221. Identification of Twenty-one Novel Constituents of Oriental Tobacco Flavour (*Nicotiana tabacum* L.) Including (*E*)-3-Methyl-non-2-en-4-one, Pentadecan-15-olide, 8α,13:9α,13-Diepoxy-15,16-dinorlabdane, (*Z*)-Octadec-9-en-18-olide, and (*E*)-2-Ethylidene-6,10,14-trimethylpentadecanal

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

Firmenich SA, Research Laboratories, 1211 Geneva 8

(4.VII.78)

Summary

Investigation by gas liquid chromatography of a small but organoleptically typical subfraction of *Oriental* tobacco condensate led to the identification of 47 compounds. Of these 21 have hitherto not been reported as *Oriental* tobacco constituents, and 14 appear to be novel to all tobacco types. The latter are (*E*)-3-methyl-non-2-en-4-one (**1**), (*E*)-1-(2,3,6-trimethylphenyl)-but-2-en-1-one (**3**), pentadecan-15-olide (**12**), 8α,13:9α,13-diepoxy-15,16-dinorlabdane (**17**), (*Z*)-octadec-9-en-18-olide (**18**), (*E*)-2-ethylidene-6,10,14-trimethylpentadecanal (**21**), the norlabdanoids **9**, **10**, **11**, **14**, **15**, **16**, tridecan-2-one, and 2-phenylethyl isovalerate. The macrolides **12** and **18** represent the first musk compounds detected in tobacco. Identifications were made by direct comparison (MS. and/or ^{1}H-NMR./IR.) with the authentic chemicals synthesized whenever necessary.

Introduction. - In sharp contrast to other major tobacco types such as *Burley* [1] or *Virginia* [2] tobaccos, the so-called *Oriental* or sun-cured tobaccos¹) contain diterpenes of the labdane series accompanied by related 'nor' compounds having 14 to 18 carbon atoms [3]. This large variation in the chemical composition of *Nicotiana tabacum* varieties is best accounted for by genetic factors [4] [5]. Notwithstanding the fact that these labdanoids and their presumed metabolites are organoleptically important, the neutral fraction of *Oriental* tobacco condensate contains many other constituents that also contribute to its typical aroma. Two of these are the macrocyclic lactones **12** and **18**²) that represent, to the best of our knowledge, the first musk compounds ever detected in *Nicotiana tabacum*.

Preparation³) and fractionation of oriental tobacco condensate. - The aqueous distillate (about 1800 l) resulting from the steam-distillation of 115 kg of aged,

---

¹) For instance Greek, Turkish, and Yugoslavian tobaccos.

²) Formulae are numbered consecutively as in the *Table* in order of increasing molecular weight.

³) *Oriental* tobacco condensate was prepared at our pilot laboratory (Dr. *H. Strickler*), to whom we are grateful.

chopped *Oriental* tobacco[4]) was acidified to pH 3-4 with 50% sulfuric acid and extracted four times with chloroform. There was thus obtained 232 g (0.20% by weight of starting tobacco) of a condensate substantially free of nicotine but presenting excellent flavouring properties. This oil was then separated according to *Scheme 1* and the miscellaneous fractions were organoleptically tested[5]). In this paper we describe the study of subfraction ON3(e) which exhibited a marked woody-type odour with amber and musk notes typical of *Oriental* tobacco.

Investigation of subfraction ON3(e). - Preliminary separation of this subfraction by semi-preparative GC. (gas liquid chromatography) afforded 15 groups of components whose R_T(*sol*)[6]) values were in the range 0.47 to 3.53 (5% silicone oil, 5 min at 170°, then 4°/min up to 225°, 2.5 m column). These groups were either directly examined by capillary GC./MS. coupling, or subjected to further semi-preparative separations by GC. combining the use of relatively polar (SP-1000[7])) and non-polar (silicone oil) columns. In certain difficult cases, this process was completed by liquid chromatography on silica gel/$AgNO_3$ 9:1, carried out with hexane/ether mixtures 19:1 to 0:1. Twenty-one of the 47 compounds thus isolated and identified (see *Table*) have hitherto not been reported as *Oriental* tobacco constituents, although 7 of them occur in other tobacco types (2-furaldehyde [2], *p*-methylacetophenone [2] [9], 2-phenylethyl hexanoate [9], compounds **2** [11], **13** [3] [17], **19** [2] [3], and **20** [20]). The 14 remaining representatives appear to be entirely novel to tobacco and deserve some comments.

(E)-*3-Methyl-non-2-en-4-one* (**1**) (≥0.036‰ in the tobacco condensate)[8]) is a novel natural ketone containing the relatively uncommon (*E*)-2-methyl-but-2-enoyl moiety. The *E*-configuration of this compound was demonstrated by the appearance of a quartet at $\delta = 6.75$ ppm (C=CH) in its ^{1}H-NMR. spectrum [23] and confirmed by synthesis from (*E*)-2-methylbut-2-enal (tiglaldehyde). Ketone **1** could possibly be formed in tobacco either by cross-aldol condensation between acetaldehyde and 3-octanone, or *via* hydration of bovolide (**23**) [9] *(Scheme 2)* and decarboxylative elimination of the hypothetical intermediate **24** thus formed. The latter reaction sequence applied to spiroxabovolide (**25**) [24] would lead to (*E*)-3-methyl-8-hydroxy-non-2-en-4-one (**26**) which was recently found in Greek tobacco [23].

Pentadecan-15-olide (**12**) (≥0.05‰ in the tobacco condensate) was identified by its mass and ^{1}H-NMR. spectra. The powerful fragrance of this naturally occurring musk compound known since 1927 [16] should contribute to the aroma of *Oriental* tobacco.

8a,13:9a,13-Diepoxy-15,16-dinorlabdane (**17**) (≥0.04‰ in the tobacco condensate) was synthesized 4 years ago [18] but not found in nature until now. It is practically odourless in spite of the fact that it is isomeric to the well-known pair of amber-like smelling acetals **27** [25] *(Scheme 2)*.

