Tobacco Chemistry. 23. Structures and Syntheses of Four New Norisoprenoid Furans from Greek *Nicotiana tabacum* L.

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The structures of *cis* and *trans* (±)-2-methyl-5-(2-methyl-5-isopropenyltetrahydro-2-furyl)-furan, *1a* and *1b*, and their dihydro derivatives, (±)-2-methyl-5-(2-methyl-5-isopropyltetrahydro-2-furyl)furan, *2a* and *2b*, isolated from Greek tobacco were elucidated from spectral data, and subsequently confirmed by total syntheses. The *cis-trans* assignments were based upon the observation of an Eu(DPM)₃ induced upfield shift of the furan methyl signal in the NMR-spectrum of the *cis*-isomer of the synthetic intermediate (±)-2-[5-methyl-5-(5-methyl-2-furyl)tetrahydro-2-furyl]-2-propanol, *6a*.

Recent research into tobacco flavour has suggested that a large number of the tobacco constituents are degradation products of terpenoid compounds.¹-⁸ The present communication describes the structural elucidation and syntheses of further new tobacco constituents possessing carbon skeletons derivable from those of aliphatic terpenoids.

The mass spectrum of the first isolate (from fraction C9)⁴ displayed a molecular ion at *m/e* 206 corresponding to the elemental composition C₁₉H₁₈O₃ or C₁₄H₁₂O. The former alternative was favoured since signals in the NMR spectrum indicated the presence of two oxygen atoms incorporated in a furan ring and a cyclic ether. A 2-methylfur-5-yl moiety was apparent from NMR signals at δ 5.84 (1 H, doublet of quartets, *J* 1.0 and 3.0 Hz), δ 6.06 (1 H, doublet of quartets, *J* 0.4 and 3.0 Hz) and δ 2.24 (3 H, doublet of doublets, *J* 0.4 and 1.0 Hz).⁴ The long-range spin-spin couplings between the methyl group and the furyl protons were established by spin decoupling experiments. Absence of further couplings to the proton in position 4 suggested that a fully substituted carbon atom was attached to position 5 of the methylfuryl moiety. The second oxygen atom represented part of a cyclic ether grouping in which the two oxygenated carbon atoms carried a methyl group (δ 1.57, singlet) and an allylic proton (δ 4.45, triplet with further splittings) respectively. Double resonance experiments demonstrated that two olefinic protons (δ 4.78, 5.02) and a vinylc methyl group (δ 1.72) were weakly, mutually coupled (*J* ca. 1 Hz) and could

![Scheme 1.](image)
be ascribed to an isopropenyl group, \( \text{CH}_2\equiv\text{C-(CH}_3\text{)}^-\). The remaining atoms, two methylene groups, were responsible for multiplets in the \( \delta 1.2-1.8 \) region and were readily accomodated in the tetrahydrofuran ring of the postulated structure that could be advanced: 2-methyl-5-(2-methyl-5-isopropenyltetrahydro-2-furyl)furan. Methyl resonances of low intensity at \( \delta 1.55 \) and \( \delta 1.68 \) indicated that the isolate was a mixture of diastereomers (ratio 3:7). Thus both the \textit{cis} and the \textit{trans} tetrahydrofuran compounds (1\(a\) and 1\(b\)) were present in the tobacco.

Subsequently the isomer 1\(a\), free of the less polar isomer (1\(b\)) was isolated from a more polar fraction of the tobacco by preparative gas chromatography. Its elemental composition was confirmed by accurate mass determination.

The mass spectra of the two isomers revealed prominent ions at \( m/e \) 109, 122, 124 and 135 for which fragments, the genesis shown in Scheme 2 may be invoked. High resolution mass spectrometry manifested the elemental compositions of the structures suggested in Scheme 2.

