178. A Chemical Study of *Burley* Tobacco Flavour (*Nicotiana tabacum* L.) VI. Identification and Synthesis of Four Irregular Terpenoids Related to Solanone, Including a 'Prenylsolanone' [1])

by **Edouard Demole** and **Paul Enggist**

Firmenich SA, Research Laboratory, 1211 Geneva 8

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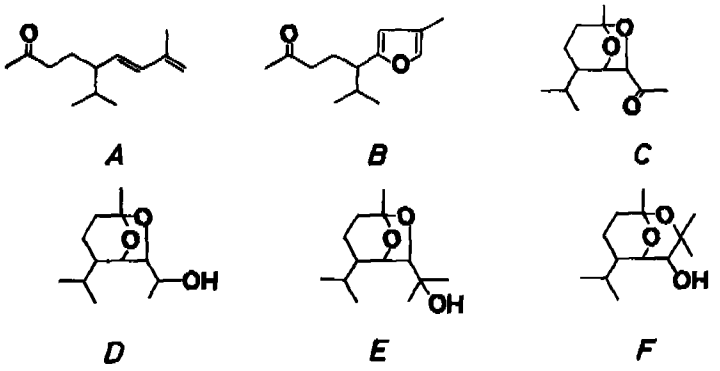
Summary. Four novel constituents of *Burley* tobacco condensate have been identified as (*E*)-5-isopropyl-7-(2-methyl-tetrahydrofur-2-yl)-hept-6-en-2-one (**G**), (*E*)-5-isopropyl-7-(2-methyl-tetrahydrofur-2-yl)-hept-6-en-2-ol (**H**), (*E*)-4-methyl-7-isopropyl-10-oxo-undec-5-en-4-olide (**I**), and (*E*,*E*)-6,12-dimethyl-9-isopropyltrideca-5,10,12-trien-2-one (**J**) or 'prenylsolanone'. Compounds **G**, **H**, and **I** were synthesized from norsolanadione (**1**), compound **J** from solanone (**A**). These substances belong to a growing family of tobacco metabolites structurally related to solanone (**A**). Their possible formation from cembrene-type precursors is briefly outlined.

Among other results, our continuing investigation of *Burley* tobacco flavour has permitted the identification in this essential oil of a number of new constituents related to solanone (**A**) [2]. Typical examples of such irregular terpenoids, that presumably arise from the breakdown of some cembrene-type precursor(s) during the tobacco processing (fermentation, curing, aging), are solanofuran (**B**) [3] as well as the 7,8-dioxabicyclo[3.2.1]octane- and 2,9-dioxabicyclo[3.3.1]nonane derivatives **C**–**F** [4][2]). We now add four further representatives, **G**–**J**[2]) (*Scheme 1*), to this class of compounds. These constituents were isolated[5]) by subjecting miscellaneous *Burley* tobacco condensate[6]) subfractions[7]) to GLC. separations.



1) For the 5th publication of this series see [1].

2) Compounds **C** and **E** were also detected in Turkish tobacco [5], and compounds **B** [6], **C**[3]), and **I** [7a][4]) in Greek tobacco.

3) Private communication from Dr. *A. J. Aasen* (*Swedish Tobacco Company*).

4) Keto-lactone **I** was simultaneously and independently identified in tobacco by *Enzell et al.* (*Swedish Tobacco Company*) and by ourselves. We are indebted to Dr. *A. J. Aasen* for informing us of this result prior to publication.

5) We thank Mr. *D. Berthet* for this isolation work.

6) *Burley* tobacco condensate was prepared as previously described [8].