---

[4]) We used a 1:1 blend of *'Yugoslavian Oriental'* and *'Northern Turkish Oriental'* tobacco brands.

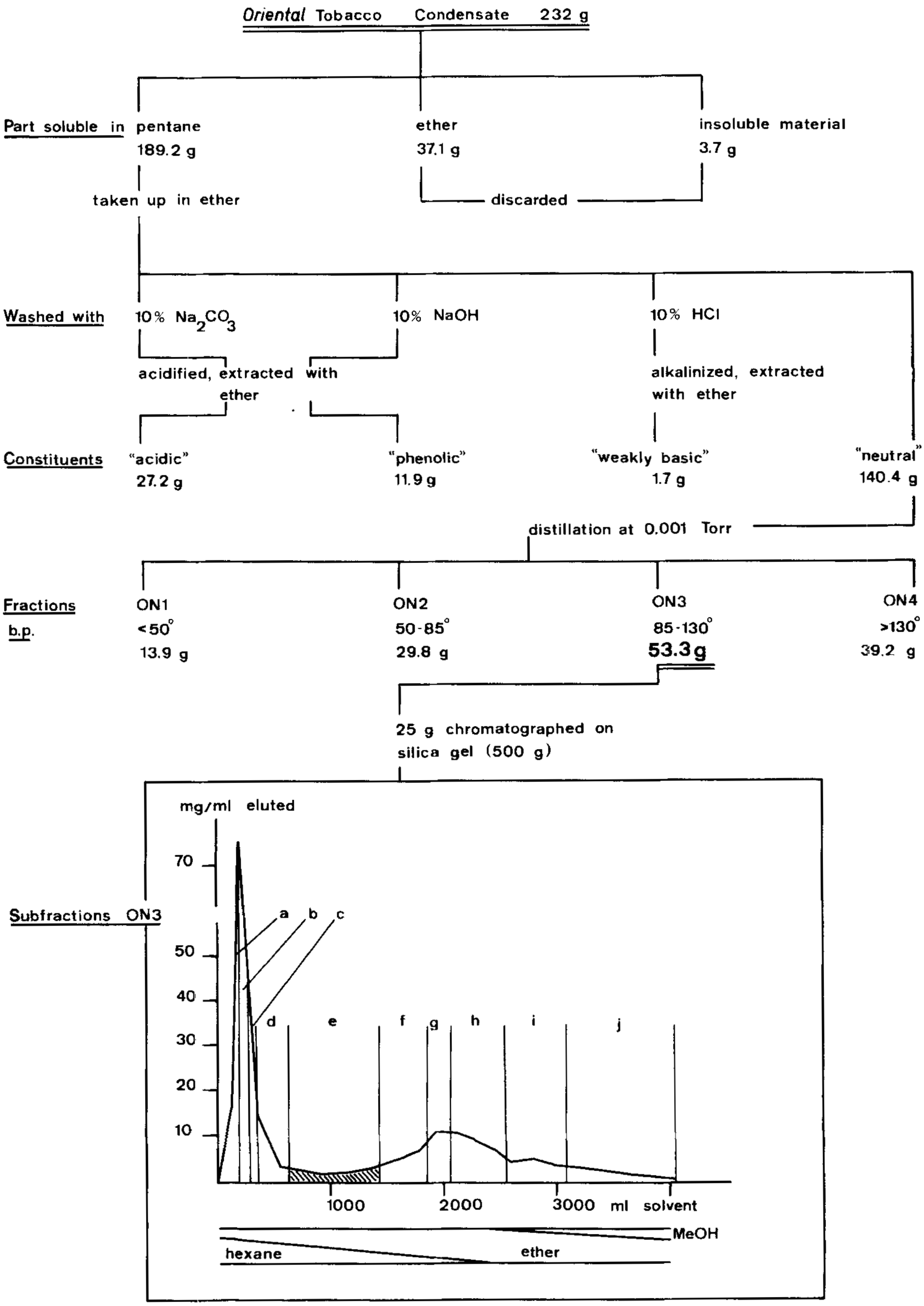
[5]) We are indebted to Dr. *P. Dietrich* and Mr. *A. Y. Smith* (*Firmenich SA*, Geneva) for evaluating the flavouring properties of these fractions.

[6]) R_T(*sol*) = retention time relative to solanone (**6**) taken as internal standard.

[7]) A modified Carbowax manufactured by *Supelco, Inc.*, Bellefonte, Pennsylvania (U.S.A.).

[8]) Ketone **1** occurs also in *Burley* (0.49‰) and *Virginia* (≥0.10‰) tobacco condensates (*E. Demole & P. Enggist*, unpublished results).

Scheme 1

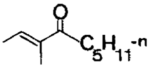

Oriental Tobacco Condensate 232 g
Part soluble in
pentane
189.2 g
ether
37.1 g
insoluble material
3.7 g
taken up in ether
discarded
Washed with
10% Na_2CO_3
10% NaOH
10% HCl
acidified, extracted with ether
alkalinized, extracted with ether
Constituents
"acidic"
27.2 g
"phenolic"
11.9 g
"weakly basic"
1.7 g
"neutral"
140.4 g
distillation at 0.001 Torr
Fractions
b.p.
ON1
<50°
13.9 g
ON2
50-85°
29.8 g
ON3
85-130°
53.3 g
ON4
>130°
39.2 g
25 g chromatographed on silica gel (500 g)
Subfractions ON3
mg/ml eluted
70
50
40
30
20
10
a
b
c
d
e
f
g
h
i
j
1000
2000
3000
ml solvent
MeOH
hexane
ether

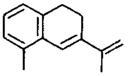
Table[a]). *Constituents of Oriental Tobacco Flavour*

