Tobacco Chemistry. 48.* Synthesis of Tobacco Labdanoids by Sensitized Photo-oxygenation of (12E)-Abienol

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The sensitized photo-oxygenation of (12E)-abienol (1) occurs with competition between four processes, the two major ones being *syn* ene reactions, which yield, after reduction, the (12S)- and (12R)-13(16),14-labdadiene-8,12-diols (2,3; 51 %) and the (11E,13S)- and (11E,13R)-11,14-labdadiene-8,13-diols (4, 5; 23 %). Smaller contributions to the overall yield are obtained from a process which is proposed to involve the attack of oxygen on the 12,13 double bond and to proceed with participation of the 8α-hydroxyl group to the (12R,13S)- and (12S,13R)-8,12-epoxy-14-labden-13-ols (6, 7; 2 %) and the (12R,13S)- and (12S,13R)-8,13-epoxy-14-labden-12-ols (8, 9), and from a Diels-Alder reaction (7 %) giving *inter alia* (12R)-12,15-epidioxy-13-labden-8-ol (10).

Subsequent chemical alterations of the initially produced compounds account for the generation of the (12S)- and (12R)-15,16-epidioxy-13-labdene-8,12-diols (13,14), the (12S)- and (12R)-15,16-epoxy-13(16),14-labdadiene-8,12-diols (15, 16), (11E)-14,15-bisnor-8-hydroxy-11-labden-13-one (17) and 12-norambreinolide (18).

Since eight of the products obtained are tobacco constituents, *i.e.* 4-9, 17 and 18, and since only four of these, 4, 5, 17 and 18, are formed on photo-oxygenation of (12Z)-abienol (19), it seems likely that both isomers of abienol (1, 19) are precursors of the labdanoids found in tobacco.

As part of a study on the biogenesis of the diterpenoids and nor-diterpenoids of tobacco, we have previously reported on the sensitized photo-oxygenation of (12Z)-abienol (19),[2] a labdanoid present in the cuticular wax of green leaves of certain tobacco cultivars. Although the results obtained strongly corroborate the

view that (12Z)-abienol (19) is a probable precursor of the majority of the labdanoids and nor-labdanoids found in processed tobacco, they also suggest that some of the tobacco labdanoids derive from a precursor such as (12E)-abienol (1).[3] In view of this we have now examined the products obtained in the reaction of singlet oxygen with (12E)-abienol (1).
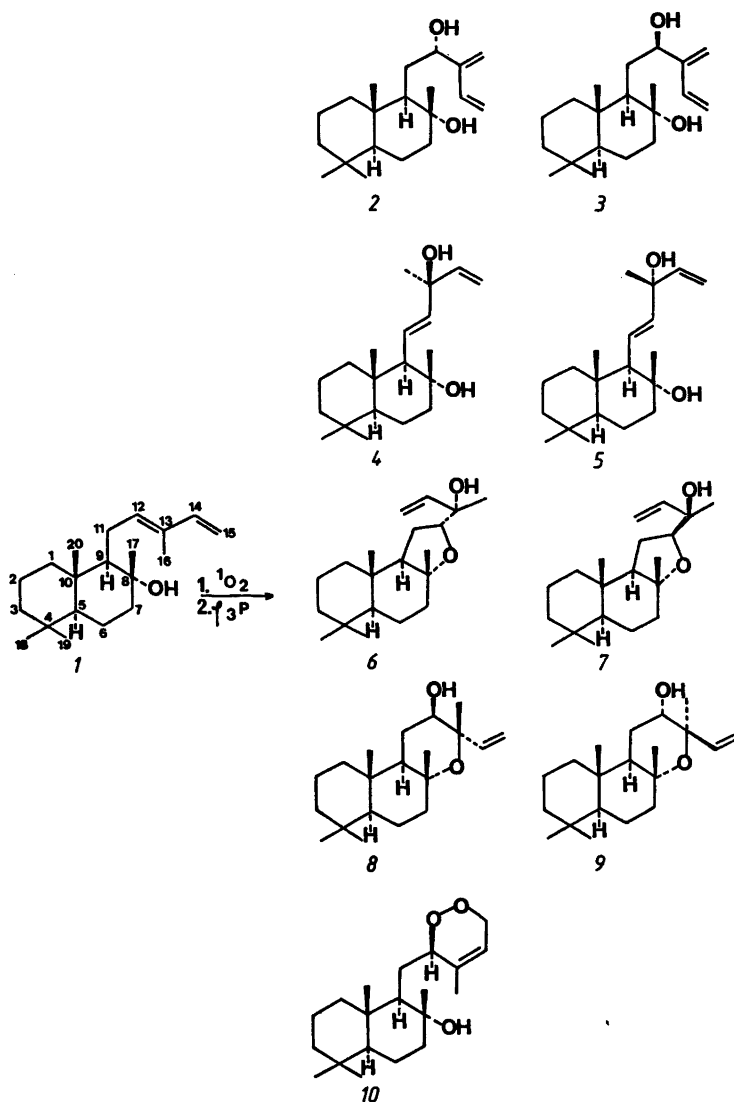
RESULTS

