

spectrum showing aromatic, hydroxyl (or amino), and carbonyl groups. This fraction, on alumina, was resolved further; a subfraction was eluted with a mixture of petroleum ether and benzene (1:1) which, on gas chromatographic analysis (2.4 m by 6.4 mm column of 20 percent SE-30 on Chromosorb W, 180°C for 15 minutes, and programmed at 8°C per minute to 265°C), showed three peaks emerging at 13, 26, and 34 minutes, respectively.

The infrared spectrum of the component eluting at 13 minutes was suggestive of an aromatic ether. Absorption at 9.57  $\mu$  indicated an ether group, and peaks at 3.45, 10.69, and 13.85  $\mu$  revealed a possible methylenedioxy-substituted benzene ring (4). Strong absorption at 6.12  $\mu$  showed *exo* unsaturation which was substantiated by bands at 10.08 and 10.92  $\mu$  (vinyl group). Aromatic absorption was apparent at 12.09  $\mu$  (one adjacent free hydrogen on the aromatic ring) and in the usual range, 3.25 to 3.40  $\mu$ . The absence of absorption at 6.29  $\mu$  indicated the lack of conjugation of the vinyl group with the aromatic ring. The ultraviolet spectrum confirmed the presence of aromaticity (broad absorption at 260 to 295 m $\mu$ ). The mass spectrum showed a parent peak at 192 and major fragment peaks at 161 (loss of -OCH<sub>3</sub>) and 165 (substituted tropylium ion). Comparison of all spectra with those of authentic myristicin (5) showed identical characteristics except for two extraneous peaks (mass/charge 153, 194) in the mass spectrum of the unknown; these peaks were probably derived from a minor contaminant structurally related (for example allyl 2,6-dimethoxyphenyl ether) or dissimilar (as a substituted indole) to myristicin. Indoles and carbazoles have been isolated from the fraction containing myristicin in the original column chromatography. Similar retention times were obtained with the isolated substance and authentic myristicin on 20 percent Apiezon L on Chromosorb W (2.4 m by 6.4 mm column operated at 275°C; retention time, 7 minutes). In addition, co-chromatography of the isolated substance and authentic myristicin on SE-30 gave a single peak. The level of myristicin in cigarette smoke is at least 0.64  $\mu$ g per cigarette based on the observed recovery, which was undoubtedly not quantitative.

The nitromethane-soluble fraction of smoke is of special interest since it contains the major carcinogenic polynuclear

aromatic hydrocarbons of smoke and has significant physiological activity. In addition to the carcinogens this fraction contains a number of other aromatic compounds, such as benzyl benzoate and benzyl cinnamate; certain heterocyclic aromatic compounds (indoles, carbazoles, etc.) have also been demonstrated (6). However, myristicin appears to be unlike these recently isolated compounds in that some distinct pharmacological activity has been attributed to it. Although controversy exists as to whether the physiological effects of nutmeg oil (nausea, tachycardia, cyanosis, stupor, and others) are due exclusively to myristicin (2), it appears safe to conclude, on the basis of available biological data (2), that myristicin has some degree of toxicity and produces some neurological effects on administration. Also, it should be noted that myristicin is an analog of safrole, which is regarded as a low-grade hepatic carcinogen for rats (7). Whether the low level of myristicin in cigarette smoke contributes to the overall physiological effect of smoke is unknown.

Since commercial American cigarettes contain flavoring additives, including natural oils and resins, the possibility exists that myristicin, as well as the other benzyl esters in smoke, is derived from this source rather than the tobacco leaf. Myristicin has been isolated from the oil of several species, and the benzyl esters are common constituents of many natural oils and resins (8).

IRWIN SCHMELTZ, R. L. STEDMAN  
J. S. ARD, W. J. CHAMBERLAIN  
*Eastern Utilization Research and  
Development Division, USDA,  
Philadelphia, Pennsylvania 19118*

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### Myristicin in Cigarette Smoke

**Abstract.** *The pharmacologically active aromatic ether, myristicin, was isolated from the smoke of commercial cigarettes. The compound was identified by spectrometry (infrared, ultraviolet, and mass) and gas chromatography. The amount of myristicin in smoke is relatively low, and its contribution, if any, to the physiological action of cigarette smoke is unknown.*

The presence of myristicin (5-allyl-2,3-methylenedioxyphenyl methyl ether) in cigarette smoke has been demonstrated (1). This compound has biological activity and is believed to be responsible, at least in part, for the narcotic effect of nutmeg oil (2).

Myristicin was found in the fraction of the neutral substances soluble in nitromethane. This fraction was obtained from 1 kg of smoke condensate (equivalent to 50,000 cigarettes) by the separation procedure described (3). Chromatography on silicic acid of the components of the nitromethane soluble fraction yielded a fraction eluting with a mixture of *n*-hexane and benzene (1:1) which had an infrared