

## Tobacco Chemistry

9. 5-Methoxy-6,7-dimethylbenzofuran,  
a New Tobacco ConstituentARNE J. AASEN, BJARNE KIMLAND,  
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Recently, we reported<sup>1</sup> on aroma-constituents of sun-cured Greek tobacco, Serres 1968. Subsequent studies<sup>2</sup> of this tobacco have led to the isolation of a new compound (3 mg), present in small amounts (0.1 ppm of dry tobacco). The present paper describes the evidence for assigning structure XII to this compound.

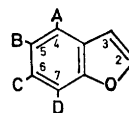
The compound was shown to have the elemental composition  $C_{11}H_{12}O_2$  by high resolution mass spectrometry (Found: 176.0838, required 176.0837). The twelve protons observed in the NMR spectrum were encountered as three three-proton signals at  $\delta$  2.27, 2.47, and 3.88 and three one-proton signals at  $\delta$  6.71, 6.91, and 7.49. The three highfield signals could be ascribed to two methyl groups and one methoxyl group attached to an aromatic ring and the signal at  $\delta$  6.91 to one aromatic proton. The protons giving rise to the signals at  $\delta$  6.71 and 7.49 were mutually coupled ( $J=2.3$  Hz) indicating the presence of either two aromatic protons *meta* to each other, or two vicinal *cis*-oriented protons in a similar electronic environment such as a furan ring. The latter possibility appeared more probable judging by their chemical shifts since protons on a benzene ring carrying only methyl and methoxyl substituents are unlikely<sup>3</sup> to resonate as far downfield as  $\delta$  7.49.

It could be concluded therefore that the compound is a benzofuran derivative carrying the three substituents on the benzene moiety. The chemical shifts and coupling constants reported<sup>4</sup> for the furyl protons of benzofuran corresponded well with the values quoted above. Moreover, the mass spectrometric fragmentation pattern, summarized in Scheme 1, was consistent with that expected for such a methoxyl and methyl substituted aromatic compound.<sup>5,6</sup>

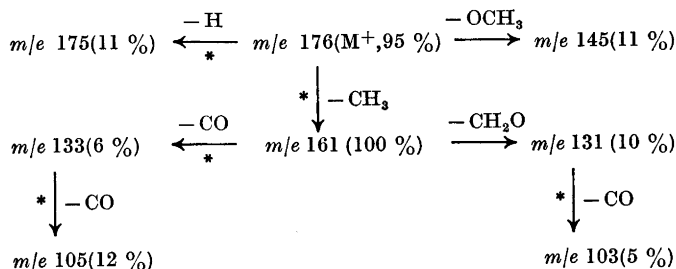
There are twelve theoretically possible isomers of this type of benzofuran derivative (I–XII); see Table 1. Eleven of these could be excluded by means of detailed examination of the 100 MHz spectrum as shown below.

*Absence of  $J_{3,7}$ :* The lines of the doublet at  $\delta$  6.71, due to the proton in the 3 position, were only slightly broadened indicat-

Table 1.



Structure	H	CH <sub>3</sub>	OCH <sub>3</sub>
I	D	BC	A
II	D	AC	B
III	D	AB	C
IV	C	BD	A
V	A	BD	C
VI	B	AC	D
VII	A	BC	D
VIII	C	AD	B
IX	B	AD	C
X	C	AB	D
XI	B	CD	A
XII	A	CD	B



Scheme 1.

ing a second coupling of *at most* 0.1 Hz. Since a long-range coupling between the protons in the 3 and 7 positions has invariably been found to be of the order 0.6–1.0 Hz for benzofurans and benzothiophenes,<sup>4,7,8</sup> one of the substituents must occupy position 7 in the tobacco compound and hence structures I, II, and III can be ruled out.

$J_{\text{H, OCH}_3}^{\text{ortho}}$ : The presence of a coupling between the methoxyl protons ( $\delta$  3.88, d,  $J=0.26$  Hz) and the aromatic proton ( $\delta$  6.91, m) was demonstrated by decoupling experiments. Since such a long range coupling is normally in the range 0.15–0.3 Hz in the case of an *ortho* relationship, 0–0.1 Hz for *meta*, and zero for *para*,<sup>9–12</sup> these results clearly suggested the *ortho* alternative for the present compound. This was confirmed by the observation of a positive nuclear Overhauser effect<sup>13</sup> when irradiating at  $\delta$  3.88 and observing the integral of the aromatic proton (15% enhancement). Consequently, structures IV, V, VI, and VII as well as I and II are unacceptable.

$J_{\text{Me, Me}}^{\text{ortho}}$ : The two methyl groups gave rise to a slightly broadened quartet (*vide infra*) and a quintet at  $\delta$  2.27 and 2.47, respectively. Double resonance experiments revealed mutual coupling of about 0.5 Hz consistent with an *ortho* or *para* configuration.<sup>8,14</sup> However, since one of the methyl groups is *para* to the single aromatic proton (*vide infra*), structures VIII and IX together with II, IV, V, and VI are considered unlikely.