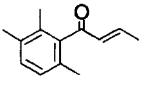
	Formula	M^+	New[b])	Ref.
2-Furaldehyde		96	+	[2]
Benzaldehyde		106		[6]
Benzyl alcohol		108		[6]
5-Methyl-2-furaldehyde		110		[7]
Phenylacetaldehyde		120		[8]
2-Phenylethyl alcohol		122		[6]
p-Methylacetophenone		134	+	[2] [9]
2-Phenylethyl formate		150		[10]
(*E*)-3-Methylnon-2-en-4-one	**1**	154	+	
3-Isopropenyl-5-methyl-1,2-dihydronaphthalene	**2**	184	+	[11]
Tridecane		184		[12]
(*E*)-1-(2,3,6-Trimethylphenyl)-but-2-en-1-one	**3**	188	+	[13]
β-Damascenone	**4**	190		[6]
β-Damascone	**5**	192		[10]
Solanone	**6**	194		[3] [6]
6,10-Dimethylundeca-5,9-dien-2-one		194		[6]
Norsolanadione	**7**	196		[3] [7]
Tetradecane		198		[12]
Tridecan-2-one		198	+	
2-Phenylethyl isovalerate		206	+	
Benzyl hexanoate		206		[10]
11-Nordrim-8-en-7-one	**8**	206		[14]
2-Phenylethyl hexanoate		220	+	[9]
Drim-8-en-11-al	**9**	220	+	[15]
Pentadecan-2-one		226		[10]
Pentadecanal		226		[6]
13,14,15,16-Tetranorlabd-8-en-12-al	**10**	234	+	[16]
13,14,15,16-Tetranorlabd-8(17)-en-12-al	**11**	234	+	[16]
Pentadecan-15-olide	**12**	240	+	[16]
Methyl tetradecanoate		242		[6]
Prenylsolanone	**13**	262	+	[3] [17]
6,10,14-Trimethylpentadeca-5,9,13-trien-2-one		262		[6]
15,16-Dinorlabd-8-en-13-one	**14**	262	+	[18]
15,16-Dinorlabd-8(17)-en-13-one	**15**	262	+	[16]
8,13-Epoxy-15,16-dinorlabdane (at least 2 stereoisomers)	**16**	264	+	[19]
6,10,14-Trimethylpentadecan-2-one		268		[6]
Methyl hexadecanoate		270		[6]
8*α*,13:9*α*,13-Diepoxy-15,16-dinorlabdane	**17**	278	+	[18]
Di-*n*-butyl phthalate		278		[6]
(Z)-Octadec-9-en-18-olide	**18**	280	+	
8,11-Epoxythunberga-2,4(18),6,12-tetraene	**19**	286	+	[2] [3]
Phytofuran	**20**	292	+	[20]
Methyl octadeca-9,12,15-trienoate		292		[21]
(*E*)-2-Ethylidene-6,10,14-trimethylpentadecanal	**21**	294	+	
Methyl octadeca-9,12-dienoate		294		[21]
Methyl octadec-9-enoate		296		[21]
8,13-Epoxylabd-14-en-12-one (2 stereoisomers)	**22**	304		[22]

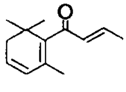
[a]) All compounds were identified by MS., and/or by ^{1}H-NMR./IR. for those having $M^+ \geq 194$.
[b]) Novel constituents of *Oriental* tobacco.

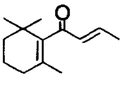
(Z)-Octadec-9-en-18-olide (**18**) ($\geq$0.05‰ in the tobacco condensate), the cyclization product of 18-hydroxyoleic acid, is a novel macrolide that exhibits a faint but tenacious musk odour with a peculiar waxywoody note. This compound was identified by direct comparison with the authentic lactone prepared according to *Scheme 2*, formulae **28**-**18** (R_T by capillary GC., ^{1}H-NMR., MS.). The *Z*-configu-

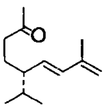

1

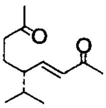

2

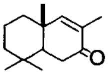

3

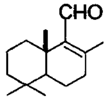

4

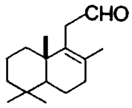

5

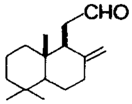

6

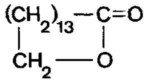

7


8


9

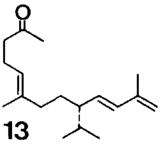

10

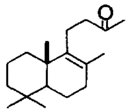

11

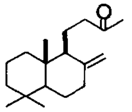


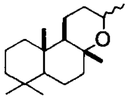
$$\begin{array}{l}(CH_2)_{13}-C=O\\ \;|\qquad\quad\;\; |\\ CH_2 \;\text{———}\; O\end{array}$$

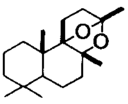
12

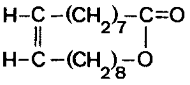

13


14


15

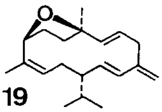

16

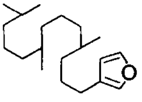

17

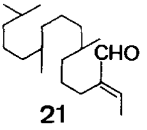


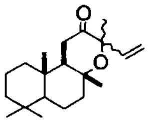
$$\begin{array}{l}H-C-(CH_2)_7-C=O\\ \quad\;\, \| \qquad\qquad\;\; |\\ H-C-(CH_2)_8-O\end{array}$$

