# Tobacco Chemistry 11
Total Synthesis of 5-Methoxy-6,7-dimethylbenzofuran, a New Tobacco Constituent

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Recently we reported on the isolation[1] and structural elucidation[2] of a minor tobacco constituent, 5-methoxy-6,7-dimethylbenzofuran (VII), the carbon skeleton of which can formally be dissected into two isoprene units. Due to shortage of material the structure was determined solely by spectroscopic means, involving the selection of one isomer out the sixty positional isomers of methoxy-dimethylbenzofuran, on the basis of detailed examination of its NMR spectrum, spin decoupling experiments and nuclear Overhauser effects.

In the present communication, we describe a total synthesis of 5-methoxy-6,7-dimethylbenzofuran (VII) which provides confirmation of the previously assigned structure. The synthesis was performed as outlined in Scheme 1.
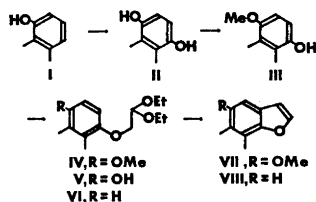
Scheme 1.

2,3-Dimethylphenol (I) was oxidized with persulphate according to the method of Aghoramurthy et al.,[3] to give 2,3-dimethyl-1,4-hydroquinone (II). The instability of the hydroquinone, II, in alkaline solutions prevented a direct synthesis of the corresponding monooxyethanal acetal derivative, V, and the methylation step was therefore introduced at this stage of the synthesis. The monomethyl ether, III, was obtained by reacting II with methyl iodide in acetone.[4] The sodium salt of III was treated with bromoacetaldehyde diethyl acetal, adapt-

ing the procedure of Pailer et al.[5] for analogous reactions with thiophenols, to give the diethyl acetal, IV.

Preliminary attempts at cyclizing the model compound VI employing anhydrous stannic chloride in chloroform, anhydrous oxalic acid or zinc chloride at elevated temperatures (as described by Banfield et al.[6] for cyclizations of arylthioacetaldehyde diethyl acetals) were unsuccessful. However, the use of acetic acid as solvent with catalytic amounts of anhydrous zinc chloride proved to give 6,7-dimethylbenzofuran (VIII) in 10 % yield. Similar treatment of IV afforded the desired 5-methoxy-6,7-dimethylbenzofuran (VII) in 17 % yield. The low-melting crystalline product exhibited NMR, UV, IR, and mass spectra which were identical in all respects to those of the natural product.[2] As the small amount of the natural compound available (3 mg) failed to crystallize, evidently due to the presence of trace amounts of impurities, the identity was further demonstrated by cochromatography. Thus, the synthetic and natural material proved to be inseparable when co-chromatographed on capillary columns coated with either Apiezon L or Emulphor. Equally, they were indistinguishable when co-chromatographed on thin-layer plates coated with silica gel or silica gel impregnated with silver nitrate.

Since the compound (VII) is likely to occur in other plants and in tobacco smoke, its IR spectrum is reproduced in Fig. 1 for identification purposes.

Experimental. Instruments. NMR spectra were recorded on a Varian A60-A spectrometer using $CDCl_3$ as solvent, unless otherwise stated, and TMS as internal reference. IR, UV, and mass spectra were obtained on a Perkin-Elmer 257, Beckman DK-2A, and LKB 9000 (70 eV) instrument, respectively. Uncorrected melting points were determined on a Leitz Wetzlar instrument.

2,3-Dimethyl-1,4-hydroquinone (II). By treating 2,3-dimethylphenol (I, 48.9 g, Fluka AG) with potassium persulphate as described by Aghoramurthy et al.[3] for similar oxidations, II (27.4 g) was obtained in 49 % yield; m.p. 215—222° (dec.), lit.: 221—224°,[7] 220° (dec.).[8]. NMR: $\delta(CH_3OD)$ 2.1 (6H,s), 6.52 (2H,s); MS: m/e (%) 138 (100), 137 (40), 123 (53); 109 (9), 95 (14), 91 (12), 77 (9), 67 (9), 55 (11). (Found: C 69.4; H 7.6. $C_8H_{10}O_2$ requires C 69.6; H 7.3.)

