15. A Chemical Study of *Burley* Tobacco Flavour (Nicotiana tabacum L.)

III. Structure Determination and Synthesis of 5-(4-Methyl-2-furyl)-6-methylheptan-2-one (*"Solanofuran"*) and of 3,4,7-Trimethyl-1,6-dioxa-spiro[4.5]dec-3-en-2-one (*"Spiroxabovolide"*), Two New Flavour Components of *Burley* Tobacco[1])

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Summary. Two novel constituents of *Burley* tobacco condensate were shown to be 5-(4-methyl-2-furyl)-6-methylheptan-2-one (*solanofuran*, **4**) and 3,4,7-trimethyl-1,6-dioxa-spiro[4.5]-dec-3-en-2-one (*spiroxabovolide*, **6**). These structures were deduced from spectral data and confirmed by synthesis.

Solanofuran (**4**) was prepared *via* the dye-sensitized photo-oxygenation of solanone (**1**). This type of reaction involving the uncommon 'diene-addition' of $^1O_2$ to a conjugated *acyclic* diene system was thus applied for the first time to the synthesis of a terpenoid furan, a route that might have some biogenetic significance.

Both solanofuran (**4**) and spiroxabovolide (**6**) display interesting organoleptic properties. Identification of these compounds increases to 210 the total number of *Burley* tobacco flavour constituents so far characterized in this laboratory.

Solanofuran (**4**) and *spiroxabovolide* (**6**) are novel flavour components which were isolated during our recent investigation of fractions B1 and B2 from *Burley* tobacco condensate [2]. Both are new chemical compounds with interesting organoleptic properties.

1a. *Isolation and structure determination of* solanofuran (**4**). Subfractions B2-PN-e and -f from *Burley* tobacco condensate [2] contained about 1.91 and 0.28% of solanofuran, respectively. This compound could be conveniently separated by gas-liquid chromatography of either of these subfractions using the experimental conditions already indicated in the schemes 8 and 9 of our first paper [2]. Solanofuran was thus eluted between compounds 92 and 97 (scheme 8, 10th chromatogram B), or after compound 41 (scheme 9, 9th chromatogram B).

The structure of solanofuran (**4**) was easily deduced from its spectral data (fig. 1). Beside the parent ion at *m/e* 208 ($C_{13}H_{20}O_2^{+\cdot}$), the mass spectrum displays two major peaks at *m/e* 150 (*M* – 58) and 43 which suggest the presence of a side-chain $CH_3COCH_2CH_2CH<$ (*McLafferty* rearrangement). This detail is confirmed by IR. (ν = 1360, 1715 cm^{-1}) and NMR. data [δ = 2.07 (3 H, *s*, CH_3CO–), 2.31 (2 H, *t*, J = 7 Hz, –$COCH_2CH_2$–)]. Moreover, the two NMR. doublets at δ = 0.80 and 0.92 (3 H each, J = 7 Hz) are likely to correspond to an asymmetrically shielded isopropyl group (diastereotopic methyls), while the 3 H singlet at δ = 2.00 reveals the presence of a fourth methyl group, presumably located on a furan ring. Indeed, a disubsti-

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[1]) For the 2nd publication of this series see [1].