18


19


20


21

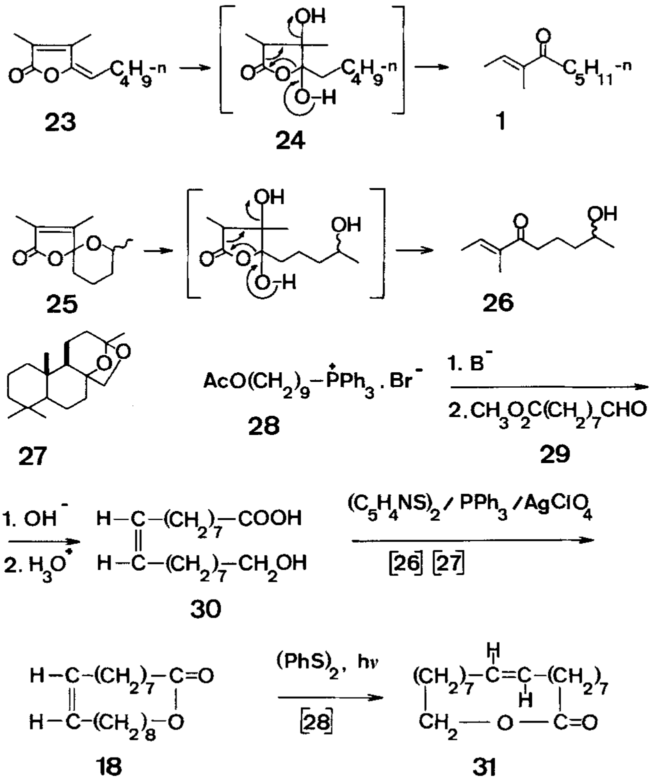

22

ration of natural **18** was further secured by comparing its R_T with that of the synthetic *E*-isomer **31** [relative R_T: 0.98 (*E*)- and 1.00 (*Z*)-isomer; OV-101, 6 min at 120°, then 2.5°/min up to 180°, 50 m × 0.3 mm column].

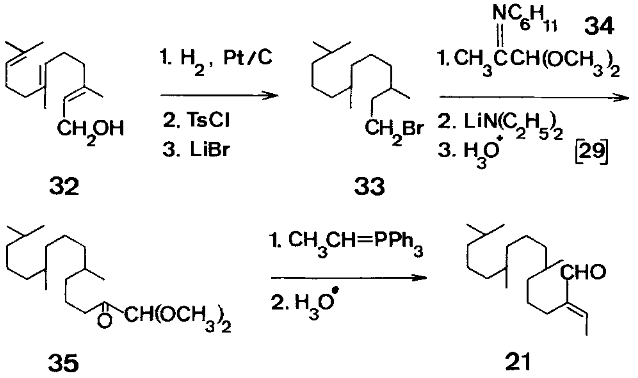
(E)-*2-Ethylidene-6,10,14-trimethylpentadecanal* (**21**) (≥ 1.06‰ in the tobacco condensate) is a novel diterpene identified by direct comparison with the authentic material synthesized as shown in *Scheme 3* (IR., ^{1}H-NMR., MS.). The *E*-configuration of natural and synthetic **21** was demonstrated by a CHO singlet appearing at $\delta = 9.37$ ppm in the ^{1}H-NMR. spectrum [δ(CHO) in (*E*)-2-methylbut-2-enal = 9.34] [30]. However, a second, weak singlet at 10.17 indicated both samples to contain about 3-4% of *Z*-isomer [δ(CHO) in (*Z*)-2-methylbut-2-enal = 10.14] [30]. The ^{13}C chemical shifts exhibited by the CHO and ethylidene groups also supported the largely prevailing *E*-configuration of **21** [corresponding, respective values recorded [30] for (*E*)- and (*Z*)-2-methylbut-2-enal are given for comparison]: CHO, 194.7 (194.5, 190.9); =CH, 149.3 (149.4, 144); CH_3, 14.7 (14.8, 12.8). The peculiar location of the aldehydic function in **21** suggests that this compound might have been formed *via* sensitized photooxygenation of the major tobacco constituent neophytadiene [7], in a way similar to that postulated for phytofuran (**20**) [20] but involving an additional, reductive step.

The 9 further constituents novel to tobacco identified in this investigation comprise (*E*)-1-(2,3,6-trimethylphenyl)-but-2-en-1-one (**3**) [13] (a plausible metabolite of *β*-damascenone (**4**)), 6 norlabdanoids (**9** [15], **10** [16], **11** [16], **14** [18], **15** [16], **16** [19]), tridecan-2-one, and 2-phenylethyl isovalerate.

Scheme 2



Scheme 3



Experimental Part

The spectra were obtained with the instruments already described [24] (the mass spectra were determined at 70 eV, inlet temperature 150°; the ^1H- and ^{13}C-NMR. spectra were measured in $CDCl_3$). GC./MS. data were obtained using a gas chromatograph *Carlo Erba*, Model 2101 AC (Ucon 5100, 90-170°, 50 m×0.3 mm glass column), coupled to a *Varian* MAT 112 mass spectrometer. GC. separations were performed on Models 1820-3 or 2720-3 gas chromatographs *(Varian Aerograph AG)*, and *Carlo Erba*, Model 2301 AC. All liquid-solid chromatographic separations were carried out on 0.05-0.2 mm silica gel for column chromatography *(Merck AG)*.

1. (E)-*3-Methyl-non-2-en-4-one* (**1**). Tiglaldehyde (21.0 g, 0.25 mol, in 100 ml of anhydrous ether) was added over 30 min at −20° to a stirred solution of pentylmagnesium bromide prepared from magnesium (6.8 g, 0.28 mol), pentyl bromide (38.0 g, 0.25 mol), and anhydrous ether (230 ml). After 2 h further stirring at 20°, the mixture was poured into an ice cold saturated NH_4Cl-solution, extracted twice with ether and washed to neutrality. The crude product was distilled at 10 Torr: fr. 1, b.p. 40-92°, 2.88 g; fr. 2, b.p. 92-95°, 26.99 g. Upon redistillation, fr. 2 gave 24.66 g (63%) of pure 3-methyl-non-2-en-4-ol, b.p. 93-95°/10 Torr; $d_4^{20}=0.858$; $n_D^{20}=1.4510$. GC. (15% Carbowax, 160°, 2.5 m column) indicated this compound to be a mixture of *E*- and *Z*-stereoisomers (*ca.* 14:1). - IR. (neat, bands with decreasing intensities): 3400, 1010, 1380, 1460, 830, 1665 cm^{-1}. - ^1H-NMR. (δ, ppm): ~0.7-1.1 (*m*, 3 H, CH_3); ~1.1-1.5 (*m*, 9 H, 4 CH_2, OH); ~1.5-2.1 (*m*, 6 H, 2 $C{=}CCH_3$); 4.00 (*t*, *J*=6 Hz, 1 H, O−CH); 5.47 (*q*, *J*~6 Hz, 1 H, C=CH).

