Tobacco Chemistry. 29. (7S)-10-Oxo-4ξ-methyl-7-isopropyl-
5E-undecen-4-olide, a New Thunbergan-type Nor-isoprenoid
Isolated from Greek Nicotiana tabacum L.

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The structure of a new C₁₅-lactone, (7S)-10-oxo-
4ξ-methyl-7-isopropyl-5E-undecen-4-olide, isolated from Greek tobacco, has been determined
mainly by ¹H NMR, ¹³C NMR and high resolution MS, and its absolute configuration estab-
lished by degradation to (2S)-5-oxo-2-isopropyl-
hexanal. The carbon skeleton of the new com-
ound indicates that it is derived from a thunbergane precursor and constitutes the first
C₁₅ nor-thunberganoid in tobacco.

Some 200 nor-isoprenoids have so far been
encountered in tobacco leaves and tobacco
smoke. Virtually all of these can be viewed as
derived from either (i) carotenoids/aliphatic
polyisoprenoids, (ii) labdanes/drimanes, or (iii)
thunberganes, and are conveniently grouped
accordingly.¹ They constitute a substantial
amount of the tobacco essential oil and many
of them are considered important for the
tobacco flavour and aroma.² In the present
communication** we present evidence for the
structure (I) of a new lactone isolated from
sun-cured Greek Nicotiana tabacum L. and
evidently derived from a thunbergane precursor.

The presence of fifteen lines in the ¹³C NMR
spectrum and precise mass determination es-
established that the new compound had the ele-
mental composition C₁₅H₂₅O₅. The three oxygen
atoms, as judged from IR, ¹³C NMR, and ¹H
NMR, were accommodated in a methyl ketone
grouping (1716 cm⁻¹; δC 208.9, s; δH 2.1, 3 H, s)
and a γ-lactone moiety (1777 cm⁻¹; δC 176.9, s).

**Presented in part at the EUCHEM-conference,
Canary Islands, Sept. 16-20, 1974, and the
CORESTA-meeting, Montreux, Sept. 22-27, 1974.


Of the additional three methyl groups revealed
by the spectral data, two were present in an
isopropyl group (1370 and 1386 cm⁻¹; δH 19.1,
q, and 20.7, q; δH 0.82, 3 H, d, and 0.88, 3 H,
d), and the third was linked to the γ-atom of the
lactone ring, and, according to the low field
chemical shift of its proton resonance (δH 1.5,
3 H, s) allylic to the trans disubstituted double
bond present in the molecule (981 cm⁻¹; δC 131.6,d, and 134.1, d; δH 5.5, 2 H, m). Examina-
tion of the high resolution mass spectrum con-
firmation the presence of these structural features
and implied structure I for the new compound.
Thus, a doublet at m/e 209 (C₁₅H₂₃O₅ and
C₁₃H₁₅O₄) was consistent with the occurrence of
the acetyl and isopropyl groups, and peaks at
m/e 153 (C₁₀H₁₁O₂), 99 (C₇H₁₄O₃), and 125
(C₉H₁₄O₄) were in accord with the presence of
the 4-methyl-4-vinylene γ-lactone unit. More-
over, an ion at m/e 194 (C₁₃H₁₉O₄) demonstrated
the loss of the elements of acetone from the
molecular ion by a McLafferty reaction and
ence, the attachment of the acetyl group to a
methylenegroup. The remaining methylene
group could be inserted in three ways giving
10-oxo-4-methyl-7-isopropyl-5E-undecen-4-
olide (I), 10-oxo-4-methyl-8-isopropyl-5E-unde-
cen-4-olide (3), or 9-oxo-4-methyl-7-isobutyl-
5E-decen-4-olide (4) of which the two last pos-
sibilities were disfavoured by MS and ¹³C NMR
evidence. Thus, the presence of an C₁₁H₁₉O₄⁺
ion is only readily rationalized on the basis of
structure I, which on electron impact should
undergo simple cleavage of the allylic C(7)—
C(8) bond extending from the tertiary C(7).
Similarly, the $^{13}$C NMR data were consistent only with structure I, since in the case of structure 3 the resonance for the methylene carbon of the keto group should occur at a lower field than observed ($\delta_C$ 41.9, t) because of the $\beta$-substitution, and in the case of structure 4 the signals due to the geminal methyl carbons, here incorporated in an isobutyl group, should occur at a lower field ($\delta_C$ 22.23) than observed ($\delta_C$ 19.1, q, and 20.7, q). Moreover, the excellent agreement of relevant $^{13}$C NMR signals observed for solanone (2) and 4-methyl-5-hexen-4-olide (7) with those of the tobacco isolate strongly supported the suggested structure: 10-oxo-4-methyl-7-isopropyl-5E-undecen-4-olide (I, see Table 1).