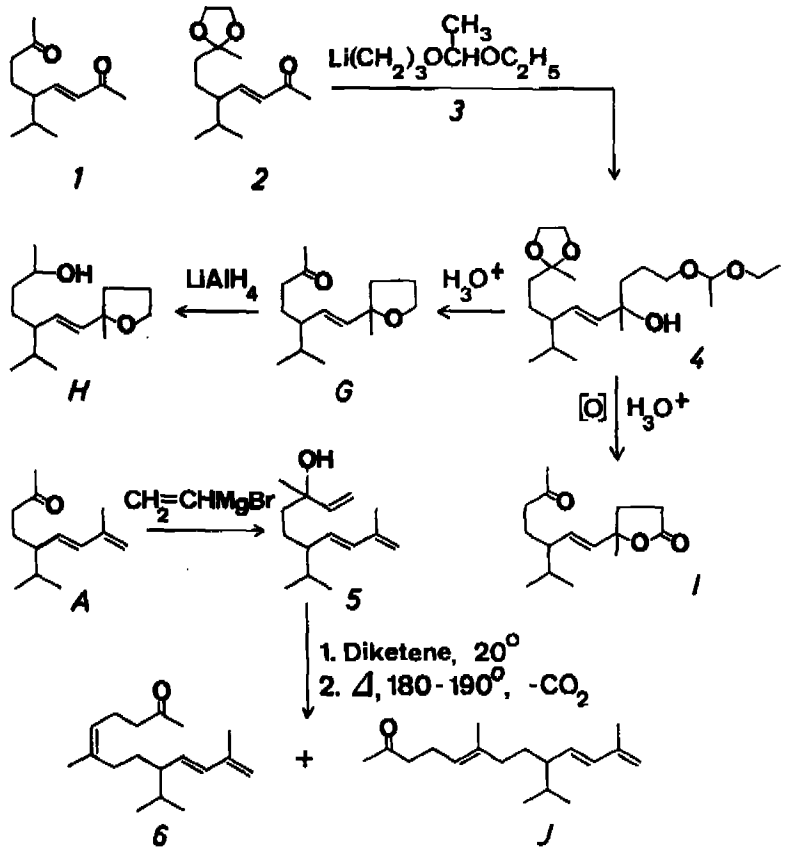
7) The preparation and study of *Burley* tobacco condensate subfractions B3-PN-a to -i will be described in a future paper.

1. (E)-*5-Isopropyl-7-(2-methyl-tetrahydrofur-2-yl)-hept-6-en-2-one* (**G**). Subfractions B3-PN-g[7]) and -h were found to contain respectively 0.89 and 1.39% of keto-ether **G**, this corresponding to a total concentration of 0.03% in the *Burley* tobacco condensate[6]). The synthesis of this substance was easily accomplished by reaction of norsolanadione (**1**) monoacetal **2** with lithio-acetal **3** [9] followed by treatment of the resulting hydroxy-diacetal **4** with dilute acid (*Scheme 1*). The synthetic material thus obtained was a ~1:1 mixture of diastereoisomers (GLC., Ucon HB 5100, 140°, 20 m×0.3 mm capillary column) that had b.p. 84–86°/0.001 Torr; $d_4^{20} = 0.925$; $n_D^{20} = 1.4629$. – IR. (neat, bands with decreasing intensities): 1705, 1360, 1030, 1160 ≃ 970, 1085, 1450 cm^{-1}. – MS. (*m/e* (% relative abundance)): 43 (100), 55 (12), 69 (8), 85 (20), 97 (30), 111 (22), 121 (9), 137 (16), 165 (7), 223 (4), $M^+ = 238$ (very weak). – NMR. ($CDCl_3$): $\delta = 0.83$ (3 H, *d*, $J = 6$ Hz); 0.87 (3 H, *d*, $J = 6$ Hz); 1.28 (3 H, *s*); 2.09 (3 H, *s*); 1.0–2.2 (8 H, *m*); 2.40 (2 H, *t*, $J = 6.5$ Hz); 3.85 (2 H, *m*); 5.40 (2 H, narrow *m*).

Synthetic and natural **G** exhibited identical spectral properties.