$C_{10}H_{20}O$ (156.26) Calc. C 76.86 H 12.90% Found C 77.15 H 13.03%

3-Methyl-non-2-en-4-ol (10 g, 64 mmol) and activated MnO_2 (100 g) in anhydrous pentane (600 ml) were stirred for 60 h at 20° under N_2. The oil resulting from usual work-up was distilled at 10 Torr, affording 7.16 g (72%) of *(E)*-3-methyl-non-2-en-4-one (**1**), b.p. 89°; $d_4^{20}=0.865$; $n_D^{20}=1.4550$. GC. (same conditions as above) indicated this compound to contain about 5% of *Z*-stereoisomer. - IR. (neat): 1670, 1380, 1470, 1075, 1250. - ^1H-NMR.: ~0.6-1.1 (*m*, 3 H, CH_3); 1.1-2.0 (*m*, 6 H, 3 CH_2); 1.77 (*s*, 3 H, $C{=}CCH_3$); 1.85 (*d*, *J*=6 Hz, 3 H, $C{=}CCH_3$); 2.65 (*t*, *J*=7 Hz, 2 H, $O{=}CCH_2$); 6.75 (*q*, *J*=6 Hz, 1 H, C=CH). - MS. (*m/e* (% relative abundance)): 154 (M^+, 1), 139 (16), 98 (34), 83 (100), 55 (73).

$C_{10}H_{18}O$ (154.24) Calc. C 77.86 H 11.76% Found C 77.72 H 11.89%

2. *Pentadecan-15-olide* (**12**) [16]. MS.: 240 (M^+, 7), 222 (13), 180 (11), 152 (7), 138 (11), 124 (13), 110 (21), 97 (41), 83 (55), 69 (72), 55 (100), 41 (91).

3. *8α,13:9α,13-Diepoxy-15,16-dinorlabdane* (**17**) [18]. ^1H-NMR.: 0.84 (*s*, 3 H, CH_3); 0.91 (*s*, 3 H, CH_3); 0.98 (*s*, 3 H, CH_3); 1.37 (*s*, 3 H, $O{-}CCH_3$); 1.51 (*s*, 3 H, $O{-}C(CH_3){-}O$); ~1.1-2.2 (*m*, 15 H, 7 CH_2, CH). - MS.: 278 (M^+, 23), 236 (13), 218 (20), 203 (14), 175 (11), 162 (7), 151 (15), 138 (14), 123 (34), 109 (63), 99 (23), 95 (28), 81 (16), 69 (24), 55 (21), 43 (100).

4a. (*Z*)-*Octadec-9-en-18-olide* (**18**). BuLi (60 ml of a 7% solution in hexane, 65.5 mmol) was added dropwise at −5°/−10° and under N_2 to 9-acetoxynonyltriphenylphosphonium bromide (**28**) [31] (36.7 g, 69.6 mmol) in anhydrous hexamethylphosphoric acid triamide (HMPA) (105 ml) and tetrahydrofuran (THF) (105 ml) [32]. Stirring was continued for 15 min at −5°, when the mixture was cooled to −60° and methyl 8-formyloctanoate (**29**) [33] (13.1 g, 70.4 mmol) was quickly added. After 15 h further stirring at 20° and 1 h at 50°, the mixture was poured into water (1 l), extracted with ether (3×), and washed to neutrality. Usual work-up gave a product (54 g) that was treated (10×) with light petroleum (b.p. 30-50°). The resulting soluble fraction (25.6 g) was slowly heated to 100° at 0.001 Torr, kept 5 min at this temperature to remove any volatile material, and refluxed for 3 h with KOH (9 g) in water (45 ml) and methanol (175 ml). Usual separation of neutral and acidic products afforded crude (*Z*)-18-hydroxy-octadec-9-enoic acid (**30**) (13.8 g, 70%). - ^1H-NMR.: 1.3 (narrow *m*, 22 H, 11 CH_2); 1.7-2.1 (*m*, 4 H, 2 $C{=}CCH_2$); 2.3 (*t*, *J*=7 Hz, 2 H, $O{=}CCH_2$); 3.6 (*t*, *J*=5 Hz, 2 H, $O{-}CH_2$); 5.3 (*t*, *J*=5 Hz, 2 H, CH=CH); 8.15 (*s*, 2 H, 2 OH).

Crude **30** (427 mg, 1.43 mmol), 2,2′-dipyridyl disulfide (380 mg, 1.72 mmol), triphenylphosphine (470 mg, 1.79 mmol), in anhydrous benzene (1.5 ml) were kept at 20° for 1.5 h. [26] [27]. The mixture was then dissolved in anhydrous acetonitrile (35 ml) and added dropwise over 3 h at 65° (±2°) to a stirred solution of $AgClO_4$ (890 mg, 4.3 mmol) in 150 ml of acetonitrile [27]. After 1 h further stirring at 65°, the mixture was cooled and evaporated to dryness *in vacuo*. The residue was taken up in ether (2×) and the ethereal solution washed with 5% NaCN (2×20 ml) and water (3×). The product (587 mg) resulting from usual work-up was chromatographed on silica gel (10 g) with hexane/toluene mixtures, yielding 196 mg (48%) of (*Z*)-octadec-9-en-18-olide (**18**), b.p. 115°/0.001 Torr; $d_4^{20}=0.943$; $n_D^{20}=1.4807$. GC. (OV-101, 6 min at 120°, then 2.5°/min up to 180°, 50 m×0.3 mm column) indicated this compound to contain about 5% of *E*-stereoisomer **31**. - IR. (neat): 1735, 1240, 1465. - ^{1}H-NMR.: 1.33 (narrow *m*, 18 H, 9 CH_2); ~1.5-1.9 (*m*, 4 H, 2 CH_2); 1.9-2.2 (*m*, 4 H, 2 $C{=}CCH_2$); 2.35 (*t*, *J*=6.5 Hz, 2 H, $O{=}CCH_2$); 4,14 (*t*, *J*=5 Hz, 2 H, $O{-}CH_2$); 5.35 (sym. *m*, 2 H, CH=CH). - MS. (from GC./MS. coupling): 280 (M^+, 11), 262 (4), 150 (5), 137 (8), 124 (13), 123 (12), 110 (20), 109 (20), 96 (70), 95 (43), 82 (100), 81 (72), 67 (70), 55 (76), 41 (60).

