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Tobacco Chemistry. 42. Structure Elucidation and Synthesis of 3,3-Dimethyl-7-hydroxy-2-octanone, a New *Seco* Nor-carotenoid Constituent of Greek Tobacco

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A new C_{10} *seco* nor-carotenoid was isolated from Greek *Nicotiana tabacum* L. and shown by spectroscopic methods and synthesis to be (+)-3,3-dimethyl-7-hydroxy-2-octanone.

Previous studies have revealed the presence in tobacco of a large number of compounds, which in all probability arise by initial oxidative cleavage of the polyene chain of cyclic carotenoids and subsequent chemical alterations.[1] Until now, however, only a few *seco* nor-carotenoids have been encountered. The present communication describes the structure elucidation and synthesis of a new C_{10} *seco* compound.

RESULTS

The title compound (*1*) was isolated in a minute amount by repeated preparative liquid and gas chromatography of a polar, volatile fraction, B 8,[2] obtained from an extract of sun-cured Greek tobacco. Accurate mass measurements, which had to be performed on the $[M-33]^+$ ion of mass 139 due to the low abundance of the molecular ion (*m/e* 172), established that the new compound (*1*) had the composition $C_{10}H_{20}O_2$. Its ^{13}C NMR spectrum confirmed the presence of ten carbon atoms and revealed that these comprised four methyl, three sp^3 methylene, one oxygen-carrying sp^3 methine, one non-protonated sp^3 carbon and one carbonyl carbon. The latter was part of a methyl ketone group, a conclusion based upon the fact that the ^1H NMR spectrum contained a methyl singlet at δ 2.12 and the IR spectrum an absorption band at 1705 cm^{-1}.

The second oxygen atom was accomodated by a hydroxyl substituent attached to the sp^3 methine carbon as shown by IR absorption at 3600 and 3450 cm^{-1} and by the presence of a one-proton sextet at δ 3.81 in the ^1H NMR spectrum. Irradiation at this frequency made a methyl doublet at δ 1.18 collapse to a singlet. Since, conversely, irradiation at the frequency of the methyl doublet converted the sextet to a broadened triplet, it followed that the hydroxyl-carrying methine carbon was attached to a methyl and a methylene group. The remaining two methyl groups, giving rise to singlets at δ 1.12 in the ^1H NMR spectrum, must be linked to the non-protonated sp^3 carbon atom.

On the basis of these results three possible structures, A, B and C, which all incorporate the remaining two sp^3 methylene groups, could be formulated for the new tobacco constituent (*1*). An examination of the mass spectrum, which displayed diagnostically important peaks at *m/e* 172 (M), 139, 129, 111, 86, 69, 45 and 43, strongly favoured structure A, *i.e.* 3,3-dimethyl-7-hydroxy-2-octanone for *1* (*cf.* Fig. 1). Thus compound A is expected to undergo a McLafferty rearrangement giving a $C_5H_{10}O$ ion of mass 86, compound B would yield an ion of mass 58, whereas no such rearrangement is possible in the fragmentation of compound C.