2. (E)-*5-Isopropyl-7-(2-methyl-tetrahydrofur-2-yl)-hept-6-en-2-ol* (**H**). Subfraction B3-PN-i was found to contain 2.26% of hydroxy-ether **H**, this representing 0.17% in the whole *Burley* tobacco condensate. Compound **H** synthesized by direct $LiAlH_4$

Scheme 1. Burley *tobacco constituents* **G**-**J** *and their synthesis*



reduction of **G** (above) had b.p. 97–98°/0.001 Torr; $d_4^{20} = 0.921$; $n_D^{20} = 1.4687$. – IR. (neat): 3450, 1025, 1360, 1085, 970, 1110, 1450 cm^{-1}. – MS.: 43 (100), 55 (36), 69 (29), 85 (63), 97 (45), 111 (46), 123 (14), 137 (13), 181 (16), 225 (7), $M^+ = 240$ (3). – NMR. ($CDCl_3$): $\delta = 0.82$ (3 H, *d*, $J = 6$ Hz); 0.88 (3 H, *d*, $J = 6$ Hz); 1.18 (3 H, *d*, $J = 6$ Hz); 1.30 (3 H, *s*); 1.0–2.2 (11 H, *m*); 3.88 (3 H, *m*); 5.42 (2 H, narrow *m*).

Synthetic and natural **H** exhibited identical spectra.

3. (E)-*4-Methyl-7-isopropyl-10-oxo-undec-5-en-4-olide* (**I**)[4]. Subfraction B3-PN-h was found to contain 1.12% of keto-lactone **I**, corresponding to 0.01% in the whole *Burley* tobacco condensate. This constituent was synthesized in the same way as keto-ether **G**, except that the intermediate hydroxy-diacetal **4** was hydrolyzed under oxidative conditions (*Scheme 1*). A moderate yield of **I** was thus obtained as a ~1:1 mixture of diastereoisomers (GLC., Ucon HB 5100, 180°, 20 m × 0.3 mm capillary column) that had b.p. 134–137°/0.001 Torr; $d_4^{20} = 1.005$; $n_D^{20} = 1.4719$. – IR. (neat): 1770, 1705, 1235, 1360, 1160, 930, 975 cm^{-1}. – MS.: 43 (100), 55 (17), 69 (8), 81 (9), 93 (15), 107 (14), 121 (15), 135 (7), 149 (6), 194 (3), 234 (1.5), $M^+ = 252$ (very weak). – NMR. ($CDCl_3$): $\delta = 0.82$ (3 H, *d*, $J = 6$ Hz); 0.87 (3 H, *d*, $J = 6$ Hz); 1.49 (3 H, *s*); 1.0–1.9 (5 H, *m*); 2.09 (3 H, *s*); 1.9–2.9 (5 H, *m*); 5.50 (2 H, narrow *m*).

Synthetic and natural **I** exhibited identical spectra.

4. (E,E)-*6,12-Dimethyl-9-isopropyl-trideca-5,10,12-trien-2-one* (**J**). Subfractions B3-PN-c and -d were found to contain respectively 2.13 and 0.31% of trienone **J**, this corresponding to a total concentration of 0.04% in the whole *Burley* tobacco condensate. The synthesis of this ketone was carried out by allowing solanone (**A**) to react with vinylmagnesium bromide, treating the resulting tertiary allyl alcohol **5** with diketene to form the corresponding acetoacetate ester [10], and heating the latter for 30 min at 180–190° (*Carroll* reaction [11]) (*Scheme 1*). There was thus obtained a 1.7:1.0 mixture of *E,E* and *Z,E* stereoisomers of the desired ketone (yield 33%), accompanied by several more volatile by-products. The stereoisomers were separated by GLC. (5% Carbowax, 200°, 2.5 m column).

(Z,E)-*6,12-Dimethyl-9-isopropyl-trideca-5,10,12-trien-2-one* (**6**): relative $R_T = 1.00$. – NMR. ($CDCl_3$): $\delta = 0.85$ (3 H, *d*, $J = 6$ Hz); 0.89 (3 H, *d*, $J = 6$ Hz); 1.69 (3 H, *s*); 1.87 (3 H, *s*); 2.15 (3 H, *s*); 1.1–2.1 (6 H, *m*); 2.1–2.6 (4 H, *m*); 4.89 (2 H, *s*); 5.06 (1 H, *m*); 5.44 (1 H, *d* × *d*, $J = 16$, $J' = 8$ Hz); 6.12 (1 H, *d*, $J = 16$ Hz).