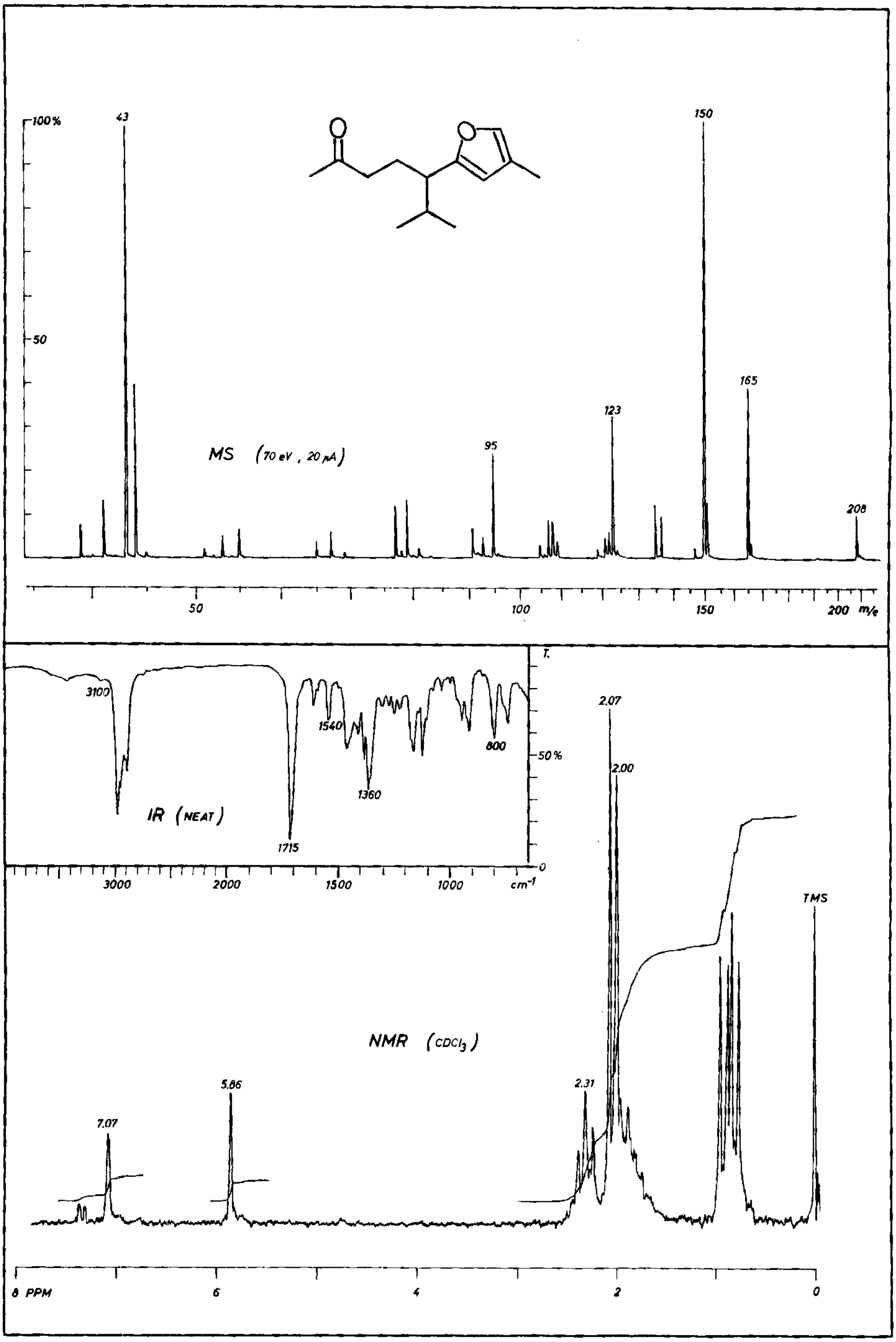
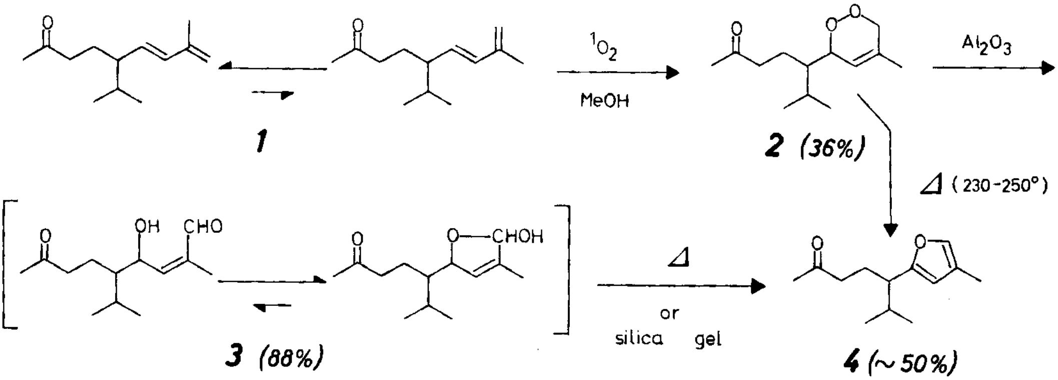


Fig. 1. *Mass, IR. and NMR. spectra of solanofuran* (**4**)

tuted furan structure would be in good agreement with the 1 H singlets at $\delta = 7.07$ and 5.86 (α and β furan protons, respectively), and also with the UV. spectrum of solanofuran ($\lambda_{\max}^{\mathrm{EtOH}} = 220$ nm, $\varepsilon = 8500$). When examined in the light of an intuitively assumed, solanone-like structure, the above facts show that solanofuran can only have the structure of a 5-(4-methyl-2-furyl)-6-methylheptan-2-one (**4**)[2].