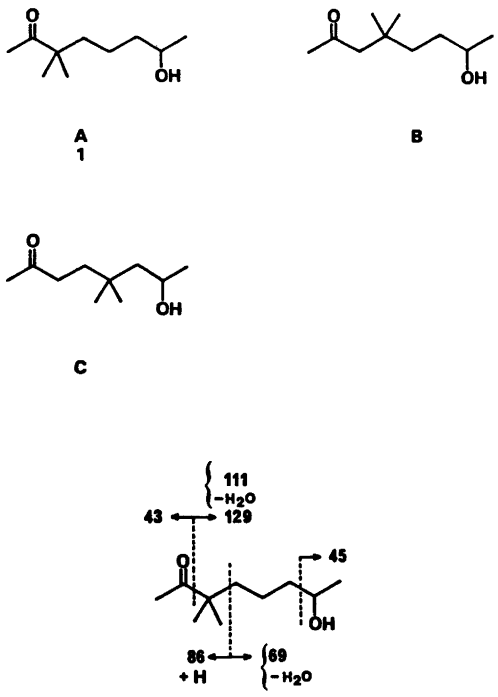
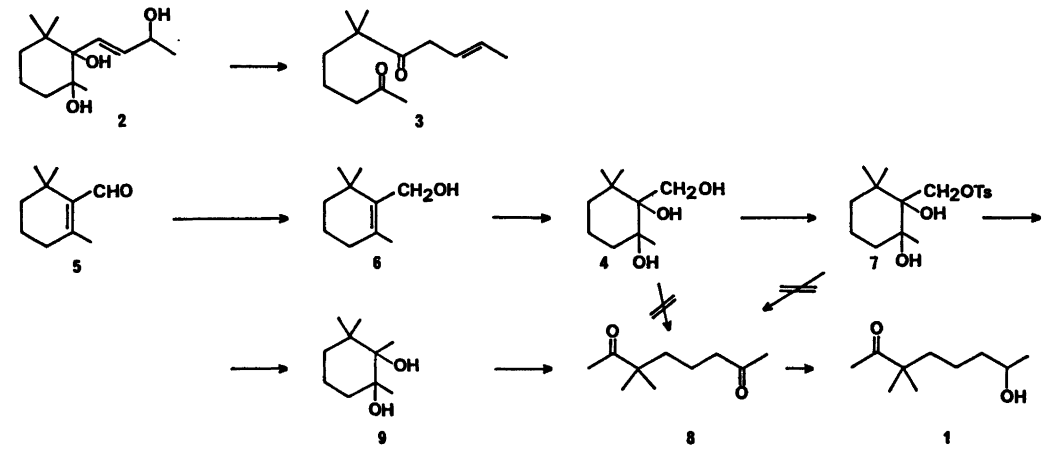


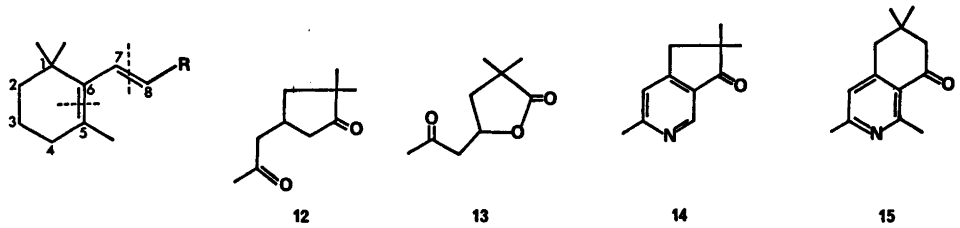
Fig. 1. MS fragmentation of compound *1*.

The structure proposed for *1* was confirmed by synthesis using a route, which involved a possibility to test a biogenetically plausible reaction (*vide infra*) analogous to the facile acid–catalysed rearrangement of the C_{13} nor-carotenoid triol (*2*) to the *seco* diketone (*3*).[3] Thus, attempts were made to convert the triol *4*, which was synthesized from β-cyclocitral (*5*) *via* hydroxylation of β-cyclogeraniol (*6*) using osmium tetroxide, as well as the monotosylate (*7*) to the desired diketone (*8*) under acidic conditions. However, these proved to be abortive and the required ring cleavage was instead achieved by chromic acid oxidation of 1,2,3,3-tetramethyl-1,2-cyclohexanediol (*9*), which was prepared from the tosylate (*7*) by LAH reduction. The diketone (*8*), which was isolated in 71 % yield, was subsequently reacted with a bulky reducing agent, lithium tri-*t*-butoxyaluminium hydride, at a low temperature (0 °C) in order to achieve selective reduction of the carbonyl group at C-7. The desired (±)-3,3-dimethyl-7-hydroxy-2-octanone (*1*), identical to the new tobacco constituent, was obtained in 35 % yield along with a similar amount of 3,3-dimethyl-2,7-octanediol (*10*) and a minor quantity of 3,3-dimethyl-2-hydroxy-7-octanone (*11*).