(12E)-Abienol (1), which has a 1,3-diene system consisting of a trisubstituted and a monosubstituted double bond, reacts smoothly with singlet oxygen. Reduction of the reaction mixture with triphenyl phospine, examination

Table 1. Relative proportions (%), as determined by GC integration, of the various products obtained on photo-oxygenation of (12E)-abienol (1).[a]

Compound	%	Compound	%
2	18	11	2
3	33	12	c
4	12	13	—
5	11	14	—
6	2	15	—
7	0.1	16	—
8	0.1	17	0.1
9	b	18	1
10	c		

[a] The reaction was stopped when all starting material had been consumed. [b] Obscured. [c] 10+12 integrate for 5 %.

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* For part 47, see Ref. 1.

Scheme 1. Compounds formed by sensitized

by GC (Table 1) and GC-MS and subsequent
separation by liquid chromatography resulted
in the identification of compounds *2 — 18*,
which are depicted in Scheme 1.

As shown in Table 1 the major products
obtained are the (12*S*)- and (12*R*)-13(16),14-
labdadiene-8,12-diols (*2, 3*) and the (11*E*,13*S*)-
and (11*E*,13*R*)-11,14-labdadiene-8,13-diols (*4,
5*). These compounds are evidently products
of ene reactions and their formation, conven-

iently visualized by the aid of Dreiding models,
may be rationalized as shown Scheme 2 (*cf.*
Ref. 2 for a more detailed discussion). Thus,
reactions involving oxygen addition to the
12,13 double bond and migration of H-16 in
conformers such as A_1 and A_2 (bottom face
attack) would afford the (12*R*)-hydroperoxide
of 13(16),14-labdadien-8-ol (*3a*), while the
(12*S*)-hydroperoxide *2a* would be generated by
analogous reactions occurring in conformers
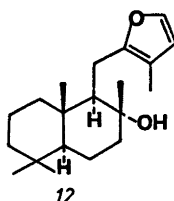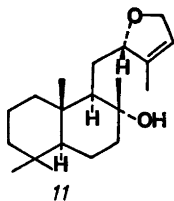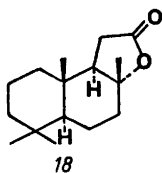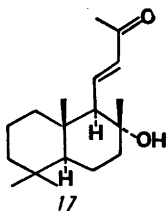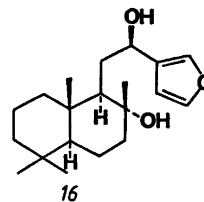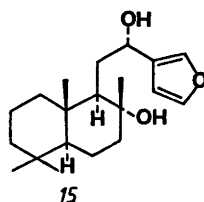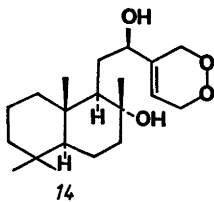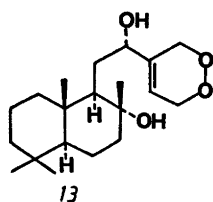
photooxygenation of (12E)-abienol (1).

A_2 (top face attack) and B_1. The formation of the (13R)-hydroperoxide of (11E)-11,14-labdadien-8-ol ($5a$) is likely to take place by abstraction of the 11α-hydrogen on oxygen attack at the 12,13 double bond in conformer A_1, whereas attack at the top face of conformer A_2 and migration of the 11β-hydrogen would produce the corresponding (13S)-hydroperoxide $4a$.