(E,E)-*6,12-Dimethyl-9-isopropyl-trideca-5,10,12-trien-2-one* (**J**): relative $R_T = 1.24$. – IR. (CCl_4): 1715, 1360, 965, 1450, 1155, 880, 1605, 3100, 1635 cm^{-1}. – MS.: 43 (100), 55 (12), 69 (12.5), 81 (25), 93 (28), 105 (12.5), 121 (22), 136 (21.5), 161 (14), 189 (4), 204 (3.5), 219 (3.5), $M^+ = 262$ (<1). – NMR. ($CDCl_3$): $\delta = 0.82$ (3 H, *d*, $J = 6$ Hz); 0.86 (3 H, *d*, $J = 6$ Hz); 1.60 (3 H, *s*); 1.85 (3 H, *s*); 2.14 (3 H, *s*); 1.1–2.1 (6 H, *m*); 2.1–2.6 (4 H, *m*); 4.87 (2 H, *s*); 5.05 (1 H, *m*); 5.39 (1 H, *d* × *d*, $J = 16$, $J' = 8$ Hz); 6.06 (1 H, *d*, $J = 16$ Hz).

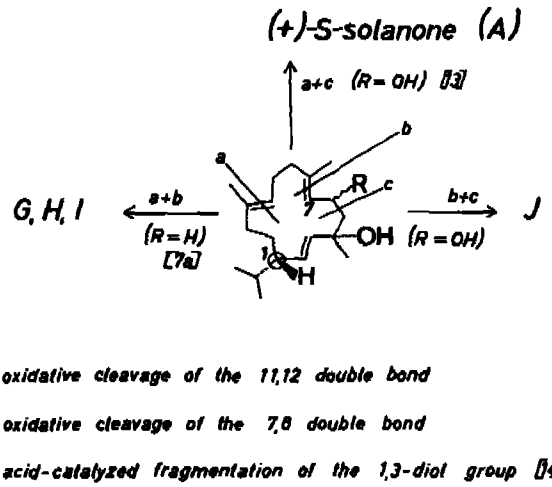
Synthetic and natural **J** exhibited identical spectra. This ketone represents the first C_{18} cembrene-type metabolite found in tobacco. Since it contains one more isoprene unit than solanone (**A**), we propose to call it *prenylsolanone*.

5. *Possible origin of compounds* **G–J** *in tobacco*. These four metabolites are likely to originate from the breakdown of diterpene alcohols structurally related to cem-

brene, several representatives of which are well-known tobacco constituents (*i.e.* α- and β-duva-4,8,13-triene-1,3-diols [12]). Such a process is formally summarized in *Scheme 2*. Accordingly, all the solanone-related tobacco constituents might well have the same *S*-configuration as this ketone [15] [7] at the carbon atom bearing the isopropyl group, as advocated by *Enzell et al.* [7]. These authors found their proposal to be indeed correct in the cases of keto-lactone **I** [7a][4]), norsolanadione (**1**)[8]), and (*E,E*)-3-methyl-6-isopropyl-9-oxo-deca-2,4-dienoic acid [7b].

We thank Miss *Monika Hagmann* for her valuable technical assistance.

Scheme 2. *Possible formation of compounds* **G**-**J** *and* (+)-*S-solanone* (**A**) *in tobacco* via *cleavage of cembrene-type precursors*



a = oxidative cleavage of the 11,12 double bond

b = oxidative cleavage of the 7,8 double bond

c = acid-catalyzed fragmentation of the 1,3-diol group [4]

Experimental Part

The spectra were obtained with the instruments already described [3] (the mass spectra were measured at 70 eV, 20 μA, inlet temperature 150°). The GLC. separations were performed on gas chromatographs *Aerograph*, Model 1820-3 (*Varian Aerograph* AG), and *Carlo Erba*, Model 2301 AC.

