on OV 17 showed two main peaks in the ratio of about 4:1. For analysis these were separated by preparative GLPC. on OV 17. The peak with shorter retention time was identical with the natural mixture of *davana ethers* (**1**): NMR.: CH_3 and CH_2 region, 16 H, with signals at 1.26, 1.30 and 1.62; $CH{-}O$ region, 1 H, *ca.* 4.6; $CH{=}CH_2$, 2 H, *ca.* 4.88 and 5.10; other vinyl protons, 3 H, 5.6 to 6.4. – UV. (λ_{max}^{EtOH}): 272 nm/ε_{max} 5710. – MS.: 43 (100), 109 (97), 124 (64), 41 and 166 (48), 55, 151, and 163 (39), 149 and 234 (M^{+}) (35). – No OH band in IR.-spectrum.

$C_{15}H_{22}O_2$ (234.3) Calc. C 76.88 H 9.46% Found C 77.09 H 9.41%

The peak with the longer retention time was identified as *2,6,10-trimethyl-cis-7,10-oxido-dodeca-3*E*,11-dien-2-ol-5-one* (**9**). NMR.: 1.00 (3 H, *d*, J = 7 Hz, CH_3—CH); 1.23 (3 H) and 1.34 (6 H) (*s*, CH_3—C); 1.6 to 2.0 (4 H, *m*, CH_2CH_2); 2.45 (1 H, *m*, $CH—\underset{\displaystyle CO}{\underset{|}{CH}}—CH_3$); 4.15 (1 H, *m*, $CH_2—\underset{\displaystyle O}{\underset{|}{CH}}—CH$), the CH=CH$_2$ signals were at 4.90 ($d \times d$); 5.14 ($d \times d$) and 5.90 ($d \times d$, J = 10 and 17 Hz); 6.32 and 6.87 (each 1 H, *d*, J = 15 Hz, *CH*=*CH*—CO). – MS.: 43 (100), 111 and 113 (60), 55 and 93 (57), 41 (45), 85 (39), 67 and 69 (37), 95 (23)... 234 (M-18^{+}) and 237 (M-15^{+}) (3). – IR. (CCl_4): 1630, 1668, 1692 cm^{-1}. A satisfactory elemental analysis was not obtained, apparently because of the presence of water in the sample.

We thank Dr. *K. H. Schulte-Elte* for discussions, and information prior to publication.

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224. Terpenoids Derived from Linalyl Oxide. Part 5. 2-(2-Methyl-2-vinyltetrahydrofur-5-yl)-2,6,6-trimethyl-2,6-dihydropyr-3-one, a New Sesquiterpenoid Isolated from *Artemisia Pallens*

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(26. VIII. 74)

Summary. Based on spectra, the structure of the title compound has been attributed to a new sesquiterpenoid isolated from *Artemisia Pallens*. From the same fraction of the oil, the conjugated unsaturated ketone, isodavanone (**2**), was identified.

Previous papers [1] have described a number of novel compounds related to linalyl oxide that have been isolated from the essential oil of *Artemisia pallens* (= davana oil). In this note, we describe an oxidized, cyclized derivative (**1a**) of