4-Methoxy-2,3-dimethylphenol (III). Monomethylation of II (5 g) was effected with
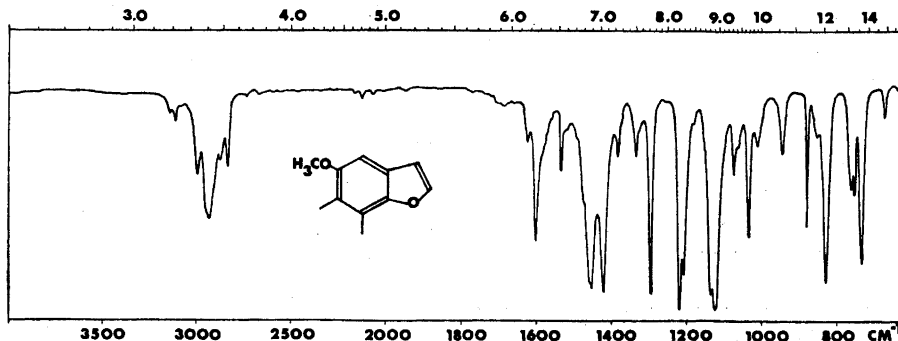
Fig. 1.

methyl iodide (7.6 g) in the presence of K_2CO_3 (5.1 g) in refluxing acetone (55 ml), following the general procedure of Vyas et al.[4] The product was purified by chromatography on silica gel to give III (1.2 g, 22 %). M.p. 97—98°, lit.[3] 95—97°; NMR: δ 2.13 (6H,s), 3.72 (3H,s), 5.4 (1H,s), 6.49 (2H,s); MS: m/e (%) 152 (87), 137 (100), 121 (6), 109 (11), 91 (15), 81 (17), 77 (12), 65 (10), 53 (12); UV: λ_{max} (EtOH) 289 nm (ε 3130); IR: (KBr) $ca.$ 3300 (s), 1490 (s), 1452 (s), 1249 (s), 1109 (s), 800 (s), 730 (s) cm^{-1}. (Found: C 70.9; H 8.0. $C_9H_{12}O_2$ requires C 71.0; H 8.0.).

4-Methoxy-2,3-dimethylphenoxyacetaldehyde diethyl acetal (IV). A mixture of III (1 g), bromoacetaldehyde diethyl acetal (2 g), and sodium iodide (300 mg) in a sodium ethoxide solution (250 mg Na in 10 ml ethanol) was refluxed for 48 h.[5] The mixture was diluted with water, extracted with ether, and the product purified by chromatography on silica gel to give a colourless oil (850 mg, 49 %). NMR: δ 1.23 (6H, t, $J = 7$ Hz), 2.14 (3H,s), 2.17 (3H,s), $ca.$ 3.7 (4H, two quartets, $J = 7$ Hz), 3.76 (3H,s), 3.94 (2H,d, $J = 5$ Hz), 4.84 (1H,t, $J = 5$ Hz), 6.64 (2H,s); MS: m/e (%) 268 (16), 151 (24), 103 (100), 91 (10), 75 (68), 61 (19), 47 (53); UV: λ_{max} (EtOH) 286 nm (ε 2640); IR: (film) 2980 (s), 2938 (s), 1483 (s), 1259 (s), 1211 (s), 1119 (s), 1071 (s), 791 (m), 749 (m) cm^{-1}. (Found: C 67.3; H 9.2. $C_{15}H_{24}O_4$ requires C 67.1; H 9.0.).

5-Methoxy-6,7-dimethylbenzofuran (VII). A solution of IV (560 mg) and anhydrous zinc chloride (50 mg) in glacial acetic acid[6] (10 ml) was kept at 100° for 2 h. The mixture was diluted with aqueous 10 % NaOH and extracted with pentane. The extract was washed with water and evaporated. The residue was chromatographed on silica gel, and the fraction

(64 mg, 17 %) which was eluted with 2 % ether in pentane proved to be 5-methoxy-6,7-dimethylbenzofuran VII, which crystallized as needles from methanol. M.p. 32—33°. (Found: C 75.3; H 6.4. $C_{11}H_{12}O_2$ requires C 75.0; H 6.9.). NMR, UV, and mass spectra (see Ref. 2) were identical to those of natural VII. UV: λ_{max} (EtOH) 248 nm (ε 12 500), 256 (ε 9700), 289 (ε 4400), 300 nm (ε 3900). IR spectrum (film), see Fig. 1. Synthetic and natural VII were inseparable when co-chromatographed on capillary columns (50 m × 0.5 mm)[1] coated with Apiezon L or Emulphor, and on thin-layer plates coated with silica gel ($R_F = 0.45$; ether/pentane = 1 : 50) and silica gel impregnated with silver nitrate ($R_F = 0.71$; ether/pentane = 3 : 50).