The new compound, (+)-*1*, whose absolute configuration could not be settled due to shortage of material, may be formed in tobacco from a cyclic carotenoid precursor by cleavage of the 5,6 and 7,8 bonds as indicated in Fig. 2. It thus constitutes an additional representative of the relatively few *seco* nor-carotenoids encountered in tobacco, which include the C_{10} diketone *12*,[4] the C_9 lactone *13* [5] and the alkaloids *14* and *15*.[4]



Scheme 1.



12 13 14 15

Fig. 2. Possible formation of *1*. Compounds *1* and *12 – 15* represent the known *seco* nor-carotenoids in tobacco.

EXPERIMENTAL

Optical rotations were measured on a Perkin-Elmer 141 polarimeter and IR spectra on Digilab FTS-14 and Perkin-Elmer 257 instruments. Mass spectra were recorded on an LKB 2091 instrument and accurate mass measurements were carried out on a Varian MAT 311 instrument at the Department of Organic Chemistry, Arrhenius Laboratory, University of Stockholm. Fourier transform ^{1}H NMR (100 MHz) and ^{13}C NMR (25.16 MHz) spectra were recorded in $CDCl_3$ solutions using TMS as internal standard on a Varian XL-100-12 spectrometer equipped with S-124 FT and disk accessories and controlled by a Varian 620/L computer. Analytical and preparative gas chromatography was performed on a Varian 1700 instrument using glass capillary columns (50 m × 0.37 mm) coated with HB 5100 and glass columns (2.8 m × 7 mm) packed with Carbowax 20 M (4 %) on Chromosorb G, respectively. High performance liquid chromatography was carried out using a Waters 6000 A solvent delivery system, a U6K injector and an R-401 differential refractometer.

Isolation of 3,3-dimethyl-7-hydroxy-2-octanone (1) from tobacco. A volatile, neutral fraction (B 8) [2] of an extract obtained from 295 kg of sun-cured Greek *Nicotiana tabacum* L. was chromatographed over silica gel using a light petrol/ether gradient. One of the sub-fractions obtained was separated further by liquid chromatography on columns packed with Bondapak C_{18}/Porasil (Waters) using water-acetone (60:40) as eluent and by preparative gas chromatography to give 1.8 mg of 3,3-dimethyl-7-hydroxy-2-octanone (*1*) as a colourless oil (Found: [M − 33]+ 139.1113. Calc. for $C_9H_{15}O$ [M − 33]+: 139.1123), $[\alpha]_{578}^{22}$ + 5.8° (*c* 0.17, $CHCl_3$); IR ($CHCl_3$) bands at 3600 (m), 3450 (m) and 1705 cm^{-1}; ^{1}H NMR peaks at δ 1.12 (6 H, s), 1.18 (3 H, d, J = 6 Hz), 2.12 (3 H, s) and 3.81 (1 H, sextet, J = 6 Hz); ^{13}C NMR peaks at δ 21.06 (t), 23.51 (q), 24.28 (q), 24.43 (q), 25.03 (q), 39.74 (t), 39.92 (t), 47.81 (s), 67.41 (d) and 214.18 (s) (s = singlet, d = doublet, t = triplet and q = quartet refer to the single frequency off resonance decoupled spectrum); MS peaks at *m/e* (composition, %): 172 (M, 1), 139 ($C_9H_{15}O$, 4) 129 ($C_8H_{17}O$, 7), 111 (C_8H_{15}, 22), 86 ($C_5H_{10}O$, 35), 69 (C_5H_9, 100), 55 (C_4H_7, 30), 45 (C_2H_5O, 14) and 43 (C_2H_3O, 42).