$J_{\text{H, Me (lowf)}}^{\text{para}}$  and  $J_{\text{H, Me (highf)}}^{\text{meta}}$ : Irradiation at  $\delta$  6.91, the resonance frequency of the aromatic proton, simplified the lowfield methyl signal at  $\delta$  2.47 to a quartet. The observed coupling constant, 0.55 Hz, indicated either a *para* or an *ortho* relationship, of which the latter could be eliminated since no Overhauser effect was observable when irradiating at  $\delta$  2.47. The coupling between the other methyl group and the aromatic proton was estimated to be *ca.* 0.3 Hz, suggesting a *meta* relationship as  $J_{\text{H, Me}}^{\text{ortho}} \approx J_{\text{H, Me}}^{\text{para}} > J_{\text{H, Me}}^{\text{meta}}$  (see Refs. 8, 15, and 16). The requirement of both a *para* and a *meta* relationship between the methyls and the aromatic proton excludes all structures but III and XII, of which III has already been excluded as demonstrated above.

Consequently, only structure XII remains and this assignment is further supported by the following facts.

The chemical shift of the 7-methyl group,  $\delta$  2.47, is compatible with that reported for related compounds, *e.g.* 2,7-dimethylbenzothiophene<sup>7</sup> ( $\delta$  2.46 and 2.51, resp.); methyl substituents in other positions on the aromatic nucleus resonate at higher field, *e.g.* 2-carbomethoxy-5,6-dimethylbenzofuran<sup>8</sup> ( $\delta$  2.3).

The observed chemical shift of the aromatic proton corresponds fairly well to that calculated with the aid of reported values for benzofuran<sup>4</sup> and compiled empirical data<sup>3</sup> for the influence of the substituents under consideration. Thus, the difference between the calculated and observed chemical shifts was 0.12 ppm for structure XII, but greater than 0.15 ppm for structures III, IV, VI, and VIII–XI.

Small long-range couplings,  ${}^4J_{3,4}$  (<0.1 Hz),  ${}^5J_{2,4}$  (*ca.* 0.2 Hz) and  ${}^7J_{2, \text{Me}(\delta)}$  (0.3 Hz), were observed when decoupling the protons at  $\delta$  7.49 and 6.91. These values accord with those previously reported for similar systems.<sup>12</sup> The value of  ${}^7J_{2, \text{Me}(\delta)}$  compared to  ${}^6J_{2,6}$  (0.4–0.6 Hz)<sup>12</sup> indicates a (partly)  $\pi$ -electron-transmitted contact coupling.<sup>17,18</sup> It is not known whether the expected sign reversal also occurs. A similar 7-bond methyl coupling (–0.35 Hz) has recently been reported for 2-methylthieno[3,2-*b*]thiophene.<sup>19</sup> Line width measurements for our compound indicate that  ${}^6J_{3, \text{Me}(\tau)}$  is less than 0.1 Hz.

A small positive nuclear Overhauser effect was found for the methyl signal at  $\delta$  2.27 (3% enhancement) when irradiating the methoxyl protons at  $\delta$  3.88, thus supporting the assigned *ortho* relationship. The signals of the lowfield methyl and furyl protons were unaffected.

It may be concluded from the above results that this new tobacco compound has structure XII. The carbon skeleton of XII can formally be dissected into two isoprene units constituting a new monoterpene. Whether or not XII is actually derived from mevalonic acid is presently unknown. The structure has since been confirmed as XII by total synthesis.<sup>20</sup>

*Experimental.* NMR spectra were recorded on a Varian A60-A instrument connected to a C-1024 CAT using deuteriochloroform as solvent and TMS as internal reference, and a Varian HA-100D instrument using deuteriochloroform as solvent and TMS as external reference. The sample was kept in a glass capillary inside an ordinary NMR tube. Mass spectra were obtained on a LKB 9000 instrument operated at 70 eV. The compound was

isolated from a tobacco fraction (C-6) by preparative gas chromatography.<sup>2</sup>

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## A CNDO/2 Study of Some Conformational Properties in Propyl Chloride, Fluoride, Cyanide, and Ethyl Formate

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In recent years, there has been an increasing application of the semi-empirical molecular orbital method CNDO/2,<sup>1</sup> in studying structural and energetic properties of molecules.<sup>1,2</sup> Some of these calculations have been rather successful,<sup>1,3</sup> whereas others indicate that the method should be used with caution.<sup>4</sup>

In the present work the CNDO/2 method has been used to study some conformational properties of a few ethyl derivatives. Only molecules were chosen for which reliable experimental information for comparison was available. The actual molecules were propyl chloride, fluoride, cyanide, and ethyl formate. For the three first molecules rotation was considered about the C<sup>1</sup>-C<sup>2</sup> bond \* and for the last about the CH<sub>2</sub>-O bond.

*Results.* The geometries used for the calculations were obtained from recent microwave investigations.<sup>5-8</sup> The energies were calculated varying the dihedral angle from 0 to 180° in steps of 30° except around the gauche positions, where 5° intervals were used.

In Table I the calculated conformational properties of the selected molecules are presented together with experimental data. The calculations predict two stable conformations. Except for propyl chloride both dihedral angles and energy differences are in satisfactory agreement with experimental values.<sup>5-8</sup> The reason why the calculations on propyl chloride fail is not clear. Possibly, the parameters used for the third row elements are not so well fitted as for the first and second. Also the approximations inherent in the method may be less correct when the third row elements are included.

For propyl fluoride and ethyl formate the experimental *trans-gauche* barriers are well reproduced. For the *gauche-gauche*

\* The molecules are denoted C<sup>3</sup>H<sub>3</sub>-C<sup>2</sup>H<sub>2</sub>-C<sup>1</sup>H<sub>2</sub>X, where X = F, Cl, C≡N.