According to a recently advanced hypothesis,[4] both sets of epimers are the expected products of *syn* * ene additions, the formation of the 8,12-diols (2, 3) however, being markedly favoured over that of the 8,13-diols (4, 5), 51 % as against 23 % (*cf.* Table 1). A comparison within the two sets of epimers obtained

* We have adopted the nomenclature proposed by Schulte-Elte *et al.*,[4] by which ene additions at the disubstituted side of a trisubstituted olefin are termed *syn* and those at the monosubstituted side *anti*.
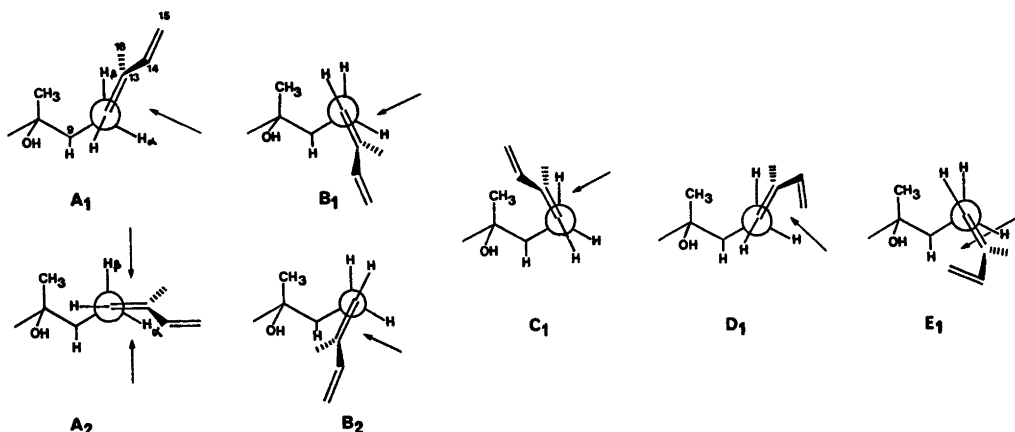
Scheme 2. Conformers about the 11,12-bond in (12*E*)-abienol (*1*).

from (12*E*)-abienol (*1*) shows that the 8,12*R*-diol (*3*) is more abundant than the 8,12*S*-diol (*2*), whereas the two 8,13-diols (*4, 5*) are formed in almost equal amounts.

The (12*R*,13*S*)- and (12*S*,13*R*)-8,12-epoxy-14-labden-13-ols (*6, 7*) as well as the (12*R*,13*S*)- and (12*S*,13*R*)-8,13-epoxy-14-labden-13-ols (*8, 9*) were obtained, after reduction, as minor components of the reaction of singlet oxygen with (12*E*)-abienol (*1*). By analogy with the formation of these four compounds (*6 − 9*) on peracid oxidation of (12*E*)-abienol (*1*)[3] and of the corresponding diastereomers on photo-oxygenation of (12*Z*)-abienol (*19*),[2] the genera-tion of compounds *6* and *9* may be rationalized by a process, which involves the attack of oxygen on the 12,13-double bond of conformer B_2 and proceeds with anchimeric assistance of the 8α-hydroxyl group through peroxirane, or epoxide, type of intermediates. A corresponding process occurring in conformer C_1 accounts for the formation of compounds *7* and *8* (Scheme 2).

A small yield of (12*R*)-12,15-epidioxy-13-labden-8-ol (*10*), (12*S*)-12,15-epoxy-13-labden-8-ol (*11*) and 12,15-epoxy-12,14-labdadien-8-ol (*12*) was also obtained. The formation of the 12*R*-epidioxide *10* may be envisaged as a 1,4-addition of oxygen to the *s-cis* 1,3-diene system in a conformer such as D_1, whereas addition to the unhindered side of conformed E_1 would afford the corresponding 12*S*-epidioxide, which is the obvious precursor of (12*S*)-12,15-epoxy-13-labden-8-ol (*11*). The furan *12* may be generated from either epidioxide.