The mass spectrum of the second isolate, obtained by preparative gas chromatography from the same fraction as 1\(a\) and 1\(b\), exhibited a molecular ion at \( m/e \) 208, corresponding to \( \text{C}_{13}\text{H}_{18}\text{O}_{5} \), and was similar to the mass spectra of 1\(a\) and 1\(b\) (abundant ions at \( m/e \) 109, 122, 124, and 135) indicating a structural relationship. The 2-methylfur-5-yl moiety was apparent from IR absorption at 782 cm\(^{-1}\) and signals in the NMR spectrum at \( \delta 2.26 \) (3 H, broad singlet), \( \delta 5.82 \) (1 H, doublet with further splittings, \( J \) 3.0 Hz) and \( \delta 6.02 \) (1 H, doublet, \( J \) 3.0 Hz). The methyl substituted tetrahydrofuran ring was indicated by a three-proton singlet at \( \delta 1.54 \) and a one-proton multiplet at \( \delta \text{ ca. } 3.74 \). The chemical shift and multiplicity of the latter signal suggested that the proton on the oxygenated carbon was non-allylic, and that this isolate was also a diastereomeric mixture. The observed lack of clear resolution of the long-range spin couplings might be explained by small differences in chemical shifts of these protons. The diastereomeric nature (ratio 2:3) of this isolate was further supported by the presence of a seven line multiplet in the \( \delta 0.8-1.0 \) region (6 H) which could be ascribed to two isopropyl groups. The two diastereomers could be assigned the structures \textit{cis} and \textit{trans} 2-methyl-5-(2-methyl-5-isopropyltetrahydro-2-furyl) furan (2\(a\) and 2\(b\)).

The proposed structures of 1\(a\), 1\(b\), 2\(a\), and 2\(b\) were confirmed by synthesis as outlined in Scheme 1, which also provided a means of determining their relative stereochemistry. Thus the alcohol 5, conveniently prepared by reacting 4-methyl-3-penten-1-ylmagnesium bromide with 2-methyl-5-acetylfuran (3) in a Grignard reaction, was converted to a 1:1 mixture of the diastereomeric tetrahydrofuran derivatives 6\(a\) and 6\(b\) in one step by epoxidation followed by spontaneous cyclization. Dehydration was effected by phosphorus oxychloride in pyridine to yield, after chromatography on silica, the desired pure olefins 1\(a\) and 1\(b\), which exhibited spectral data and gas chromatographic behaviour (co-injection on a capillary column) indistinguishable from those of the natural mixture.

The last step also yielded three by-products evidently arising via rearrangement of an enol ether, namely the isomeric unsaturated ketones 2-methyl-6-(5-methyl-2-furyl)-6-hepten-3-one, (8), and 5E and 5Z isomers of 2-methyl-6-(5-methyl-2-furyl)-5-hepten-3-one, (7a and 7b).

The pure dihydro derivatives 2a and 2b were prepared from 1a and 1b, respectively, by catalytic hydrogenation of the isopropenyl groups. Synthetic 2a and 2b exhibited spectral data identical to those of the natural products. The seven line multiplet in the NMR-spectrum, ascribed to the isopropyl signals, could be reconstructed by superposition of the spectra of synthetic 2a and 2b. Furthermore, synthetic 2a and 2b had different GC retention times but when coinjected separately with the natural diastereomeric mixture each, in turn, enhanced the signal for the respective natural isomer.

The relative stereochemistry of the tetrahydrofuran compounds was determined by measuring the relat. lanthanide induced chemical shifts 5,14 for the alcohols 6a and 6b. Attempts to separate the synthetic intermediate mixture of 6a and 6b were only moderately successful, even by preparative gas chromatography, and these compounds were therefore prepared by hydration 8 of the respective olefins 1a and 1b, which could be separated easily by liquid chromatography.

Addition of the shift reagent Eu(DPM)3 to the alcohol 6 obtained from the more polar olefin 1a, produced an upfield shift of the furan methyl signal, while for the other isomer, this signal showed the usual downfield shift. Upfield shifts are predicted for O—Eu—H angles between 54.7 and 125.3° and have been observed in a number of cases.5 Only when the hydroxy-isopropyl group and furan ring have a cis relationship (6a) can the angle subtended by the europium atom, the hydroxyl oxygen and the furan methyl group be such as to give rise to an upfield lanthanide induced shift. Also, in a competition experiment on a 1:1 mixture, the trans isomer showed much stronger co-ordination to the Eu-complex.

The skeletons of these four new tobacco compounds 1a, 1b, 2a, and 2b suggest they are of terpenoid origin and pseudionone, a known tobacco constituent, could be a possible precursor. The co-occurrence of an unsaturated isoprenoid and its saturated counterpart (e.g. 1a and 2a) is relatively common in tobacco isolates.10 1a isolated from tobacco showed no optical activity, and it is assumed that 1a and the related tobacco constituents described here are racemates.