1. (E)-*5-Isopropyl-7-(2-methyl-tetrahydrofur-2-yl)-hept-6-en-2-one* (**G**). A mixture of 23 g (0.117 mol) of norsolanadione (**1**) [2] [16][9]), 750 mg *p*-toluenesulfonic acid, and 80 ml 2-methyl-2-ethyl-dioxolan was stirred for 3 h at 20° [17]. It was then slowly distilled at 50–55° under reduced pressure through a 20 cm *Vigreux* column, while keeping the volume constant by adding portions of fresh 2-methyl-2-ethyl-dioxolan at regular intervals. From time to time, a sample of the mixture was examined by GLC. (5% Carbowax, 220°, 2.5 m column). About 90% of the norsolanadione had reacted after 2–3 h. The cooled mixture was poured into excess 5% sodium hydrogencarbonate and extracted twice with ether. Usual work up afforded 20.9 g (74%) of monoacetal **2**, b.p. 94–96°/0.001 Torr, ~95% pure. A sample further purified by silica gel chromatography[10]) (ether/light petroleum 1:1 to 3:1) had b.p. 94–95°/0.001 Torr; $d_4^{20} = 0.987$; $n_D^{20} \approx 1.4712$. – IR. (neat): 1665, 1245, 1045, 1360, 1615, 980, 850 cm^{-1}. – MS.: 43 (50), 55 (4), 59 (5), 73 (11), 87 (100), 99 (9),

8) Private communication from Dr. *A. J. Aasen, Swedish Tobacco Company.*

9) Norsolanadione (**1**) can be efficiently synthesized from 2-isopropyl-5-oxo-hexanal and triphenyl-acetonylidenephosphorane (yield 80%) (*E. Demole & C. Demole*, to be published).

10) «Kieselgel 0.05–0.2 mm für die Säulenchromatographie» (*Merck* AG).

225 (2.6). – NMR. ($CDCl_3$): δ = 0.86 (3 H, *d*, *J* = 6.5 Hz); 0.91 (3 H, *d*, *J* = 6.5 Hz); 1.27 (3 H, *s*); 1.4–2.0 (6 H, *m*); 2.23 (3 H, *s*); 3.90 (4 H, *s*); 6.0 (1 H, *d*, *J* = 16 Hz); 6.63 (1 H, *d* × *d*, *J* = 16, *J'* = 8 Hz).

$C_{14}H_{24}O_3$ (240.34) Calc. C 69.96 H 10.07% Found C 69.84 H 10.09%

A solution (5 ml) of acetaldehyde ethyl-3-bromopropylacetal [9] (15.8 g, 0.074 mol, in 50 ml anhydrous ether) was added at 20° under N_2 to a stirred suspension of granulated lithium (1.045 g, 0.150 mol) in anhydrous ether (30 ml). The mixture was cooled to −10° as soon as the reaction started (cloudiness), and the remainder of the bromo-acetal solution was added dropwise at this temperature. After 2 h of additional stirring at −5°, the organolithium reagent **3** was introduced into a stirred solution of monoacetal **2** (12 g, 0.050 mol) in anhydrous ether (50 ml), over 10 min at 0°. After further stirring for 2 h at 0° and 15 h at 20°, the reaction mixture was poured into 100 ml of chilled, saturated ammonium chloride solution, and worked up as usual. There was obtained 19.5 g of crude hydroxy-diacetal **4**. This product was taken up in acetone (150 ml) and 10% hydrochloric acid (30 ml). The resulting solution was set aside for 18 h at room temperature, sodium hydrogencarbonate (10 g) was added, the mixture was stirred for 15 min, evaporated to dryness in vacuum, and the residue extracted twice with ether. Usual work up afforded 12.5 g of a crude product from which pure keto-ether **G** was isolated by chromatography (silica gel[10], 300 g; ether/light petroleum 2:1). Yield after distillation 4.81 g (40%). The properties of this compound have already been described in the theoretical part.