1b. *Synthesis of solanofuran* (**4**). Solanofuran can be considered as a *solanone* (**1**) [3] metabolite[3] which probably arises from photo-oxidation of this ketone during the aerobic treatment of the tobacco leaves[4]. We tried to prepare this compound following an analogous synthetic path involving, as a key reaction, the dye-sensitized photo-oxygenation of solanone. These experiments met with success and fully confirmed the proposed structure **4** for solanofuran (*scheme 1*)[2].

Scheme 1



To the best of our knowledge, scheme 1 represents the first successful synthesis of a *terpenoid furan* based upon the sensitized photo-oxygenation of an acyclic conjugated diene[5]. This result contradicts the tacit belief[6] that such photo-oxygenation reactions are generally ineffective because they involve a concerted 1,4-addition of $^1O_2$ to the *unstable s-cis* conformers of the acyclic dienes [5] [6]. Normally, *s-trans* conformers are strongly preferred [8][7] so that both the 'ene-addition' of $^1O_2$ and the

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[2] Optical rotation of solanofuran (**4**) could not be measured since only about 0.5 mg of this substance was isolated from *Burley* tobacco condensate. However, the synthesis of an enantiomer of **4** from optically active solanone (**1**) is in progress in this laboratory.

[3] Solanone (**1**) and its numerous metabolites are important constituents of *Burley* tobacco condensate [1] [2].

[4] It is generally agreed that sensitized photo-oxygenation reactions, or formally similar reactions, may be involved in such natural processes as, for instance, the oxidative degradation of carotenoids [4] [5].

[5] *Rio & Berthelot* [6] also obtained a furan derivative in the course of their study of the sensitized photo-oxygenation of *trans, trans*-1,4-diphenyl-1,3-butadiene, evidently a favourable acyclic conjugated diene.

[6] Examples of sensitized photo-oxygenations of *purely aliphatic* 1,3-dienes are extraordinarily scarce in the literature, and practically limited to the case of substituted buta-1,3-dienes [7].

[7] *s-trans* Conformers are thermodynamically preferred even in the case of β-ionone and related compounds in which *s-cis* conformers still appear to be stabilized to some extent by steric effects [5].