Table 1. $^{13}$C chemical shifts (ppm relative to TMS) and assignments recorded for (7S)-10-oxo-4-4-methyl-7-isopropyl-5E-undecen-4-olide (I), and model compounds 2 and 7.

<table>
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<tr>
<th>Chemical shifts$^a$ (δ) and No. of lines</th>
<th>(n)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<td>t</td>
<td>28.7</td>
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<td>114.7</td>
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<td>C(4)</td>
<td>85.4</td>
<td>s</td>
<td>141.8</td>
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<td>C(5)</td>
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<td>d</td>
<td>132.2$^c$</td>
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<td>134.6$^c$</td>
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<td>d</td>
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<td>q</td>
<td>19.3</td>
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<td>C(15)</td>
<td>20.7</td>
<td>q</td>
<td>20.8</td>
<td>q</td>
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$^a$ Measured in proton noise-decoupled spectrum; $^b$ No. of lines observed in off-resonance proton-decoupled spectrum (s' = singlet etc.); $^c$ Tentative.

Conclusive evidence for the presence of a 2-oxo-5-isopropylhex-1-ylidene moiety was obtained by the isolation of 5-oxo-2-isopropylhexanal (5) on ozonolytic degradation of the lactone. This ketoaldehyde (5) was optically active and exhibited the same positive rotatory power as the corresponding material (5) similarly prepared from solanone (2) thereby establishing the absolute configuration at C(7) as S.

Additional evidence for the chemically unverified part of the molecule and for the trans configuration of the double bond was obtained by spectral examination of the triol diacetate.

$^*\text{Dr. E. Demole, Firmenich SA, Geneve, has independently and simultaneously identified 10-oxo-4-methyl-7-isopropyl-5E-undecen-4-olide as a new constituent of Burley tobacco (private communication).}$

$^{**}\text{Originally the L-configuration was erroneously attributed to solanone.}^{*}\text{The correct } S \text{(or } D) \text{-configuration was later established through correlation with (2S)-5-oxo-2-isopropylhexanoic acid by Fuku-}zumi \text{et al.}^{*}\text{who, however, applied the sequence rules of Cahn, Ingold and Prelog,}^{*}\text{further exemplified by Weidon}^{*}\text{incorrectly by assigning the } R \text{-configuration to solanone.}$

(6; 3460 cm⁻¹; δH 4.1, 2 H, t, and 4.8, 1 H, m) prepared by LiAlH₄-reduction of the tobacco constituent (I) and subsequent acetylation under mild conditions. Thus, electron impact generated the structurally required fragments, notably the important M−101 (74 %) produced by cleavage of the labile allylic C(3)–C(4) bond extending from the hydroxylated tertiary carbon, and its daughter ions M−101−60 (100 %, m* 135.9) and M−101−60−18 (42 %, m* 146.8) formed by consecutive losses of acetic acid and water. It exhibited IR absorption (979 cm⁻¹) characteristic of a trans disubstituted double bond and displayed, after addition of Eu(dpm)₃ to the ¹H NMR sample, a 16 Hz vicinal spin-spin coupling constant for the two olefinic protons constituting the AB-part of an ABX-system.

Shortage of material prevented configurational assignment of the second chiral centre, C(4). However, the CMR and ¹H NMR spectra (including those recorded after addition of shift reagent) indicated that the tobacco isolate was configurationally homogeneous as no additional resonances were observed; this, as previously found for the structurally related methyl 3-hydroxy-3-methyl-6-isopropyl-4E-octenoate,¹¹,¹² would have been expected if two C(4)-epimers were present.

The structural relationship of this new lactone with the macrocyclic thunbergane dipterpenoids, which are quite abundant in tobacco, places it in the growing family of volatile tobacco constituents assumed to be derived from such dipterpenoids. A possible precursor, although as yet not detected in tobacco, is the hydrated thunbergene, thunberga-2,7,11-trien-4-ol (8)* which under the influence of oxygen and light could undergo oxidative cleavages of the C(7)−C(8) and C(11)−C(12) bonds furnishing the C₁₅-lactone. Most of the thunbergan-derived nor-isoprenoids previously encountered in tobacco are either C₁₂- or C₁₄-compounds and the new lactone therefore represents the first member of a new subgroup. Nine of the eleven thunbergan-dipterpenoids found in tobacco¹ are hydroxylated and unsaturated at positions corresponding to those in the present lactone, and, being potential precursors, they might all possess the same S-configuration at the carbon atom carrying the isopropyl group.

EXPERIMENTAL

¹H NMR,¹³C NMR (accuracy of δC: ±0.05 ppm), IR, UV, and mass spectra were recorded on Varian XL-100, Digilab FTS-14, Beckmann DB-2A, and LKB 9000 instruments, respectively.