Secondary products. The (12*S*)- and (12*R*)-15,16-epidioxy-13-labdene-8,12-diols (*13, 14*) and the (12*S*)- and (12*R*)-15,16-epoxy-13(16),14-labdadiene-8,12-diols (*15, 16*) are derived from the 12-hydroperoxides of 13(16),14-labdadien-8-ol (*2a, 3a*). This conclusion was based on chemical results, which also were used to settle the structures of the epidioxides *13* and *14*. Thus, the 8,12*S*- and 8,12*R*-diols *2* and *3* were reacted with singlet oxygen to afford the epi-dioxides *13* and *14*, respectively, as major prod-ucts and these were converted to the 12*S*- and 12*R*-hydroxyfurans *15* and *16*, respectively, by treatment with $FeSO_4$.[5]

The remaining two secondary products, (11*E*)-14,15-bisnor-8-hydroxy-11-labden-13-one (*17*) and 12-norambreinolide (*18*) are likely to arise by Hock-Criegee cleavages of the 13-hydroperoxides of (11*E*)-11,14-labdadien-8-ol (*4a, 5a*) and the 13-hydroperoxides of 14-labden-8,12-epoxide (*6a, 7a*), respectively.

DISCUSSION

A comparison shows that the reaction of (12*E*)-abienol (*1*) with singlet oxygen involves two favoured *syn* ene additions leading to the formation of the 8,12- and 8,13-diols *2 − 5* (74 %), whereas (12*Z*)-abienol (*19*) is only amenable to one *syn* ene addition giving the 8,13-diols *4 − 5* (68 %). The 8,12-diols *2, 3*, obtained in minor proportions (3 %) from (12*Z*)-abienol (*19*), are then produced by a less favoured *anti* ene reaction.[2,4] Both abienols (*1, 19*) undergo

the Diels-Alder addition of oxygen to the 12,14-diene system giving compounds *10 – 12* in 7 and 5 % overall yield, respectively. Due to the geometric differences, the complex addition reaction, which requires participation of the 8α-hydroxyl group, leads to the generation of complementary sets of diastereomeric 8,12- and 8,13-epoxy bridged compounds for the two abienols (*1, 19*).[2]

Since eight (*4 – 9, 17* and *18*)[6-10] of the products obtained from (12*E*)-abienol (*1*) are tobacco constituents and since four of these (*6 – 9*) are not formed on photo-oxygenation of the (12*Z*)-abienol (*19*), it is reasonable to assume that both abienols (*1, 19*) may be precursors of the labdanoids found in tobacco. This view is further corroborated by the fact that the presence of (12*E*)-abienol (*1*) in tobacco has most recently been ascertained.[6]

EXPERIMENTAL

For instrumental details: see Ref. 11.

*Photo-oxygenation of (12*E*)-abienol (1).* A solution of 3.0 g of (12*E*)-abienol (*1*)[3] and 300 mg of Rose Bengal in 25 ml of methanol in a tube cooled by a water jacket was irradiated with a 400 W sodium high pressure lamp placed outside the tube, while oxygen was bubbled through the reaction mixture. After 8 h, when TLC showed that all (12*E*)-abienol (*1*) had been consumed, the solvent was removed at reduced pressure. The residue was dissolved in 50 ml of toluene and stirred with 3.5 g of triphenyl phosphine at room temperature for 24 h. Evaporation, examination by GC and GC-MS and chromatography over silica gel using a hexane/acetone gradient afforded twelve fractions. These were separated further by high performance liquid chromatography to give compounds *2 – 7, 10 – 16*.

The (12*S*)- and (12*R*)-13(16),14-labdadiene-8,12-diols (*2, 3*),[2] the (11*E*,13*S*)- and (11*E*, 13*R*)-11,14-labdadiene-8,13-diols (*4, 5*),[2] the (12*R*,13*S*)- and (12*S*,13*R*)-8,12-epoxy-14-labden-13-ols (*6, 7*),[3,7] (12*R*)-12,15-epidioxy-13-labden-8-ol (*10*),[2] (12*S*)-12,15-epoxy-13-labden-8-ol (*11*),[2] 12,15-epoxy-12,14-labdadien-8-ol (*12*)[2] and the (12*S*)- and (12*R*)-15,16-epoxy-13(16),14-labdadiene-8,12-diols (*15, 16*)[2] gave IR, mass, ^{1}H and ^{13}C NMR spectra identical to those of authentic samples.