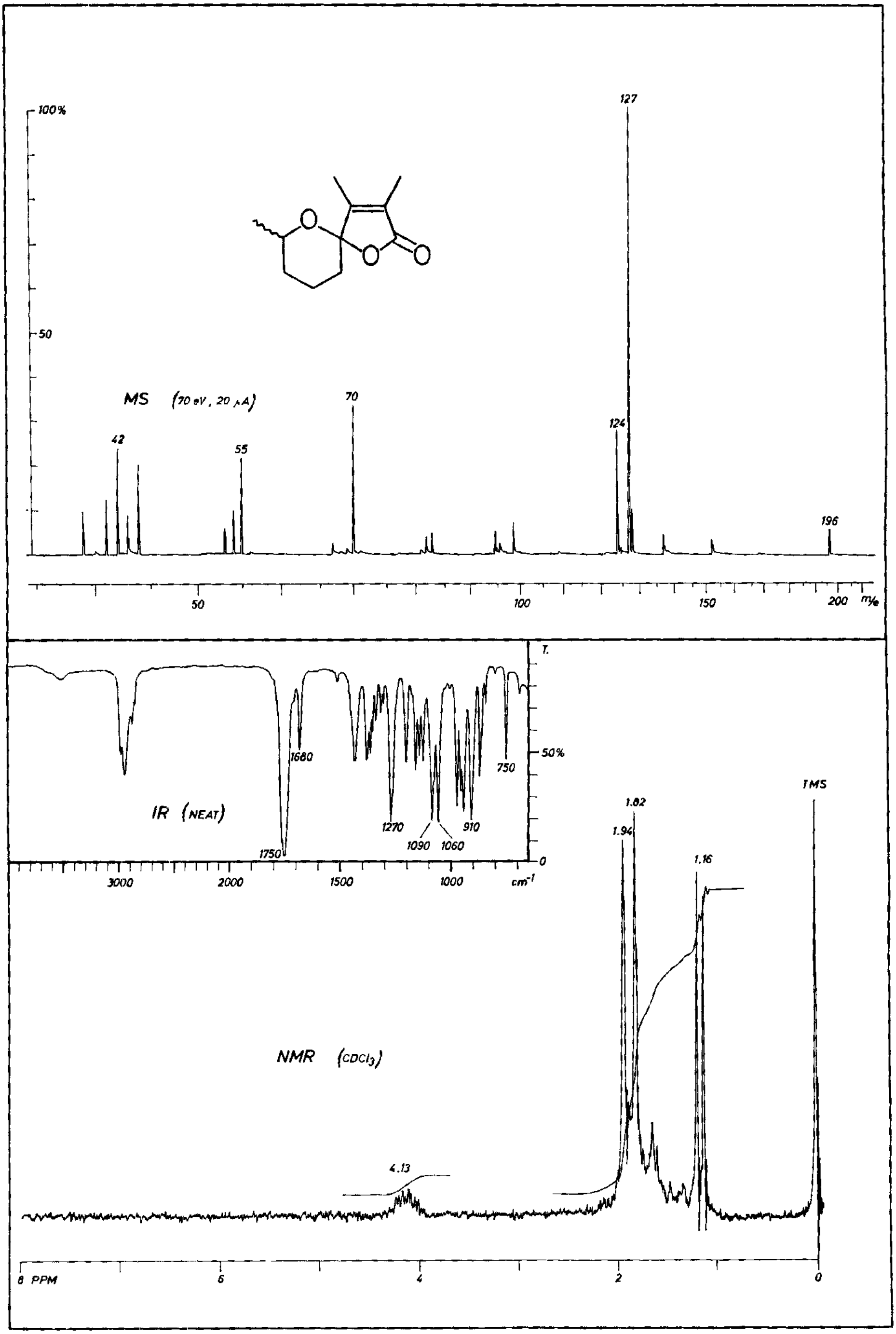


Fig. 2. *Mass, IR. and NMR. spectra of spiroxabovolide* (**6**)

formation of polymeric material would usually predominate over the 'diene-addition' process.

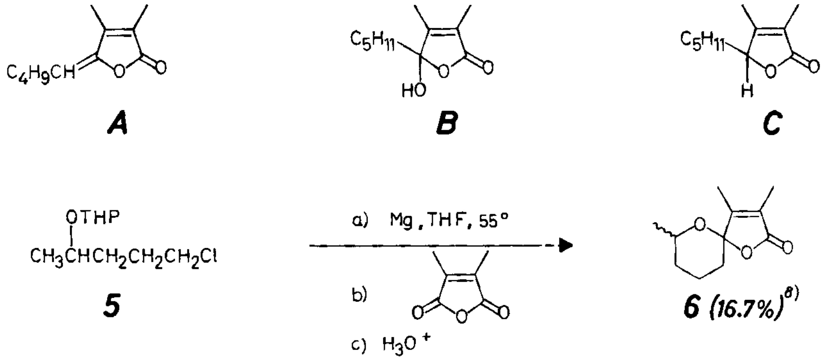
These restrictions do not preclude solanone (**1**) from undergoing the 'diene-addition' of $^1O_2$ with a 36% yield. We see no reason why this compound should be unique in this respect, and suspect that the scope of our solanofuran (**4**) synthesis could be easily extended to other terpene furans. Moreover, the present results also suggest the possibility that certain naturally occurring terpenoid furans are biosynthesized from their diene precursors[4]).

2a. *Isolation and structure determination of spiroxabovolide* (**6**). Beside solanofuran (**4**), subfractions B2-PN-e and -f from *Burley* tobacco condensate contained about 0.47 and 0.22% of spiroxabovolide, respectively. This substance was separated by gas-liquid chromatography using the conditions already stated in the schemes 8 and 9 of our first paper [2], and was eluted after compound 101 (scheme 8, 11th chromatogram B), or between compounds 88 and 92 (scheme 9, 11th chromatogram B).

The structure of spiroxabovolide (**6**) clearly results from a study of its spectra (fig. 2). First, the mass spectrum displays a parent ion at *m/e* 196 ($C_{11}H_{16}O_3^{+\cdot}$) and a base peak at *m/e* 127 ($M-69$) which is highly suggestive of certain derivatives of *bovolide* (**A**). For instance, *hydroxy-dihydrobovolide* (**B**) also splits off this fragment attributable to the loss of the side-chain ($M-71=127$). Second, IR. ($\nu=1680$, 1750 cm^{-1}), UV. ($\lambda_{max}^{EtOH}=213$ nm, $\varepsilon=10068$ [9]) and NMR. data [$\delta=1.82$, 1.94 (2×3 H, *s*, 2 CH_3–$\overset{|}{C}$=)] confirm that spiroxabovolide should have the partial structure of a 4-substituted 2,3-dimethylbut-2-en-4-olide. Third, the further NMR. signals which appear at $\delta=1.16$ (3 H, *d*, $J=6$ Hz, CH_3–$\overset{|}{C}$H–O–), 4.13 (1 H, *m*, CH_3–$\overset{|}{C}H$–O–) and between 1.33 and 2.44 (6 H, *m*, 3 –CH_2–) unequivocally show that it contains a 6-methyl-tetrahydro-pyran-2-ylidene grouping as a second moiety. All of these facts can be reconciled only if spiroxabovolide is 3,4,7-trimethyl-1,6-dioxa-spiro[4.5]-dec-3-en-2-one (**6**, stereochemistry unknown).