6,7-Dimethylbenzofuran (VIII). Under conditions similar to those described above for the synthesis of IV and VII, I was reacted with bromoacetaldehyde diethyl acetal to the corresponding phenoxyacetal which subsequently was cyclized to 6,7-dimethylbenzofuran. NMR: δ 2.28 (3H,s), 2.35 (3H,s), 6.59 (1H,d, $J = 2.5$ Hz), 6.94 (1H,d, $J = 8$ Hz), 7.25 (1H,d, $J = 8$ Hz), 7.45 (1H,d, $J = 2.5$ Hz).

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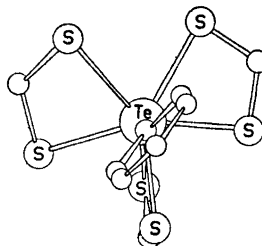
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Fig. 1. The $[Te(Et_2NCS_2)_3C_6H_5]$ molecule (I), seen along the normal to the equatorial TeS_5 plane. All Et_2N- groups are omitted, and the smallest spheres represent carbon atoms.

On the Crystal Structures of Two Highly Coordinated Tellurium(IV) Complexes

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The crystal structures of the two complexes, tris(diethyldithiocarbamato) phenyltellurium(IV), $[Te(Et_2NCS_2)_3C_6H_5]$, and tetrakis(diethyldithiocarbamato)tellurium(IV), $[Te(Et_2NCS_2)_4]$, have been determined by three-dimensional X-ray crystallographic methods.

The yellow crystals of $[Te(Et_2NCS_2)_3C_6$-$H_5]$, (I), are monoclinic with $a = 10.791(5)$ Å, $b = 16.090(6)$ Å, $c = 18.417(9)$ Å $\beta = 117.63(6)°$ and $Z = 4$. Density, calc. 1.52, found 1.51 g/cm³; space group $P2_1/c$.

Intensities of 4183 reflections greater than the background were recorded with a Siemens AED-1 diffractometer, using MoKα-radiation. The structure was solved by conventional heavy atom methods. No absorption correction was applied. Full-matrix least squares refinement with anisotropic temperature factors for Te and S, excluding hydrogen atoms, has given an R value of 6.2 %. The coordination around the central tellurium atom is shown in Fig. 1.

The orange crystals of $[Te(Et_2NCS_2)_4]$, (II), are orthorhombic with $a = 19.805(2)$ Å, $b = 9.371(2)$ Å, $c = 35.178(4)$ Å and $Z = 8$.

Density, calc. and found 1.46 g/cm³; space group $Pna2_1$. On basis of a three-dimensional Patterson synthesis and packing considerations, the space group $Pna2_1$ was chosen instead of $Pnma$, thus giving two molecules in the asymmetric unit. The Patterson synthesis gave the x and y coordinates of the two Te atoms and also the difference in their z-coordinates. The value of z for Te1 was arbitrarily chosen as 0.000, and the structure then solved by successive Fourier syntheses. It is being refined by full-matrix least squares methods, based at present on 2645 observed diffractometer reflections obtained with CuKα radiation. The R value, with absorption correction undertaken, and with anisotropic temperature factors only for Te, is at present 8.8 %. The content of one asymmetric unit is shown in Fig. 2.

From the figures, it is seen that in the complexes I and II, the central Te atom is, respectively, seven- and eight-coordinated. In I, the coordination is best described as distorted pentagonal bipyramidal, in II as distorted dodecahedral.

Thus the coordination around the central Te atoms in I and II is not that expected on the basis of distributions of 8 and 9 valence electron pairs, respectively, according to the VSEPR theory.[1] The structures found here can to a first approximation be explained by assuming the 5s lone pair to be stereochemically inert. This is as found for octahedral hexahalotellurates.[1]

The main distortion in $[Te(Et_7NCS_2)_3$-$C_6H_5]$, (I), the long $Te-S$ bond of 3.23 Å *trans* (144.6°) to the phenyl group ($Te-C = 2.12$ Å), may be due to the strong *trans* effect of the latter, rather than to the lone pair. Also the narrow $S-S$ "bite" distance