$C_{18}H_{32}O_2$ (280.44) Calc. C 77.09 H 11.50% Found C 77.36 H 11.71%

4b. (E)-*Octadec-9-en-18-olide* (**31**). *Z*-lactone **18** (1.92 g, 6.85 mmol) and diphenyl disulfide (96 mg) in anhydrous benzene (450 ml) were irradiated at 15° and under N_2 with a UV.-lamp (type *Philips* HPK 125) (quartz vessel) [28]. The isomerization process could be conveniently followed by capillary GC. using the conditions given above for **18**. Two further portions of diphenyl disulfide (96 mg each) were added to the reaction mixture after 25 and 45 h of irradiation. After a total of 88 h of irradiation, a photostationary state was reached consisting approximately of 25% of *Z*-lactone **18** and 75% of the desired *E*-stereoisomer **31**. The reaction solution and that resulting from a preliminary isomerization of 1.12 g of **18** were then combined, and the solvent removed *in vacuo*. Chromatography of the product (3.76 g) on silica gel/$AgNO_3$ 9:1 (120 g) with hexane/ether (99:1 to 9:1) allowed successive elution of pure (*E*)-octadec-9-en-18-olide (**31**) (650 mg), a mixture of **18** and **31** (2.12 g), and pure **18** (312 mg). After rechromatography of the intermediate fraction there was obtained a total yield of 1.41 g (46%) of (*E*)-octadec-9-en-18-olide (**31**), b.p. 109-110°/0.001 Torr; $d_4^{20}=0.939$; $n_D^{20}=1.4792$. - IR. (neat): 1735, 1240, 1460, 970. - ^{1}H-NMR.: 1.33 (narrow *m*, 18 H, 9 CH_2); ~1.5-1.9 (*m*, 4 H, 2 CH_2); 1.9-2.2 (*m*, 4 H, 2 $C{=}CCH_2$); 2.35 (*t*, *J*=6.5 Hz, 2 H, $O{=}CCH_2$); 4,14 (*t*, *J*=5 Hz, 2 H, $O{-}CH_2$); 5.34 (sym. *m*, 2 H, CH=CH). - MS.: 280 (M^+, 18), 262 (4), 137 (9), 123 (20), 109 (35), 96 (78), 82 (100), 67 (90), 55 (100), 41 (92).

$C_{18}H_{32}O_2$ (280.44) Calc. C 77.09 H 11.50% Found C 77.27 H 11.24%

5. (E)-*2-Ethylidene-6,10,14-trimethylpentadecanal* (**21**). Farnesol (**32**) (66.6 g, 0.3 mol) in anhydrous ethanol (300 ml) was hydrogenated for 22 h at 20°/830 Torr in the presence of 10% Pt/C (2.5 g) (H_2 uptake 23.7 l or 3.5 equiv.). The resulting product was distilled at 0.001 Torr: fr. 1, b.p. 55-75°, 28.59 g; fr. 2, b.p. 75-98°, 5.24 g; fr. 3, b.p. 98-100°, 30.49 g. Fr. 3 represented hexahydrofarnesol (yield 44%). - IR. (neat): 1470, 3375, 1380, 1060. - ^{1}H-NMR.: 0.88 (*d*, *J*=6 Hz, 12 H, 4 CH_3); ~1.0-1.9 (*m*, 17 H, 7 CH_2, 3 CH); 2.0 (*s*, 1 H, OH); 3.65 (*t*, *J*=6.5 Hz, 2 H, $O{-}CH_2$).

p-Toluenesulfonyl chloride (35 g, 183 mmol) was added in several portions over 15 min at 10° to hexahydrofarnesol (40 g, 175 mmol) in anhydrous pyridine (55 ml). After 16 h further stirring at 20° the mixture was poured into ice water (350 ml) and conc. HCl-solution (52.5 ml), extracted with ether (4×), and washed with water (1×), 5% NaOH (1×), and water (1×). Usual work-up afforded 59 g (154 mmol, 88%) of crude hexahydrofarnesyl tosylate. This compound and LiBr (16.7 g, 192 mmol) in anhydrous acetone (580 ml) were stirred for 40 h at 20° and under N_2. After solvent removal at 30° *in vacuo*, the product was taken up in ether (2×), washed to neutrality, and distilled at 0.001 Torr: fr. 1, b.p. 48-74°, 1.25 g; fr. 2, b.p. 74-79°, 0.84 g; fr. 3, b.p. 79-93°, 40.40 g. Fr. 3 represented hexahydrofarnesyl bromide (**33**) (yield 79%). - IR. (neat): 1465, 1375. - ^{1}H-NMR.: 0.88 (*d*, *J*=5.5 Hz, 12 H, 4 CH_3); ~1.0-2.2 (*m*, 17 H, 7 CH_2, 3 CH); 3.40 (*t*, *J*=7 Hz, 2 H, $Br{-}CH_2$).