2b. *Synthesis of spiroxabovolide* (**6**). This compound was prepared by means of a modification of the *Schumacher* & *Roberts* synthesis of bovolide (**A**) and hydroxy-dihydrobovolide (**B**) [10], thus confirming the proposed structure **6** (*scheme 2*).

Scheme 2



After bovolide (**A**) and dihydro-bovolide (**C**), *spiroxabovolide* (**6**) represents the third 2,3-dimethylbut-2-en-4-olide derivative found to occur in *Burley* tobacco condensate [2]. Its structure in which both a but-2-en-4-olide and a 1,6-dioxa-spiro[4.5]decane are combined appears to be unique among the natural odorous substances. However, it should be noticed that certain other naturally occurring compounds such as, for instance, *actein* (rings E and F) [9], and some constituents of *Chrysanthemum spp.* [11], also belong to the 1,6-dioxa-spiro[4.5]decane class.

Experimental

The spectra were measured on the following instruments: IR. spectrometer *Perkin-Elmer* 720; UV. spectrometers *Optica* CF4 N.I. and *Beckman*; mass spectrometer *Atlas* CH4 IV 58 (*Atlas Werke* AG); NMR. spectrometers *Bruker* HFX-90/3–15 inch (90 MHz) and *Hitachi Perkin-Elmer* R 20 B (60 MHz).

1. *Synthesis of solanofuran* (**4**) (*scheme 1*). A solution of 1 g (5.1 mmoles) of solanone (**1**) and 180 mg of *Bengal red* in 200 ml of methanol was irradiated[9]) at 20° in the presence of a constant flow of dry oxygen (80 ml/min)[10]). The characteristic UV. absorption of solanone at 230 nm (ε = 27300) decreased progressively during the reaction to fall to about 1/3 of its initial value after 40 h. The solution was then evaporated to dryness in the cold, the residue taken up in ether, washed with water, concentrated, and chromatographed on 20 g of silica gel[11]). A fraction of 250 mg of unchanged solanone (**1**) was first eluted with benzene, followed by 320 mg (36%) of the expected *cyclic peroxide* **2** (benzene/ethyl acetate 95:5), and by 390 mg of a third, ill-defined fraction[12]) (benzene/ethyl acetate 1:1). The structure of peroxide **2** was confirmed by IR. [neat, ν = 1150, 1360, 1700 cm^{-1}, no OH band] and by NMR. data [CCl_4, δ = 0.75–1.10 (6 H, *m*, isopropyl), ~ 1.15–1.90 (4 H, *m*), 1.73 (3 H, *s*, $CH_3-\overset{|}{C}=$), 2.05 (3 H, *s*, CH_3CO-), 2.20–2.70 (2 H, *m*, $-CH_2-$ $-CO-$), 4.15–4.70 (3 H, *m*, $-CH_2-O-$ and $>CH-O-$), 5.60 (1 H, *broad s*, $H-\overset{|}{C}=$)]. This peroxide is unstable thermally and cleanly rearranged to *solanofuran* (**4**) (~45% yield) when injected into a gas chromatograph[13]). To carry out the classical *Kornblum & DeLaMare*'s rearrangement [13], 300 mg of **2** in 3 ml of benzene were left in contact with 10 g of basic alumina[15]) for 2 h at 20°. Subsequent elution with ether/methanol 4:1 gave 264 mg (88%) of *crude* hemiacetal **3** showing IR. bands at ν = 1030, 1360, 1710 and 3450 cm^{-1}. This compound readily dehydrated[16]) to solanofuran (**4**), either upon injection into a gas chromatograph[13]) or when chromatographed over silica gel[11]) in the presence of benzene containing an increasing amount (2 → 20%) of ethyl acetate (yield about 55%).

