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Tobacco Chemistry. 22. Structures and Syntheses of a Nor- and a Seco-terpenoid of the Drimane Series Isolated from Tobacco

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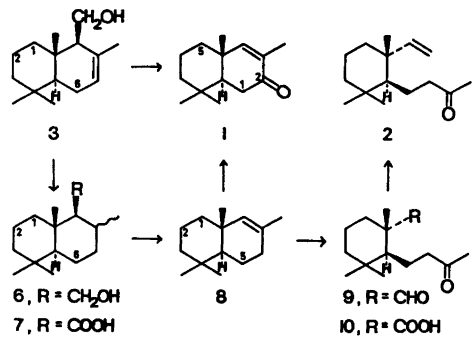
The structures of two new tobacco compounds, (4a*R*,8a*S*)-4a,5,6,7,8,8a-hexahydro-3,4a,8,8-tetramethylnaphthalen-2(1H)-one (*1*) (isonordrimenone) and (1′*S*,6′*S*)-4-(2′,2′,6′-trimethyl-6′-vinylcyclohexyl)-2-butanone (*2*) were assigned on the basis of the spectral data and confirmed by synthesis. Both compounds are likely products of degradation of cyclic terpenoid precursors.

A neutral fraction of the volatile material from an extract of sun-cured Greek tobacco, *Nicotiana tabacum* L., yielded two minor components which were identified as the α,β-unsaturated ketone (*1*) and the vinyl ketone (*2*).[1] We now wish to report the structure elucidations, limited to a consideration of the spectral data because of the small quantities isolated, and the syntheses of these compounds from a common bicyclic intermediate (*8*) obtained by degradation of the sesquiterpene alcohol drimenol (*3*).

(4aR,8aS)-4a,5,6,7,8,8a-Hexahydro-3,4a,8,8-tetramethylnaphthalen-2(1H)-one (*1*). Accurate mass measurement of the molecular ion (*m/e* 206) in the mass spectrum of this tobacco compound gave the molecular formula $C_{14}H_{22}O$. The carbonyl absorption (ν_{max} 1673 cm^{-1}) and ultra-violet absorption (λ_{max} (EtOH) 237 nm, ε 6200) indicated a disubstituted α,β-unsaturated ketone. The NMR spectrum displayed singlets for three methyl groups (δ 0.88, 0.91 and 1.07) and a doublet for a methyl group on a double bond (δ 1.72, *J* 1 Hz). Irradiation at the frequency of the vinylic methyl group showed that the single olefinic proton (δ 6.37, q, *J* 1 Hz) was coupled to this methyl group. With no evidence for further unsaturation in



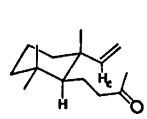
the molecule the molecular formula indicated a bicyclic compound, and the IR and UV spectral data supported a substituted α,β-unsaturated cyclohexanone structure. The downfield position of the quartet in the NMR spectrum for the olefinic proton indicated that it was β to the carbonyl group, and the collapse of the signal to a singlet in the above double irradiation experiment showed it to be coupled only to the methyl group and, hence, adjacent to a quaternary carbon atom. On addition of $Eu(fod)_3$-d_{27} a two proton multiplet at δ 2.12 – 2.62, assigned to the methylene group adjacent (α′) to the carbonyl function, was resolved into the strongly downfield-shifted AB part of an ABX system; the less strongly downfield-shifted X part was ascribed to a single proton, β′ to the carbonyl group, which lacked further spin-spin couplings and had to be adjacent to two fully substituted carbon atoms. These spectral data require the presence of a 2-methylcyclohex-2-en-1-one moiety and demonstrate how six of the remaining seven carbon atoms are linked to the ring. Since

three of these carbon atoms are present as tertiary methyl groups and another is quaternary it follows that the three remaining carbon atoms (C_3H_6) are present as methylene groups and the tobacco compound has structure *1*. The strong lanthanide induced shifts (LIS) observed in the NMR spectrum for C(3)CH_3 and C(1)H_2 and the less strongly induced shifts for the olefinic proton and C(8a)H are as expected. The relatively strong induced shift observed for C(4a)CH_3 and the weak induced shifts for C(8)(CH_3)$_2$ support the *trans*-fused structure *1*.