Small chips of Li (1.3 g, 187 mmol), freshly distilled diethylamine (12.15 g, 166 mmol), HMPA (34.7 ml), and anhydrous benzene (31 ml) were stirred for 2 h at 18° and under N_2. THF (42 ml) was added to the mixture, followed by imino-acetal **34** [29] (27.62 g, 138 mmol, in 41 ml of THF) over 10 min at −60°. After 1 h further stirring at −50°, hexahydrofarnesyl bromide (**33**) (40.38 g, 138 mmol, in 21 ml of THF) was in turn added over 20 min at −20°. The stirring was continued for 16 h at 20°, when the mixture was poured into ice water, extracted twice with ether, washed to neutrality, and evaporated to dryness *in vacuo*. The crude product was taken up in THF (350 ml), 2N HCl (208 ml) was quickly added, and the mixture was stirred for 2 min. Ethereal extraction (2×, 5% $NaHCO_3$ and water washings) afforded an oil (54.7 g) that was distilled at 0.001 Torr: fr. 1, b.p. 32-85°, 4.66 g; fr. 2, b.p. 85-134°, 6.16 g; fr. 3, b.p. 134-135°, 31.72 g. Fr. 2 and 3 corresponded to keto-acetal **35** (yield 83%); $d_4^{20} = 0.897$; $n_D^{20} = 1.4454$. - IR. (neat): 1075, 1725, 1465. - ^1H-NMR.: 0.87 (*d*, $J = 5.5$ Hz, 12 H, 4 CH_3); ~1.0-2.0 (*m*, 19 H, 8 CH_2, 3 CH); 2.53 (*t*, $J = 6.5$ Hz, 2 H, $O{=}CCH_2$); 3.38 (*s*, 6 H, 2 $O{-}CH_3$); 4.42 (*s*, 1 H, O-CH-O).

$C_{20}H_{40}O_3$ (328.52) Calc. C 73.12 H 12.27% Found C 73.31 H 12.29%

BuLi in hexane (67.1 ml of a 1.3M solution, 87.2 mmol) was added over 10 min at 20° and under N_2 to a slurry of ethyltriphenylphosphonium bromide (33.7 g, 90.8 mmol) in anhydrous ether (300 ml). After 1 h further stirring, keto-acetal **35** (22.9 g, 69.8 mmol, in 300 ml of anhydrous ether) was added over 30 min at 20°. The stirring was continued for 15 h at 20° when the reaction mixture was quenched with anhydrous acetone (10 ml) and evaporated to dryness *in vacuo*. The crude product was taken up in hexane, the insoluble white material removed by filtration, and the clear filtrate concentrated to dryness *in vacuo*. The remaining oil (23.39 g) was stirred for 4 h at 20° in acetone (170 ml) containing 2N H_2SO_4 (18.35 ml). After addition of a slight excess of 5% $NaHCO_3$-solution, the solvent was removed *in vacuo*, and the residue was extracted twice with ether and washed to neutrality. The product was distilled at 0.001 Torr: b.p. 114-118°, 14.36 g. Chromatography of the distillate on silica gel (300 g) with pure toluene followed by toluene/ethyl acetate 98:2 finally afforded (*E*)-2-ethylidene-6,10,14-trimethylpentadecanal (**21**), b.p. 112-118°/0.001 Torr, 9.35 g (45.5%); $d_4^{20} = 0.851$; $n_D^{20} = 1.4620$. - IR. (neat): 1685, 1460, 1375, 1640, 2725, 830. - ^1H-NMR.: 0.86 (*d*, $J = 6$ Hz, probably 3 H, CH_3); 0.90 (*d*, $J = 6$ Hz, probably 9 H, 3 CH_3); ~0.8-1.9 (*m*, 19 H, 8 CH_2, 3 CH); 2.01 (*d*, $J = 7.5$ Hz, 3 H, $C{=}CCH_3$); 2.1-2.4 (*m*, 2 H, $C{=}CCH_2$); 6.57 (*q*, $J = 7$ Hz, 1 H, C=CH); 9.37 (*s*, 1 H, O=CH). - MS. (from GC./MS. coupling): 294 (M^+, 4), 140 (32), 111 (100), 98 (74), 83 (33), 69 (45), 57 (72), 43 (79).

$C_{20}H_{38}O$ (294.50) Calc. C 81.56 H 13.01% Found C 81.60 H 13.04%

6. (E)-*1-(2,3,6-Trimethylphenyl)-but-2-en-1-one* (**3**). For spectral data see [13].

7. *Drim-8-en-11-al* (**9**) [15]. - MS.: 220 (M^+, 50), 205 (49), 191 (95), 149 (35), 135 (59), 121 (81), 109 (100), 95 (93), 81 (60), 69 (64), 55 (80), 43 (78), 41 (85).

8. *13,14,15,16-Tetranorlabd-8-en-12-al* (**10**) [16]. - ^1H-NMR.: 0.85 (*s*, 3 H, CH_3); 0.92 (*s*, 3 H, CH_3); 0.95 (*s*, 3 H, CH_3); 1.55 (*s*, 3 H, $C{=}CCH_3$); ~0.8-2.0 (*m*, 9 H, 4 CH_2, CH); 2.1 (*m*, 2 H, $C{=}CCH_2$); 3.10 (broad *s*, 2 H, $C{=}CCH_2C{=}O$); 9.55 (*t*, $J = 2$ Hz, 1 H, O=CH).

9. *13,14,15,16-Tetranorlabd-8(17)-en-12-al* (**11**) [16]. - ^1H-NMR. 0.70 (*s*, 3 H, CH_3); 0.82 (*s*, 3 H, CH_3); 0.89 (*s*, 3 H, CH_3); ~1.0-2.3 (*m*, 10 H, 4 CH_2, 2 CH); 2.45 (*m*, 4 H, $O{=}CCH_2$, $C{=}CCH_2$); 4.40 and 4.82 (2*s*, 1 H each, $C{=}CH_2$); 9.65 (*t*, $J \sim 1.5$ Hz, 1 H, O=CH).

10. *15,16-Dinorlabd-8-en-13-one* (**14**) [18]. - MS.: 262 (M^+, 3), 229 (25), 204 (20), 189 (41), 133 (23), 121 (41), 105 (26), 95 (41), 81 (19), 69 (36), 55 (33), 43 (100), 41 (60).