EXPERIMENTAL

NMR, IR, UV, rotations, and mass spectra were recorded on Varian A60-A; HA-100D and XL-100, Digilab FTS-14, Beckmann DK-2A, Perkin-Elmer 141, and LKB 9000 (70 eV) instruments, respectively. Accurate mass determinations were carried out at the Laboratory for Mass Spectrometry, Karolinska Institute, Stockholm. Analytical and preparative gas chromatography was performed on a Varian 1700 instrument using steel capillary columns (50 m x 0.25 mm) coated 11 with Ucon Oil HB 2000, and a 3 m x 3.2 mm glass column packed with 5% Carbowax 20 M on Chromosorb G, respectively. The extraction of 295 kg sun-cured Greek tobacco, Nicotiana tabacum L., and the fractionation of the extract has been described in previous communications.4 The natural compounds were isolated by preparative gas chromatography.

2-Methyl-5-(2-methyl-5-isopropyltetrahydro-2-furyl)furan (1a + 1b). Isolated as a mixture of 1a and 1b in ratio 3:7 (7.2 mg) from fraction C9.14 For spectral data, see synthetic 1a and 1b. (+)-cis-2-Methyl-5-(2-methyl-5-isopropyltetrahydro-2-furyl)furan (1a): Isolated from subfraction No. 5 of fraction B2 (8 mg).

2-Methyl-5-(2-methyl-5-isopropyltetrahydro-2-furyl)furan (2a and 2b). Isolated from fraction C9,14 isomeric ratio 2:3. Spectral data are given under synthetic 2a and 2b.

Synthetic products

2-Methyl-5-acetylfuran (3) was prepared as described by Farrar and Levine.15
4-Methyl-3-penten-1-yl bromide (4) was obtained 95% pure from dimethylcyclopentyl carbinal as outlined by Medina and Manjarrez except for omitting the NaHCO3-treatment and subsequent distillation.

(±)-6-Methyl-2-(5-methyl-2-furyl)-5-heptene-2-one (5), 4-Methyl-3-penten-1-yl bromide (4, 2.6 g) in anhydrous ether (10 ml) was added dropwise to a suspension of Mg (340 mg) and ether (40 ml). Stirring was prolonged until the Mg was dissolved and the ketone (3, 600 mg) in ether (20 ml) was added dropwise to the cooled (0°C) solution of the Grignard reagent. The reaction mixture was stirred for 1 h after the addition of the ketone and the temperature maintained at 0°C. Crushed ice was added and the mixture stirred for 10 min, followed by

extraction with ether. Removal of the solvent and subsequent chromatography on silica gel furnished the furan derivative (5, 580 mg, 57 %) as a colourless oil. MS: m/e 208 (M⁺, 11), 125 (100), 147 (46), 43 (33), 122 (31), 126 (18), 190 (15), 69 (15), 41 (15); r max (film) 3400 (broad), 2978 (s), 2928 (s), 2860 (m), 1450 (m), 1355 (m), 1378 (m), 1321 (m), 1117 (m), 1100 (m), 1022 (s), 944 (m), 786 (s); δ (CDCl₃) 1.47 (3 H, s), 1.65 (3 H, m), 1.67 (3 H, m), 1.82 (2 H, m), 2.23 (3 H, d, J 0.8 Hz), 2.9 (OH), 5.09 (1 H, m), 5.83 (1 H, dq, J ca. 0.8 and 3.0 Hz), 6.03 (1 H, d, J 3.0 Hz).

cis and trans (±)-2-[5-Methyl-5-(5-methyl-2-furyl)tetrahydro-2-furyl]-2-propanol (6a + 6b). To a cooled (−5 °C) solution of the alcohol (5, 500 mg) in ether (50 ml) was added 3-chloroperbenzoic acid (600 mg) and the reaction mixture was kept at −5 °C overnight. The ether solution was extracted with diluted NaOH, washed with water, concentrated, and chromatographed on silica gel furnishing the tetrahydrofuran derivative as a colourless oil (216 mg, 40 %). The two diastereomers being present in equal amounts could only be separated by capillary GC.

cis Isomer (6a). A solution of H₂O₃A₅H₂O (171 mg) in water (0.9 ml) was diluted with tetrahydrofuran (0.9 ml) and the pure olefin 1a (vide infra), the more polar of the isomers, 90 mg) added to the yellow suspension. The solution was stirred for 55 min before adding 2 M NaOH (1.5 ml) and NaBH₄ (15 mg). The reaction mixture was diluted with ether, washed with brine and dried (Na₂SO₄). The pale yellow residue after evaporation was chromatographed on silica (25 % ether in pentane) to yield 6a (39 mg). MS: m/e 224 (M⁺, 9), 122 (100), 165 (53), 123 (43), 43 (42), 109 (21), 59 (16), 147 (13), 137 (12). IR: r max (film) 3560 (m), 3460 (broad), 3110 (w), 2980 (s), 1385 (m), 1375 (m), 1224 (m), 1092 (s), 1086 (s), 1052 (m), 1024 (s), 784 (s). NMR: The r values given refer to relative induced shifts, on addition of Eu(DPM)₃. δ (CDCl₃) 1.73 (3 H, s, r 0.21), 1.7–2.3 (4 H, m), 2.25 (3 H, broad s, r −0.015), 3.90 (1 H, m, r 0.88), 5.85 (1 H, dq, J 3.0 and 1.0 Hz, r 0.009), 6.04 (1 H, d, J 3.0 Hz, r 0.13).