This tobacco compound (*1*) has not been isolated previously from a natural source but it has been reported as an oxidation product of the sesquiterpene alcohol drimenol (*3*).[2] Oxidation of the bicyclic olefin *8*, prepared from the sesquiterpene alcohol drimenol (*3*) as described below, with chromium trioxide in acetic acid solution provided an unambiguous synthesis of *1*. This product is identical in all respects to *1* isolated from tobacco. We have also confirmed that oxidation of drimenol (*3*) with chromium trioxide in pyridine gives isonordrimenone (*1*).[2]

(1'S,6'S)-4-(2',2',6'-Trimethyl-6'-vinylcyclohexyl)-2-butanone (2). The IR spectrum of this tobacco compound (*2*) with molecular formula $C_{15}H_{26}O$ (accurate mass measurement of molecular ion at *m/e* 222) showed absorptions characteristic of a carbonyl (1718 cm^{-1}) and a vinyl group (1637, 1008, 917 cm^{-1}). The three protons of the vinyl group appeared as an ABC system in the NMR spectrum (δ 4.89, H_A; 4.92, H_B; 5.64, H_C; $J_{AB} \sim 1$, J_{BC} 10, J_{AC} 18 Hz) and the absence of any coupling to other protons indicated that it was attached to a quaternary carbon atom. The presence of the $>CHCH_2CH_2COCH_3$ residue was established from the NMR spectrum (δ 2.06, CH_3CO) and the lanthanide induced shifts observed on the addition of Eu(fod)$_3$-d_{27}. The two proton multiplet at δ 2.15–2.5 for the methylene protons α to the carbonyl group was resolved into a strongly downfield-shifted triplet; spin-decoupling experiments confirmed the coupling of these protons to the two protons at C-4 which appeared as a less strongly downfield-shifted multiplet and, in turn, were coupled to the single proton γ to the carbonyl group which gave rise to a weakly downfield-shifted triplet. The absence of any further couplings to this last proton indicated that the $>CHCH_2CH_2COCH_3$ residue was attached to two fully substituted carbon atoms. The presence of the butanone sidechain was also supported by a prominent peak in the mass spectrum at *m/e* 164 ($M-C_3H_6O$) evidently arising from a McLafferty-type cleavage. With the vinyl group, the two quaternary carbon atoms carrying the 2-oxo-5-pentylidene moiety and the three methyl groups that appear as singlets in the NMR spectrum (δ 0.90, 0.92 and 1.02) there remains three methylene groups (C_3H_6) to construct the one ring required to satisfy the molecular formula. Since the two carbon atoms of the six-membered ring adjacent to the carbon atom bearing the butanone sidechain must be tetrasubstituted the structure *2* (stereochemistry undetermined) follows for this tobacco compound.

The relative stereochemistry may be deduced by distinguishing between the two configurations *4* and *5* possible when only chair conformations with the butanone sidechain in an equatorial position are considered. This was possible from an analysis of the LIS observed in the NMR spectrum on the addition of Eu(fod)$_3$-d_{27}. The preferred position of the europium complex about the carbonyl group



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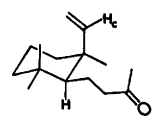

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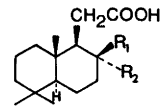
would be on the sterically less hindered side, α-side in *4* and *5*, and this is supported by the relatively strong LIS observed for C(1')H. The observed relative LIS for the three methyl groups and the vinyl proton H_c are in the order $Me \geq H_c \gg 2Me$ which is as expected for *4* but does not support the alternative configuration (*5*) for which the signals for the two α-methyl groups would be expected to display similar LIS which, in turn, would be greater than those for the β-methyl and the vinyl proton, H_c.

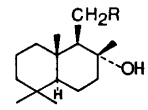
The structure *2* for this tobacco compound with stereochemistry as shown in *4* was confirmed by synthesis from the sesquiterpene alcohol drimenol (*3*) as outlined in the scheme.

The crude mixture of epimeric alcohols (*6*) obtained by the catalytic hydrogenation of drimenol (*3*)[3] was oxidised with chromium trioxide in 80 % acetic acid at room temperature in the presence of potassium hydrogen sulphate to give a 70 % yield of the epimeric acids *7*. Smooth decarboxylation of *7* was effected with lead tetraacetate in refluxing benzene in the presence of cupric acetate and pyridine[4] for an 80 % yield of the desired octahydronaphthalene intermediate *8*.