Preparation of β-cyclogeraniol (6). A solution of 1.80 g of β-cyclocitral (*5*) in ether was treated with lithium aluminium hydride at room temperature for 2 h. The reaction mixture was diluted with aqueous H_2SO_4, extracted with ether, dried and evaporated. The residue was chromatographed over silica gel using ethyl acetate-hexane (20:80) as eluent, which furnished 0.80 g of β-cyclogeraniol (*6*) m.p. 40 – 42 °C (lit. 43 – 44°);[6] IR (KBr) bands at 3400 (m) and 1660 (w) cm^{-1}; ^{1}H NMR peaks at δ 1.06 (6 H, s), 1.76 (3 H, broad s) and 4.16 (2 H, s); ^{13}C NMR peaks at δ 19.49 (t), 19.64 (q), 28.55 (2 q), 32.93 (t), 34.03 (s), 39.64 (t), 58.23 (t), 132.90 (s) and 137.43 (s); MS peaks at *m/e* (%): 154 (M, 38), 139 (29), 136 (15), 123 (71), 121 (100), 93 (60), 81 (29), 79 (43), 67 (16), 55 (24) and 43 (20).

Preparation of 2-hydroxymethyl-1,3,3-trimethyl-1,2-cyclohexanediol (4). To a solution of 934 mg of osmium tetroxide in 5 ml of pyridine was added 570 mg of β-cyclogeraniol (*6*) dropwise. After stirring at room temperature for 2 h a solution of 1.80 g of sodium bisulfite in 30 ml of aqueous pyridine (40 %) was added. The reaction mixture was diluted with water, extracted with ethyl acetate, washed with aqueous HCl, dried and evaporated. The residue was chromatographed over silica gel using ethyl acetate-hexane (40:60) as eluent to afford 592 mg of 2-hydroxymethyl-1,3,3-trimethyl-1,2-cyclohexanediol (*4*), which had m.p. 158 – 161 °C (hexane); IR (KBr) bands at 3500 (s) and 3400 (s) cm^{-1}; ^{1}H NMR peaks at δ 0.96 (3 H, s), 1.03 (3 H, s), 1.47 (3 H, s), 3.12 (−O*H*, t, J = 6 Hz), 3.55 (−O*H*, s), 3.65 (−O*H*, s), 3.77 (1 H, dd, J = 6 and 12 Hz) and 4.05 (1 H, dd, J = 6 and 12 Hz) (AB part of an ABX system); ^{13}C NMR peaks at δ 19.44 (t), 24.17 (q), 25.65 (q), 27.30 (q), 36.89 (t), 37.04 (t), 37.33 (s), 64.11 (t), 76.30 (s) and 77.05 (s); MS peaks at *m/e* (%): 170 (M − 18, 2), 157 (13), 139 (15), 111 (26), 86 (100), 71 (28), 69 (32), 55 (26) and 43 (60). The preparation method used requires that the 1,2-diol system in *4* is *cis*. A corresponding *trans*-1,2-diol, having different properties, has been described previously.[7]

Preparation of 2-hydroxymethyl-1,3,3-trimethyl-1,2-cyclohexanediol monotosylate (7). A solution of 510 mg of 2-hydroxymethyl-1,3,3-trimethyl-1,2-cyclohexanediol (*4*) in pyridine was treated with 1 mol excess of *p*-toluenesulfonyl chloride at 0 °C for 24 h. Work up and chromatography over silica gel using ethyl acetate-hexane (40:60) as eluent produced 260 mg of the monotosylate (*7*): IR (film) bands at 3500 (m), 1190 (s), 1175 (s) cm^{-1}; ^1H NMR peaks at δ 0.95 (3 H, s), 1.00 (3 H, s), 1.33 (3 H, s), 2.46 (3 H, s), 4.19 (1 H, d, $J = 10$ Hz) and 4.39 (1 H, d, $J = 10$ Hz) (AB spectrum), 7.38 (2 H, d, $J = 9$ Hz) and 7.82 (2 H, d, $J = 9$ Hz) (AB spectrum).