trans Isomer (6b). It was prepared as described for the cis isomer but from 1b (30 mg) to yield 11 mg. MS: m/e 224 (M⁺, 5), 122 (100), 43 (34), 123 (25), 165 (27), 109 (16), 59 (14), 135 (9), 127 (9). IR: r max (film) 3470 (broad), 3110 (w), 2980 (s), 1386 (m), 1375 (m), 1224 (m), 1118 (s), 1056 (m), 1052 (m), 1026 (s), 1022 (s), 785 (s). NMR: For notations, see cis isomer. δ (CDCl₃): 1.15 (3 H, s, r 1.0), 1.23 (3 H, s, r 0.97), 1.55 (3 H, s, r 0.17), 1.7–2.3 (4 H, m), 2.26 (3 H, broad s, r 0.048), 3.89 (1 H, t, J 7.0 Hz, r 0.83), 5.85 (1 H, dq, J 3.0 and 1.0 Hz, r 0.048), 6.05 (1 H, d, J 3.0 Hz, r 0.12).

(±)-2-Methyl-5-(2-methyl-5-isopropenyltetrahydro-2-furyl) furan (1a and 1b). To a cooled (−10 °C) solution of the diastereomeric alcohols


6a and 6b (500 mg) in dry pyridine (50 ml) was added POCl₃ (1.5 ml) dissolved in pyridine (5 ml). The mixture was kept at −10 °C for 24 h, diluted with water and extracted with ether. The extract was washed with diluted H₂SO₄, water, NaHCO₃, water, concentrated and chromatographed on silica gel. The two diastereomers 1a and 1b were separated and collected in fractions 2 and 1, respectively. Three slightly more polar products (double-spot on TLC) were found in fraction 3 (160 mg). r max (film): 1714 cm⁻¹; NMR of fraction 3 revealed the presence of the following three compounds (ratio ca. 5:1:4): 2-methyl-6-(5-methyl-2-furyl-5E-hepten-3-one, (7a), δ 1.91 (3 H, m), δ 3.34 (2 H, d, J 7 Hz); irradiation at δ 0.18, and δ 1.91 respectively simplified the multiplet at δ 1.91, and increased (6 %) the intensity of the doublet at δ 3.34, 2-methyl-6-(5-methyl-2-furyl)-5Z-hepten-3-one, (7b), δ 2.02 (ca. 3 H, m), δ 3.66 (ca. 2 H, d, J 7 Hz), and 2-methyl-6-(5-methyl-2-furyl)-6-hepten-3-one (8), δ 4.89 (1 H, m), δ 5.45 (1 H, m). Signals also occurred at δ 1.12 (6 H, dd), 2.30 (3 H, m), δ ca. 2.66 (ca. 4 H, m), δ 5.95 (1 H, m), δ ca. 6.18 (ca. 2 H, m). Less of the desired olefins and more of these side-products were produced when higher reaction temperatures were employed.

trans Isomer (1b) (70 mg; yield: 31 %, based on the weight of one of the diastereomers of δ): MS: m/e 206 (M⁺, 6), 109 (100), 43 (55), 124 (48), 67 (37), 122 (27), 121 (21), 125 (20), 41 (16), 82 (14); r max (film): 1373 (m), 1301 (w), 1262 (m), 1221 (m), 1181 (w), 1149 (w), 1104 (m), 1044 (m), 1020 (s), 958 (w), 943 (w), 900 (s), 872 (w), 784 (s); δ (CDCl₃): 1.98 (3 H, s), 1.73 (3 H, m), 2.24 (3 H, dd, J 1.0 and 0.4 Hz), 4.45 (1 H, t, J ca. 6.5 Hz), 4.79 (1 H, broad s), 5.02 (1 H, broad s), 5.83 (1 H, dq, J 1.0 and 3.0 Hz), 6.05 (1 H, d, J 3.0 and 0.4 Hz). Irradiation at δ 1.73 simplified the peaks at δ 4.79 and 5.02, while irradiation at δ 2.24 simplified the signals at δ 5.83 and 6.05 to doublets. No separation from the natural isomer could be observed when co-injected with fraction B1 on a capillary GC column.

cis Isomer (1a) (75 mg; yield 33 %). MS: m/e 206 (M⁺, 17), 109 (100), 43 (78), 67 (30), 122 (26), 148 (25), 135 (25), 41 (23), 124 (23), 121 (20).