Ozonolysis of *8* at −78° in methylene chloride solution containing pyridine (1 equiv.) followed by a reductive work-up with zinc and acetic acid gave, in high yield, the unstable keto-aldehyde *9*. This essentially pure product was used in the next step without further purification. Only small amounts of the keto-aldehyde *9* were detected in the reaction product when ozonolysis of *8* in methanol suspension at −30° was followed by reduction of the hydroperoxides with dimethyl sulphide.[5] The main product of this reaction appeared to be the keto-acid (*10*). The attempted selective Wittig condensation of methylene triphenylphosphorane with the more reactive carbonyl group of *9* to give the desired vinyl ketone *2* gave a complex mixture of products. Eventually, inverse addition of a solution of methylenetriphenylphosphorane (1 equiv.) in dry dimethyl sulphoxide to a solution of the keto-aldehyde *9* in dry dimethyl sulphoxide at room temperature gave a low yield of the vinyl ketone *2*. The product was isolated by preparative gas-chromatography and displayed NMR, IR, and mass spectra identical to those of the tobacco compound *2*. The natural and synthetic products did not separate when co-injected on a capillary GC-column. The low specific rotation ($[\alpha]_D$ −0.5°) measured for the tobacco compound *2* in comparison to that for the synthetic material ($[\alpha]_D$ −10°) could not be used to establish the stereochemistry of the natural product. However, the very similar partial ORD curves of the natural and synthetic products obtained by measurement of the specific rotation at five different wavelengths (365 − 589 nm) confirmed that the synthetic product *2* and the tobacco compound *2* have identical absolute configurations. This is the first isolation of the C_{15} compound *2* from a natural source although it had been identified previously[6] as a cleavage product in the electrolytic decarboxylation of salts of the acids *11* and *12*.



11, $R_1 = CH_3$, $R_2 = OH$
12, $R_1 = OH$, $R_2 = CH_3$



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The formation of isonordrimenone (*1*) and the vinyl ketone *2* by oxidation[2] of drimenol (*3*) and electrolysis of the salts of *11* and *12*, respectively, makes it attractive to suggest that bicyclic sesqui- or diterpenoids of the drimane (*e.g. 3*) or labdane type (relevant part of the labdane skeleton as in *13*) might act as precursors for the new nor- and seco-sesquiterpenoids *1* and *2*. Several natural products in the series *13* have recently been identified in Greek tobacco,[7] and related compounds such as 12-norambreinolide,[8] 8,13- and 8,13β-epoxylabd-14-en-12-one,[9] 12α-hydroxy-13-epimanoyl oxide,[10] and epimeric levantenolides,[11] are known tobacco leaf or smoke constituents.

EXPERIMENTAL

NMR, IR, UV, and mass spectra were recorded on Varian HA 100D and A60-A, Digilab FTS-14 and Perkin-Elmer 257, Beckmann DK-2A and LKB 9000 (70 eV) instruments, respectively. Optical rotations were measured on a Perkin-Elmer 141 instrument. Accurate mass measurements were carried out at the Laboratory for Mass Spectrometry, Karolinska Institutet, Stockholm. The mass spectra were obtained by gas liquid chromatography in combination with mass spectrometry (GLC-MS). A steel capillary column (0.5 mm × 50 m, Handy and Harman grade 316-S) coated with Emulphor by the dynamic packing method[12] was used for GLC-MS and analytical gas chromatography. A Varian 1700 gas chromatograph equipped with a glass column (3.2 mm × 3 m) packed with 5 % Carbowax 20M on Chromosorb G was used for preparative GLC.

Isolation. Compounds *1* and *2* were isolated from fraction B3 of an extract of sun-cured *Nicotiana tabacum* L. by a combination of liquid and preparative gas chromatography.[1]

(*4a*R,*8a*S)-*4a,5,6,7,8,8a-Hexahydro-3,4a,8-tetramethylnaphthalen-2-(1H)-one* (*1*) MS: *m/e* 206 (M^+, 42 %), 83 (100), 109 (48), 55 (34), 108 (33), 41 (33), 121 (27), 69 (26), 163 (24), 123 (23);

accurate mass measurement: $C_{14}H_{22}O$, found 206.1672, calc. 206.1671; λ_{max}(EtOH) 237 nm (ε 6200); λ_{max}(film) 1673 (s), 1640 (w), 1017 (m) cm^{-1}; δ ($CDCl_3$) 0.88 (3 H, s), 0.91 (3 H, s), 1.07 (3 H, s), 1.72 (3 H, d, J 1 Hz), 2.12–2.62 (2 H, m), 6.37 (1 H, q, J ~1 Hz). On addition of Eu(fod)$_3$-d_{27}: C(1)H_2 and C(8a)H appear as an ABX, r (relative induced shift) = 3.88 [C(5)H_2, 8 lines, J 4, 14, 18 Hz], 2.56 [C(3)CH_3, broad s], 1.9 [C(8a)H, dd, J 4, 14 Hz], 1.12 [C(4)H, broad s], 1.0 [C(4a)CH_3, s], 0.28 and 0.36 [C(8) (CH_3)$_2$, 2 s]. $[\alpha]_D^{20}$ +17.6 (c 0.21 in benzene).