The (12*R*,13*S*)- and (12*S*,13*R*)-8,13-epoxy-14-labden-12-ols (*8, 9*),[3,8] (11*E*)-14,15-bisnor-8-hydroxy-11-labden-13-one (*17*)[9] and 12-nor-ambreinolide (*18*) were identified by comparison of the GC-retention times and mass spectra with those of the corresponding authentic samples.

(12*S*)-15,16-Epidioxy-13-labdene-8,12-diol (*13*) had m.p. 170 – 172 °C (Found: [M – 18]·+ 320.2356. Calc. for $C_{20}H_{32}O_3$: 320.2351) IR (CCl_4) band at 3380 cm^{-1}; ^{1}H NMR ($CDCl_3$) peaks at δ: 0.79 (6 H, s), 0.89 (3 H, s), 1.19 (3 H, s), 3.99 (1 H, dd, $J = 5$ and 8 Hz), 4.63 (4 H, overlapping signals) and 5.91 (1 H, m); ^{13}C NMR ($CDCl_3$) chemical shifts (δ) and assignments: C-1 39.3, C-2 18.4, C-3 41.9, C-4 33.2, C-5 56.0, C-6 20.4, C-7 43.7, C-8 72.6, C-9 59.1, C-10 39.2, C-11 32.2, C-12 74.0, C-13 139.3, C-14 117.5, C-15 69.8, C-16 69.8, C-17 24.6, C-18 33.4, C-19 21.5, and C-20 15.4; MS peaks at m/e (%): 320 (M – 18, 2), 302 (34), 287 (63), 269 (11), 259 (6), 206 (67), 192 (32), 191 (58), 177 (73), 163 (20), 150 (31), 137 (67), 123 (81), 109 (73), 95 (89), 81 (86), 69 (88), 55 (72) and 43 (100).

(12*R*)-15,16-Epidioxy-13-labdene-8,12-diol (*14*) had m.p. 134 – 136 °C. (Found: [M – 18]·+ 320.2354. Calc. for $C_{20}H_{32}O_3$: 320.2351) IR (CCl_4) band at 3350 cm^{-1}; ^{1}H NMR ($CDCl_3$) peaks at δ: 0.80 (6 H, s), 0.88 (3 H, s), 1.23 (3 H, s), 4.45 (1 H, t, $J = 6$ Hz), 4.63 (4 H, overlapping signals) and 5.92 (1 H, m); ^{13}C NMR ($CDCl_3$) chemical shifts (δ) and assignments: C-1 39.9, C-2 18.6, C-3 41.7, C-4 33.4, C-5 56.0, C-6 20.4, C-7 44.9, C-8 73.7, C-9 54.6, C-10 38.6, C-11 30.9, C-12 70.7, C-13 138.9, C-14 118.0, C-15/C-16 70.4/69.9, C-17 24.3, C-18 33.5, C-19 21.6 and C-20 15.6; MS peaks at m/e (%): 320 (M – 18, 1), 302 (20), 287 (34), 269 (6), 259 (4), 237 (3), 206 (23), 192 (42), 191 (41), 177 (92), 163 (18), 149 (32), 137 (52), 123 (68), 109 (57), 95 (68), 81 (78), 69 (100), 55 (53) and 43 (90).

Conversion of the (12S)- and (12R)-13(16),14-labdadiene-8,12-diols (2, 3) into the (12S)- and (12R)-15,16-epoxy-13(16),14-labdadiene-8,12-diols (15, 16). Photo-oxygenation using the apparatus described above converted the (12*S*)- and (12*R*)-13(16),14-labdadiene-8,12-diols (*2, 3*) into the (12*S*)- and (12*R*)-15,16-epidioxy-13-labdene-8,12-diols (*13, 14*; ~80 % yield) respectively.

A solution of 25 mg of $FeSO_4 \cdot 7H_2O$ in water was added to a solution of 25 mg of epidioxide *13* in 2.5 ml of tetrahydrofuran.[5] The mixture was stirred for 1 h and worked up. Chromatography over silica gel afforded 20 mg of (12*S*)-15,16-epoxy-13(16),14-labdadiene-8,12-diol (*15*). Treatment of epidioxide *14* with $FeSO_4 \cdot 7H_2O$ gave (12*R*)-15,16-epoxy13(16),14-labdadiene-8,12-diol (*16*) in almost quantitative yield.

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