Accurate mass determinations (measured on natural 1a)

Compo-
sition:
C₆H₅O₂C₆H₄O C₆H₄O C₆H₄O calc. = 206.1307 135.0810 124.0524 124.0888
found = 206.1311 135.0807 124.0524 124.0888

Compo-
sition:
C₆H₅O₂C₆H₄O C₆H₄O C₆H₄O calc. = 222.0739 109.0286 109.0657 109.1022
found = 222.0732 109.0290 109.0653 109.1017

The tree ions at m/e 109 are given in the order of decreasing abundance. r max (film): 1373 (m), 1309 (w), 1289 (w), 1269 (w), 1269 (m), 1206 (w),
1181 (w), 1153 (m), 1100 (s), 1022 (s), 982 (w), 960 (w), 946 (w), 928 (w), 901 (s), 870 (w), 848 (w), 785 (s); δ (CDCl₃): 1.56 (3 H, s), 1.69 (3 H, m), 2.23 (3 H, dd, J 0.4 and 3.0 Hz), 4.46 (1 H, m), 4.78 (1 H, broad s), 5.0 (1 H, broad s), 5.81 (1 H, dq, J 1.0 and 3.0 Hz), 6.05 (1 H, dq, J 0.4 and 3.0 Hz).

The synthetic product was indistinguishable from the natural compound isolated from fraction B2 when co-injected on a capillary GC column.

trans (±)-2-Methyl-5-(2-methyl-5-isopropyltetrahydro-2-furyl) furan (2b). Ib (22 mg) in ethanol (2 ml) was hydrogenated at room temperature and atmospheric pressure using platinum oxide (ca. 5 mg) as catalyst. The hydrogen uptake was completed in 10 min and the reaction mixture was diluted with water and extracted with pentane. Removal of the solvent furnished the dihydro derivative (19 mg) essentially pure. MS: m/e 208 (M⁺, 5), 109 (40), 109 (32), 98 (19), 87 (16), 165 (15), 123 (11), 122 (10), 121 (8), 125 (8), 124 (6); vmax (film): 1388 (m), 1371 (m), 1278 (w), 1222 (m), 1178 (w), 1047 (s), 912 (s), 858 (w), 944 (w), 902 (w) 869 (w), 785 (s); δ (CDCl₃): 0.88 (3 H, d, J 6.8 Hz), 0.95 (3 H, d, J 6.0 Hz), 1.63 (3 H, s), 2.24 (3 H, d, J 1.0 Hz), 3.78 (1 H, q, J ca. 6.5 Hz), 5.83 (1 H, dq, J 1.0 and 3.0 Hz), 6.02 (1 H, d, J 3.0 Hz).

cis (±)-2-Methyl-5-(2-methyl-5-isopropyltetrahydro-2-furyl) furan (2a). Ia (28 mg) was hydrogenated as described above yielding the pure dihydro derivative (27 mg). MS: m/e 208 (M⁺, 9), 109 (100), 98 (40), 109 (35), 165 (32), 123 (30), 122 (28), 125 (25), 124 (20), 55 (20), 121 (15), 122 (13); vmax (film): 1386 (m), 1370 (m), 1290 (w), 1279 (w), 1221 (m), 1108 (s), 1041 (m), 1025 (s), 958 (w), 945 (w), 918 (w), 901 (w), 845 (w), 785 (s); δ (CDCl₃): 0.84 (3 H, d, J 6.8 Hz), 0.98 (3 H, d, J 6.5 Hz), 1.51 (3 H, s), 2.21 (3 H, dd, J 0.4 and 1.0 Hz), 3.72 (1 H, q, J ca. 7.8 Hz), 5.80 (1 H, dq, J 1.0 and 3.0 Hz), 6.02 (1 H, dq, J 0.4 and 3.0 Hz). The two dihydro derivatives could only be separated on capillary GC columns and were found indistinguishable from the natural diastereomeric mixture when co-injected.

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