(1'S,6'S)-4-(2',2',6'-Trimethyl-6'-vinylcyclohexyl)-2-butanone (*2*) MS: *m/e* 222 (M$^+$, 4.5 %), 43 (100), 41 (42), 109 (42), 81 (40), 82 (40), 95 (38), 67 (37), 55 (35), 69 (34), 123 (34); accurate mass measurement: $C_{15}H_{26}O$, found 222.1990, calc. 222.1984; $C_{12}H_{20}$, found 164.1558, calc. 164.1565; ν_{max}(film) 1718 (s), 1637 (w), 1162 (m), 1008 (w), 917 (m) cm^{-1}; δ ($CDCl_3$) 0.90 (3 H, s), 0.97 (3 H, s), 1.02 (3 H, s), 2.06 (3 H, s), 2.15–2.5 (2 H, m), $-CH=CH_2$ appears as an ABC: 4.89, H_A; 4.92, H_B; 5.64, H_C; J_{AB} 1, J_{BC} 10, J_{AC} 18 Hz. On addition of Eu(fod)$_3$-d_{27} r = 3.2 [C(3)H_2, t, J ~8 Hz], 3.2 [C(1)H_3, s], 2.4 [C(4)H_2, m], 1.0 [C(1')H, broad t, J ~5 Hz], 0.86 ($-CH=CH_2$,m), 0.5 and 0.58 ($-CH=CH_2$, 2 m), 0.66 (3 H, s), 0.44 (3 H, s), 0.34 (3 H, s). $[\alpha]^{20}$ −0.5° (589 nm), −12.7° (578), −15.2° (546), −33.3° (436), −74.2° (365) (c 0.2 in chloroform).

8ξ-Drimanol (*6*). Drimenol (*3*) (1 g) was hydrogenated in ethyl acetate solution (50 ml) with Adams catalyst (150 mg) at 20°/1 atm.[3] Filtration and removal of solvent afforded a colourless oil (1 g) that crystallised slowly on standing. No attempt was made to separate the minor product of hydrogenation, 8α-drimanol, from the major product, 8β-drimanol.

8ξ-Driman-11-oic acid (*7*). Oxidation of the crude product *6* from the hydrogenation of drimenol (*3*) by the method of Appel, Brooks and Overton [3] gave a poor yield of 8ξ-driman-11-oic acid *(7)*. The following procedure gave a 70 % yield of crystalline acid: A solution of chromium trioxide (345 mg) in 80 % acetic acid (12 ml) containing potassium hydrogen sulphate (340 mg), was added dropwise at room temperature to a stirred solution of the crude hydrogenation product *6* (1 g) in 10 % acetic acid (12 ml). After stirring at room temperature for a further 2 h the reaction mixture was diluted with water and extracted with ether. The combined ether extracts were washed with saturated sodium bicarbonate solution (to remove only 39 mg of acidic material that contained no *7* on acidification and extraction into ether) followed by 2 M sodium hydroxide solution. The combined alkaline extracts were acidified and extracted with ether, the ether fractions washed with water and the solvent evaporated to yield crystalline 8ξ-driman-11-oic acid (*7*) (0.55 g). The neutral residue (0.35 g) from this oxidation contained unreacted drimanol (6) and related aldehydes which, on further oxidation in 80 % acetic acid solution (5 ml) with chromium trioxide (230 mg) in 80 % acetic acid (5 ml) containing potassium hydrogen sulphate (230 mg) and work-up as described above, gave a further 0.2 g of crystalline 8ξ-driman-11-oic acid (*7*) ν_{max}(KBr) 2500–3600 (broad), 1700 cm^{-1} (s).