* Nomenclature according to J. W. Rowe Oct. 1968; private communication.
tively. Rotations were measured on a Perkin-Elmer 141 instrument, and precise mass determinations were carried out at the Laboratory for Mass Spectrometry, Karolinska Institutet, Stockholm.

7(S)-10-Oxo-4-ethyl-7-isopropyl-5E-undecen-4-olide (I, 35 mg) was isolated from a medium-volatile, neutral fraction 44 of an extract, 35 obtained from 295 kg sun-cured Greek Nicotiana tabacum L., employing liquid chromatography on silica gel and AgNO₃-impregnated silica gel. The fractionation of this medium-volatile material will be described elsewhere. 13 MS (20 eV); m/e 252 (M⁺, 6), 43 (100), 121 (44), 107 (33), 99 (31), 93 (31), 95 (25), 81 (24), 109 (24), 97 (22), 71 (22), 123 (22), 135 (22), 149 (22), 151 (22), 111 (21), 194 (19), 59 (19), 69 (18), 119 (18), 125 (18), 83 (18), 137 (17), 134 (17), 139 (16), 112 (12), 105 (11), 108 (11), 135 (11), 122 (9), 179 (9), 191 (9), 161 (9), 163 (8), 59 (8), 234 (8); accurate mass determination: C₁₉H₂₅O₃, found 252.1726; calc. 252.1725; C₁₉H₂₅O₃, found 99.0540, calc. 99.0448; rₓ max (film): 2965 (s), 2948 (s), 2876 (m), 1777 (s), 1716 (s), 1386 (shoulder), 1370 (m), 1240 (m), 1206 (m), 1169 (m), 1141 (m), 1078 (m), 981 (m), 932 (m), 0.42 (CDCl₃); 0.42 (CDCl₃); 0.22 (3 H, d, J 6.5 Hz), 0.88 (3 H, d, J 6.5 Hz), 1.50 (3 H, s), 2.0 - 2.8 (ca. 4 H, m), 2.12 (3 H, s), 5.5 (2 H, m); addition of Eu(dpm); r° (relative induced shifts) 0.57 and 0.65 (C(7)-CH(C₆H₅), overlapping doublets), 1.0 [C(4)CH₃, s], 1.24 [C(5)H(C₆H₅), m], 3.35 [C(11)H, s]; δc (CDCl₃): see Table I; [1]⁺ = +1.3° (589 nm), +1.7° (578), +2.4° (946), +5.7° (436), (c 1.8, CHCl₃).

4-Hydroxy-1,10-diacetoxy-4-ethyl-7-isopropyl-5E-undecene (6): (7S)-10-oxo-4-ethyl-7-isopropyl-5E-undecen-4-olide (I, 10 mg) dissolved in dry ether (3 ml) was added dropwise to a solution of LiAlH₄ (8 mg) in dry ether (20 ml) and the mixture stirred for 1 h at room temperature. Moist ether, followed by water (10 ml) was added to the reaction mixture and the products extracted with ether. Removal of the solvent left a homogeneous (TLC) product (13 mg) which was acetylated without further purification. The residue was dissolved in dry pyridine (1.5 ml) and acetyl anhydride (0.5 ml) and kept at ambient temperature for 6 h. Excess anhydride was destroyed with a few drops methanol, water (10 ml) was added and the acetal extract with ether. The extract was washed with H₂SO₄ (dil.), water, NaHCO₃, water, dried and evaporated leaving the diacetaate as a colourless oil which was chromatographed on a silica gel column. The diacetate (9 mg) was eluted with 50% ether/pentane. MS (20 eV, ion source temp. 120 °C): m/e 342 (M⁺, not visible), 181 (100), 241 (74), 43 (42), 111 (42), 163 (42), 137 (29), 71 (33), 123 (28), 264 (21), 182 (15); metastables were observed at m/e 215.1, 185.0, 149.8, and 172.6, respectively, corresponding to the transitions 324 (M⁻ 18) → 264 (M⁻ 18 - 60) → 221 (M⁻ 18 - 60 - 43), 241 (M⁻ 101) → 181 (M⁻ 101 - 60) → 163 (M⁻ 101 - 60 - 18), and 207 (M⁻ 15 - 2 × 60) → 189 (M⁻ 15 - 2 × 60 - 18); rₓ max (film): 3460 (broad), 2959 (m), 2936 (shoulder), 2871 (m), 1739 (s), 1455 (w), 1383 (shoulder), 1372 (m), 1368 (m), 1247 (s), 1130 (w), 1051 (m), 970 (w), 962 (w); δc (CDCl₃): 0.91 (3 H, d, J 6.5 Hz, 0.96 (3 H, d, J 6.5 Hz), 1.19 (3 H, d, J 6 Hz), 1.30 (3 H, s), 2.01 (3 H, s), 2.03 (3 H, s), 4.07 (2 H, t with further splittings), ca. 4.83 (1 H, m), 5.43 (2 H, m); irradiations at δ 1.19 and 1.58, respectively, simplified the multiplet at δ ca. 4.83 to a distorted triplet and the multiplet at δ 4.07 to a broad singlet; irradiation at δ ca. 4.83 collapsed the doublet at δ 1.19 to a singlet; addition of Eu(dpm); r° (relative induced shifts) 0.18 and 0.23 [C(7)CH(C₆H₅), m], 0.42 and 0.46 [C(11)H, 2 × d], 0.65 and 0.67 [2 × COCH₃], 1.0 [C(1)H₃, t], 1.23 [C(10)H₃, m], 1.26 [C(6)H, m], 1.81 [C(5)H, d, J 16 Hz], 1.75 and 1.82 [C(4)CH₂, 2 × s]; decoupling experiments performed on the Eu(dpm)₉-treated sample: irradiation at δ 5.80 [C(10)H, r 1.23] collapsed the two doublets at δ 1.52 (r 0.42) and δ 1.55 (r 0.46), respectively, to a broad singlet [C(11)H₃]; irradiation at δ 1.54 sharpened the multiplet at δ 5.80 [C(10)H, r 1.23].