11. *15,16-Dinorlabd-8(17)-en-13-one* (**15**) [16]. - MS.: 262 (M^+, 16), 247 (16), 229 (18), 204 (28), 177 (25), 137 (85), 107 (39), 95 (58), 81 (62), 69 (49), 55 (40), 43 (100), 41 (60).

12. *8,13-Epoxy-15,16-dinorlabdane* (**16**). For spectral data see [19].

REFERENCES

[1] *E. Demole & P. Dietrich*, in 'Recent Advances in the Chemical Composition of Tobacco and Tobacco Smoke', Amer. chem. Soc. Symposium, 173rd Amer. chem. Soc. Meeting, Agric. & Food chem. Division, New Orleans 1977, p. 1.

[2] *R.A. Lloyd, C.W. Miller, D.L. Roberts, J.A. Giles, J.P. Dickerson, N.H. Nelson, C.E. Rix & P.H. Ayers*, Tobacco Sci. *20*, 43 (1976).

[3] *C.R. Enzell,* in 'Recent Advances in the Chemical Composition of Tobacco and Tobacco Smoke', Amer. chem. Soc. Symposium, 173rd Amer. chem. Soc. Meeting, Agric. & Food Chem. Division, New Orleans 1977, p. 37; *C.R. Enzell, I. Wahlberg & A.J. Aasen,* in «Fortschritte der Chemie organischer Naturstoffe», Vol. *34,* p. 1, edited by W. Herz, H. Grisebach & G.W. Kirby, Springer-Verlag, Wien-New York 1977.

[4] *J.C. Gray, S.D. Kung, S.G. Wildman & S.J. Sheen,* Nature *252,* 226 (1974).

[5] *A. Colledge, W.W. Reid & R.A. Russell,* Annales du Tabac (S.E.I.T.A.) *11,* section 2, 159 (1974); *W.W. Reid,* ibid., p. 176.

[6] *B. Kimland, R.A. Appleton, A.J. Aasen, J. Roeraade & C.R. Enzell,* Phytochemistry *11,* 309 (1972).

[7] *J.N. Schumacher & L. Vestal,* Tobacco Sci. *18,* 43 (1974).

[8] *J.R. Hlubucek, A.J. Aasen, B. Kimland & C.R. Enzell,* Phytochemistry *12,* 2555 (1973).

[9] *E. Demole & D. Berthet,* Helv. *55,* 1866 (1972).

[10] *B. Kimland, A.J. Aasen & C.R. Enzell,* Acta chem. Scand. *26,* 2177 (1972).

[11] *E. Demole & P. Enggist,* Helv. *61,* 1335 (1978).

[12] *C.R. Enzell, A. Rosengren & I. Wahlberg,* Tobacco Sci. *13,* 127 (1969).

[13] *K.H. Schulte-Elte, M. Gadola & G. Ohloff,* Helv. *56,* 2028 (1973).

[14] *J.R. Hlubucek, A.J. Aasen, S.-O. Almqvist & C.R. Enzell,* Acta chem. Scand. B*28,* 18 (1974).

[15] *M. Stoll & A. Commarmont,* Helv. *32,* 1836 (1949).

[16] *G. Ohloff,* in «Fortschritte der chemischen Forschung», Vol. *12,* p. 185, edited by A. Davison, M.J.S. Dewar, K. Hafner, E. Heilbronner, U. Hofmann, K. Niedenzu, Kl. Schäfer & G. Wittig, Springer-Verlag, Berlin Heidelberg New York 1969. References cited therein.

[17] *E. Demole & P. Enggist,* Helv. *58,* 1602 (1975).

[18] *M.S. Hadley & T.G. Halsall,* J. chem. Soc. (Perkin I) *1974,* 1334.

[19] *G. Ohloff, W. Giersch, K.H. Schulte-Elte & C. Vial,* Helv. *59,* 1140 (1976).

[20] *T. Fujimori, R. Kasuga, H. Kaneko & M. Noguchi,* Agric. biol. Chemistry *38,* 2293 (1974); *T. Fujimori, R. Kasuga, H. Matsushita, H. Kaneko & M. Noguchi, ibid. 40,* 303 (1976).

[21] *B. Kimland, A.J. Aasen & C.R. Enzell,* Acta chem. Scand. *26,* 1281 (1972).

[22] *A.J. Aasen, B. Kimland, S.-O. Almqvist & C.R. Enzell,* Acta chem. Scand. *26,* 832 (1972).

[23] *Dan Behr, I. Wahlberg, T. Nishida & C.R. Enzell,* Acta chem. Scand. B*31,* 573 (1977).

[24] *E. Demole, C. Demole & D. Berthet,* Helv. *56,* 265 (1973).

[25] *U. Scheidegger, K. Schaffner & O. Jeger,* Helv. *45,* 400 (1962).

[26] *E.J. Corey & K.C. Nicolaou,* J. Amer. chem. Soc. *96,* 5614 (1974).

[27] *H. Gerlach & A. Thalmann,* Helv. *57,* 2661 (1974); *H. Gerlach, K. Oertle & A. Thalmann,* Helv. *59,* 755 (1976).

[28] *K.H. Schulte-Elte & G. Ohloff,* Helv. *51,* 548 (1968).

[29] *T. Cuvigny & H. Normant,* Synthesis *1977,* 198.

[30] *U. Vogeli & W. von Philipsborn,* Org. magn. Resonance *7,* 617 (1975).

[31] *G. Goto, T. Shima, H. Masuya, Y. Masuoka & K. Hiraga,* Chem. Letters *1975,* 103.

[32] *P.E. Sonnet,* J. org. Chemistry *39,* 3793 (1974).

[33] *E.H. Pryde, D.E. Anders, H.M. Teeter & J.C. Cowan,* J. org. Chemistry *25,* 618 (1960).