trans-1,2,3,4,4aα,5,6,8a-Octahydro-4α,4β,7,8aβ-tetramethylnaphthalene (8). A mixture of 8ξ-driman-11-oic acid (0.5 g), lead tetraacetate (2.5 g, freed of excess acetic acid under high vacuum), copper(II) acetate (0.4 g) and pyridine (0.25 ml) in dry benzene (60 ml) was heated under reflux for 2 h in a nitrogen atmosphere.[4] The insoluble lead salts were filtered off at room temperature and the filtrate was washed with water, dried (Na_2SO_4) and the benzene removed under reduced pressure. The crude product was filtered through silica (25 g) in 1 % ether/pentane to yield pure *8* (320 mg, 80 %). Accurate mass measurement: $C_{14}H_{24}$, found 192.1886, calc. 192.1878; δ ($CDCl_3$) 0.85 (3 H, s), 0.90 (3 H, s), 0.94 (3 H, s), 1.58 (3 H, broad s), 5.06 (1 H, q, J ~1.5 Hz); ν_{max}(film) 3000 (m), 1390 (m), 1379 (m), 1370 (m), 1030 (w), 848 (m) cm^{-1}; $[\alpha]_D^{20}$ +56.8° (c 0.95 in pentane).

Keto-aldehyde 9. Ozone was bubbled through a solution of *8* (320 mg) in methylene chloride solution (10 ml) containing pyridine (140 mg) at −78° until there was an excess of ozone at the outlet from the reaction vessel. Zinc (600 mg) and acetic acid (1.5 ml) were added and the reaction mixture was brought quickly to room temperature. After 2 h stirring at room temperature the reaction mixture was diluted with water and extracted with ether. The combined ether extracts were washed with water, saturated sodium chloride solution and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave the keto-aldehyde *9* as a pale yellow liquid (368 mg). This unstable but essentially pure reaction product darkened quickly on standing and could not be purified successfully by chromatography on silica. It was reacted in the next step without further purification. MS: *m/e* 224 (M$^+$, 1 %), 43 (100), 69 (65), 41 (38), 95 (33), 81 (30), 109 (28), 123 (25), 55 (24); δ ($CDCl_3$) 0.92 (3 H, s), 0.95 (3 H, s), 1.10 (3 H, s), 2.07 (3 H, s), 2.2–2.45 (2 H, m), 9.28 (1 H, s). ν_{max} (film) 2690 (w), 1720 (s).

Vinyl ketone 2. A solution of methylene triphenylphosphorane (1 mM) in anhydrous dimethyl sulphoxide (10 ml), from the *in situ* reaction of methylsulphinyl carbanion (generated with 24 mg of sodium hydride) and methyl triphenylphosphonium bromide (360 mg),[14] was added under nitrogen pressure to a stirred solution of the crude keto-aldehyde *9* (224 mg, 1 mM) in anhydrous dimethyl sulphoxide (20 ml) over 1 h at room temperature. After a further hour at room temperature the reaction

mixture was diluted with water, acidified, and extracted with ether. The combined ether extracts were washed with water, saturated sodium chloride solution and dried (Na_2SO_4). Evaporation of the solvent gave a yellow oil (240 mg) which TLC showed to be a complex mixture of compounds. Pure vinyl ketone *2* was isolated in low yield by preparative gas chromatography. It displayed NMR and IR spectra indistinguishable from the spectra of *2* isolated from the tobacco. The synthetic and natural products did not separate when co-injected on a capillary GC column. $[\alpha]^{20}$ −10.0° (589 nm), −15.2 (578), −17.7 (546), −36.5 (436), −78.6 (365) (*c* 0.52 in chloroform).

Isonordrimenone (*1*). (i) The octahydronaphthalene *8* (20 mg) in acetic acid (2 ml) at 70° was treated dropwise (20 min) with a solution of chromium trioxide (20 mg) in acetic acid (1 ml). After a further 30 min at 70° the cooled reaction mixture was diluted with water and extracted with ether. The combined ether extracts were washed with saturated sodium bicarbonate solution, water and dried (Na_2SO_4). Chromatography on silica of the residue obtained on evaporation of the solvent gave pure isonordrimenone (*1*) (8 mg). It displayed NMR, IR, and mass spectra identical to those obtained for *1* isolated from the tobacco, and the synthetic and natural products did not separate when co-injected on a capillary GC column. $[\alpha]_D^{20}$ + 21.8° (*c* 0.22 in benzene).

(ii) Oxidation of drimenol (*3*) (30 mg) with chromium trioxide (75 mg) in dry pyridine (0.75 ml) as described by Appel, Brooks and Overton [3] gave a mixture of compounds from which isonordrimenone (*1*) (3 mg) was isolated by column chromatography on silica. This material was identical in all respects to *1* isolated from the tobacco and prepared by oxidation of *8* as described above.

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