Ozonolysis of (7S)-10-oxo-4-ethyl-7-isopropyl-5E-undecen-4-olide (I). The natural lactone (I, 15 mg) dissolved in CH₂Cl₂ (15 ml) and pyridine (0.1 ml) was treated with excess ozone at -65 °C. Zinc-powder (500 mg) and acetic acid (2 ml) were added and the mixture stirred 35 min, during which the temperature was slowly raised to 20 °C. The solution was decanted, the reaction vessel with its residue was washed with CH₂Cl₂, and the combined solutions washed four times with water. Removal of the solvent left a slightly yellow oil which was chromatographed on silica gel furnishing pure (25)-5-oxo-2-isopropylhexanal (5, 2 mg); MS: m/e 156 (M⁺, 2), 43 (100), 38 (75), 41 (55), 71 (23), 69 (22), 55 (18), 95 (18), 70 (10), 59 (10), 96 (10), 86 (9), 110 (9), 132 (8), 85 (8), 81 (8), 132 (7); rₓ max (film): 2967 (m), 2935 (m), 2879 (w), 2720 (w), 1722 (w), 1719 (s), 1372 (m), 1170 (m); lit.: 13 rₓ max (film): 1709 (C=O); δc (CDCl₃) 0.97 (3 H, d, J 7 Hz, 1.00 (3 H, d, J 7 Hz), 2.13 (3 H, s), 2.3 - 2.6 (2 H, m), 9.63 (1 H, d, J 2 Hz); lit.: 13 δ 1.0 (isopropyl methyls, J 6 Hz), 2.07 (acetyl methyl): [1]⁺ = +47° (589 nm), +49° (578), +60° (546), +165° (436), +415° (365), (c 0.2, CHCl₃). The ketoaldehyde did not separate from the corresponding ketoaldehyde δ prepared from solanone (vide infra) when co-injected on a glass capillary GC-column.

Ozonolysis of solanone. Solanone (55)-8-methyl-5-isopropyl-6E,8-nonadien-2-one, 18mg; [1]⁺ = +16.7° (589 nm), +17.1° (578), +20.6° (546), +45.6° (436), +114.3° (365), (c 0.62, CHCl₃);
lit. \([\alpha]_D^{13} + 13.6^\circ\) (neat)\(^4\) \([\alpha]_D^{18} + 14.2^\circ\) (CHCl\(_3\))\(^4\) previously procured from the same tobacco (fraction B3)\(^1,4\) was ozonolyzed and the ketoaldehyde 5 (6.2 mg) isolated as described above; \([\alpha]_D^{13} + 43.7^\circ\) (589 nm), +45.9\(^\circ\) (578), +55.6\(^\circ\) (546), +133.3\(^\circ\) (436), +364.8 (365), (c 0.54, CHCl\(_3\)); the NMR, IR and mass spectra were indistinguishable from those of the ketoaldehyde obtained from the tobacco constituent.

**Model compounds.** Solanone (2), isolated from Greek tobacco\(^1,2\) and 4-methyl-5-hexen-4-olide (7), obtained in almost quantitative yield by CrO\(_3\)/AcOH oxidation of linalool oxide, was used for comparison of \(^13\)C NMR data, see Table 1.

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**REFERENCES**


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