A sample of solanofuran (**4**) obtained in this way showed IR., UV., NMR. and mass spectra identical to that of the compound isolated from *Burley* tobacco condensate, and had Eb 75°/0.001 Torr; d_4^{20} = 0,9617; n_D^{20} = 1.4700.

$C_{13}H_{20}O_2$ Calc. C 74.96 H 9.68% Found C 74.76 H 9.45%

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[8]) We made no attempt to optimize this yield.

[9]) UV. lamp, type *Philips* HPK 125 W. An all-glass (pyrex) apparatus was used.

[10]) After 24 h the colour of the reaction mixture faded somewhat, and a second portion of 180 mg of *Bengal red* was added.

[11]) 'Kieselgel 0.05–0.2 mm für die Säulen-Chromatographie' (*Merck* AG).

[12]) This polar fraction was examined by gas-liquid chromatography (Carbowax 20 M, 200°) after reduction with triphenylphosphine [12]. It turned out to be a mixture, separable with difficulty, of compounds including *norsolanadione* (a well-known autoxidation product of solanone [3]), *solanofuran* (**4**), a *keto-aldehyde* and several *keto-alcohols*.

[13]) *Aerograph*, Model 1820-3 (*Varian Aerograph* AG), fitted with a 0.4 × 250 cm column packed with 15% of silicone oil[14]) on *Chromosorb W* (*Johns-Manville*). Injection port temperature 235°, column temperature 220°.

[14]) 'Embaphase' (*May & Baker* Ltd).

[15]) *Woelm*, activity grade I.

[16]) 5-Monosubstituted 2,5-dihydro-furan-2-ols are labile compounds, which readily dehydrate to the corresponding furans either spontaneously or in the presence of catalysts [14].

2. *Synthesis of spiroxabovolide* (**6**) (*scheme 2*). Small portions of sodium borohydride (2.50 g, 0.066 mole) were added over a 45 min period at +5° to a stirred solution of 24.0 g (0.20 mole) of 5-chloropentan-2-one in 300 ml of anhydrous methanol. The mixture was kept overnight at 20° and worked up as usual to give 17.2 g (70%) of 5-chloropentan-2-ol, Eb 46–48°/0.001 Torr, which was immediately mixed with 13 g (0.155 mole) of 2,3-dihydropyran under external cooling (ice water, exothermal reaction). After $3^1/_2$ h at room temperature, the reaction mixture was stirred for 15 min with some anhydrous potassium carbonate, filtered and concentrated to dryness. Distillation afforded 21.9 g (75%) of tetrahydropyranyl ether **5**, Eb 70–74°/0.001 Torr [NMR. (CCl_4): $\delta = 1.15$ (3 H, *t*, $J = 6$ Hz), 1.30–2.20 (10 H, *m*), 3.30–4.00 (5 H, *m*), 4.60 (1 H, *broad s*); mixture of diastereomers].

A solution of 8.28 g (40 mmoles) of tetrahydropyranyl ether **5** in 8 ml of anhydrous tetrahydrofuran was allowed to react with 1.2 g (49.5 mAt) of magnesium turnings for 45 min at 55° with vigorous stirring, according to the *Feugeas'* procedure [15]. After 2 h of additional stirring at 55°, the reaction mixture was diluted with 1 vol of tetrahydrofuran and the resulting solution added over a period of 2 h at +5° to 4.8 g (38 mmoles) of dimethylmaleic anhydride dissolved in 40 ml of benzene/tetrahydrofuran 1:1. The mixture was kept overnight at 20°, acidified with dilute sulfuric acid, stirred for 1 h at 20° and worked up (ether extraction, etc.). The crude product (13 g) was first heated at 100°/0.001 Torr to remove about 5 g of volatile impurities, and then refluxed for $1^1/_2$ h in 40 ml of benzene containing 400 mg of *p*-toluenesulfonic acid (*Dean-Stark* separator). The benzene solution was washed with 5% sodium hydrogencarbonate, evaporated to dryness and the recovered product (6.4 g) chromatographed over 120 g of silica gel[11]) in the presence of ether. As forerun there was eluted 1.25 g (16.7%)[8]) of *spiroxabovolide* (**6**), Eb 80–82°/0.001 Torr, which proved to be identical (IR., UV., NMR., MS.) with the substance isolated from *Burley* tobacco condensate, and had $d_4^{20} = 1.077$; $n_D^{20} = 1.4822$.

$C_{11}H_{16}O_3$ Calc. C 67,32 H 8.22% Found C 67.11 H 8.15%

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