$C_{15}H_{26}O_2$ (238.37) Calc. C 75.58 H 11.00% Found C 75.48 H 10.94%

2. (**E**)-*5-Isopropyl-7-(2-methyl-tetrahydrofur-2-yl)-hept-6-en-2-ol* (**H**). Keto-ether **G** (2.95 g, 12.3 mmol, in 15 ml anhydrous ether) was added dropwise to a stirred suspension of lithium aluminium hydride (0.235 g, 6.2 mmol) in anhydrous ether (40 ml) at 20°. After 1 h refluxing, a slight excess of water was cautiously added at 0° and the mixture was stirred for 15 min. The precipitated salts were removed by filtration, and the ethereal solution was dried over sodium sulfate and evaporated to dryness. There was obtained 2.45 g (83%) of hydroxy-ether **H**, exhibiting the properties described in the theoretical part.

$C_{15}H_{28}O_2$ (240.38) Calc. C 74.95 H 11.74% Found C 75.08 H 11.84%

3. (**E**)-*4-Methyl-7-isopropyl-10-oxo-undec-5-en-4-olide* (**I**). *Brown* [18] chromic acid reagent (90 ml) was added dropwise over 1½ h at 20° to a stirred solution of crude hydroxy-diacetal **4** (8.5 g) in ether (85 ml). After 2 h of further stirring at 20°, the mixture was extracted twice with ether and the organic layer washed with 10% sodium carbonate and water. The crude product (5.7 g) obtained after solvent removal was taken up in acetone (150 ml) and 10% sulfuric acid (10 ml). After 3 h at 20°, excess solid sodium hydrogencarbonate was added, the mixture was stirred for 15 min, evaporated to dryness in vacuum, the residue was taken up in ether, and the ethereal solution washed with 5% sodium hydrogencarbonate and water. The product finally obtained (5.0 g) was chromatographed on silica gel[10] (150 g), affording a first fraction representing recovered norsolanadione (**1**) (2.0 g, eluted with ether/light petroleum 1:1 to 9:1), followed by keto-lactone **I**. Yield of the latter 1.10 g (20%) after distillation. The properties of this compound have already been described in the theoretical part.

$C_{15}H_{24}O_3$ (252.35) Calc. C 71.39 H 9.59% Found C 71.13 H 9.43%

4. (**E,E**)-*6,12-Dimethyl-9-isopropyl-trideca-5,10,12-trien-2-one* (**J**). A vinylmagnesium bromide solution was prepared [19] from vinyl bromide (5.04 g, 47 mmol) and magnesium (0.94 g, 39 mmol) in anhydrous tetrahydrofuran (5 ml). The reaction mixture, which had been heated for 1½ h at 70–80°, was cooled to +5° when solanone (**A**) (6.0 g, 31 mmol, in 7.5 ml anhydrous ether) was added at this temperature. After standing overnight at 20°, the mixture was decomposed at 0° with saturated ammonium chloride solution and worked up as usual (ethereal extraction). There was thus obtained 5.88 g of a product consisting of 39% of recovered solanone (**A**) and 61% of desired alcohol **5** (52%), as indicated by GLC. (5% Carbowax, 180°, 2.5 m column). This mixture (4.1 g) was chromatographed on silica gel[10] (100 g) in the presence of hexane containing increasing amounts of ether, whereby pure alcohol **5** (1.61 g) was eluted after solanone (**A**) (1.05 g) and miscellaneous solanone-containing fractions. Alcohol **5** had d_4^{20} = 0.883. – IR. (neat): 965, 920, 880, 1370, 3450, 1455, 995, 1605, 3100, 1640 cm^{-1}. – MS.: 41 (57), 43 (80), 55 (45), 71 (69), 81 (93),

93 (100), 105 (38), 121 (73), 136 (100), 161 (45), $M-18$ at *m/e* 204 (7.5), no discernible parent ion. – NMR. ($CDCl_3$): δ = 0.87 (6 H, *m*); 1.25 (3 H, *s*); 1.87 (3 H, *s*); 1.0–2.2 (7 H, *m*); 4.90 (2 H, *s*); 4.90–6.40 (5 H, *m*).