Preparation of 1,2,3,3-tetramethyl-1,2-cyclohexanediol (9). To a solution of 40 mg of lithium aluminium hydride in ether was added an ethereal solution of 242 mg of the tosylate (*7*) dropwise. The mixture was stirred at room temperature for 1 h. Work-up and chromatography over silica gel using ethyl acetate-hexane (20:80) as eluent furnished 112 mg of 1,2,3,3-tetramethyl-1,2-cyclohexanediol (*9*) as a colourless glass, which had IR (film) bands at 3500 cm^{-1}; ^1H NMR peaks at δ 0.98 (3 H, s), 1.09 (3 H, s), 1.18 (3 H, s) and 1.27 (3 H, s); ^{13}C NMR peaks at δ 18.51 (q), 19.02 (t), 25.74 (q), 25.93 (q), 26.18 (q), 37.01 (t), 37.38 (t), 38.53 (s), 75.16 (s) and 77.78 (s); MS peaks at *m/e* (%): 172 (M, 2), 154 (4), 139 (4), 136 (11), 128 (12), 111 (75), 96 (62), 84 (65), 71 (70), 69 (52) and 43 (100).

Preparation of 3,3-dimethyl-2,7-octanedione (8). To a solution of 93 mg of *9* in 1 ml of acetic acid was added 100 mg of CrO_3 dissolved in 2 ml of aqueous acetic acid (90 %). The mixture was stirred at room temperature for 2 h, diluted with water and extracted with ether, washed with aqueous $NaHCO_3$, dried and evaporated to give 66 mg of 3,3-dimethyl-2,7-octanedione (*8*) [8,9] as a colourless oil, which had IR (film) bands at 1715 (s) and 1705 (s) cm^{-1}; ^1H NMR peaks at δ 1.12 (6 H, s), 2.12 (3 H, s) and 2.13 (3 H, s); ^{13}C NMR peaks at δ 18.99 (C-5), 24.24 (C-9 and C-10), 24.90 (C-1), 29.73 (C-8), 39.18 (C-4), 43.58 (C-6), 47.57 (C-3), 207.76 (C-7) and 212.93 (C-2); MS peaks at *m/e* (%): 170 (M, 1), 152 (1), 127 (8), 109 (43), 86 (28), 71 (18), 69 (70) and 43 (100). Oxidation of the natural product (*1*) using Jones' reagent gave a product indistinguishable from *8* (GC-MS, ^1H NMR).

Preparation of (±)-3,3-dimethyl-7-hydroxy-2-octanone (1). To a cooled (0 °C) solution of 19 mg of *8* in tetrahydrofuran was added 29 mg of lithium tri-*t*-butoxyaluminium hydride. After 10 min the reaction mixture was worked up and chromatographed over silica gel using ethyl acetate-hexane (30:70) as eluent, which gave three fractions. The least polar of these contained 4 mg of unreduced diketone (*8*). The second fraction was purified further by liquid chromatography on columns packed with μ-porasil (Waters) to afford 5.3 mg of (±)-3,3-dimethyl-7-hydroxy-2-octanone (*1*), which was indistinguishable (GC_{RT}, IR, ^1H NMR, ^{13}C NMR and MS) from the new tobacco constituent, and 0.7 mg of 3,3-dimethyl-2-hydroxy-7-octanone (*11*), which had ^1H NMR peaks at δ 0.84 (3 H, s), 0.86 (3 H, s), 1.12 (3 H, d, $J = 6.4$ Hz), 2.14 (3 H, s) and 3.60 (1 H, q, $J = 6.4$ Hz); MS peaks at *m/e* (%): 139 (M − 33, 2), 128 (26), 110 (32), 109 (49), 71 (49), 69 (79) and 43 (100). The most polar fraction contained 5.0 mg of 3,3-dimethyl-2,7-octanediol (*10*), which had MS peaks at *m/e* (%): 141 (M − 33, 2), 129 (8), 112 (22), 111 (20) and 69 (100).

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