$C_{15}H_{26}O$ (222.37) Calc. C 81.02 H 11.79% Found C 81.19 H 11.80%

Carroll reaction [10] [11]. A mixture of sodium (1 mg, 0,04 mmol) and alcohol **5** (1.10 g, 4.95 mmol) was stirred for $5^1/_2$ h at 20°, when almost all the sodium had reacted. Diketene (0.625 g, 7.45 mmol) was then added and the mixture further stirred for 3 days at 20°. Usual work-up (ethereal extraction, 5% sodium carbonate washings) afforded 1.51 g of crude **5**-acetoacetate, which was heated at 180–190° in a small distillation flask. As soon as the CO_2 evolution subsided ($\sim^1/_2$ h), the product was allowed to cool and was distilled: b.p. ~100–130°/0.001 Torr, 800 mg. G.L.C. (Ucon HB 5100, 130°, 50 m × 0.3 mm capillary column) indicated the distillate to contain about 34% of prenylsolanone (**J**), 20% of the *Z,E*-stereoisomer **6**, and 46% of miscellaneous, relatively volatile impurities. Chromatography of this mixture on silica gel[10] (30 g) in the presence of hexane containing increasing amounts of ether afforded 439 mg of a product still containing some solanone (**A**), which was removed by very slow fractional distillation under 0.001 Torr. The spectral properties of prenylsolanone (**J**) and its stereoisomer **6** have already been described in the theoretical part. The *mixture* of both compounds had b.p. ~120°/0.001 Torr; $d_4^{20} = 0.880$; $n_D^{20} = 1.4859$.

$C_{18}H_{30}O$ (262.43) Calc. C 82.38 H 11.52% Found C 82.07 H 11.36%

REFERENCES

[1] *E. Demole & C. Demole*, Helv. *58*, 523 (1975).
[2] *R. R. Johnson & J. A. Nicholson*, J. org. Chemistry *30*, 2918 (1965).
[3] *E. Demole, C. Demole & D. Berthet*, Helv. *56*, 265 (1973).
[4] *E. Demole, C. Demole & D. Berthet*, Helv. *57*, 192 (1974).
[5] *J. N. Schumacher & L. Vestal*, Tobacco Sci. *18*, 43 (1974).
[6] *J. R. Hlubucek, A. J. Aasen, B. Kimland & C. R. Enzell*, Phytochemistry *12*, 2555 (1973).
[7] a) *A. J. Aasen, J. R. Hlubucek & C. R. Enzell*, Acta chem. scand., Ser. B, in press; b) *A. J. Aasen, C. R. Enzell & T. Chuman*, Agric. biol. Chemistry, in press; c) *A. J. Aasen, N. Junker, C. R. Enzell, J.-E. Berg & A.-M. Pilotti*, Tetrahedron Letters *1975*, 2607.
[8] *E. Demole & D. Berthet*, Helv. *55*, 1866 (1972).
[9] *P. E. Eaton, G. F. Cooper, R. C. Johnson & R. H. Mueller*, J. org. Chemistry *37*, 1947 (1972).
[10] *W. Kimel & A. C. Cope*, J. Amer. chem. Soc. *65*, 1992 (1943).
[11] *M. F. Carroll*, J. chem. Soc. *1940*, 704, 1266; *1941*, 507.
[12] *D. L. Roberts & R. L. Rowland*, J. org. Chemistry *27*, 3989 (1962).
[13] *G. W. Kinzer, T. F. Page, Jr., & R. R. Johnson*, J. org. Chemistry *31*, 1797 (1966); *J. L. Courtney & S. McDonald*, Tetrahedron Letters *1967*, 459.
[14] *H. E. Zimmerman & J. English, Jr.*, J. Amer. chem. Soc. *76*, 2285, 2291, 2294 (1954).
[15] *T. Fukuzumi, H. Kaneko & H. Takahara*, Agric. biol. Chemistry *31*, 607 (1967).
[16] *H. Shigematsu, R. Ono, Y. Yamashita & Y. Kaburahi*, Agric. biol. Chemistry *35*, 1751 (1971).
[17] *G. Bauduin & Y. Pietrasanta*, Tetrahedron *29*, 4225 (1973).
[18] *H. C. Brown & C. P. Garg*, J. Amer. chem. Soc. *83*, 2952 (1961).
[19] *H. Normant*, Advances in Organic Chemistry, Vol. 2, p. 1, Interscience Publishers, Inc., New York 1960.