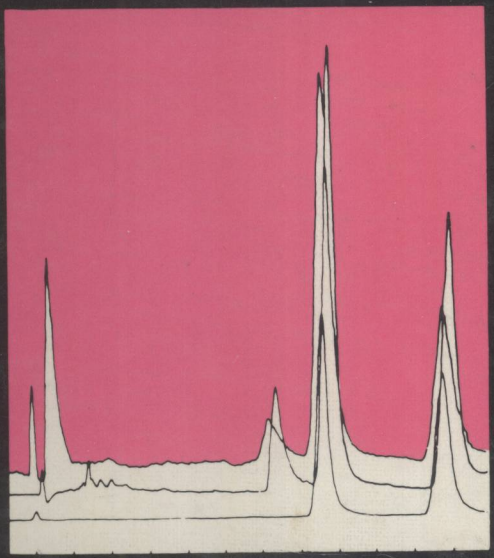
Analysis of Drugs and Metabolites by Gas Chromatography-Mass Spectrometry

Volume 7

Natural, Pyrolytic, and Metabolic Products of Tobacco and Marijuana



Benjamin J. Gudzinowicz
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ANALYSIS OF DRUGS AND METABOLITES BY GAS CHROMATOGRAPHY–MASS SPECTROMETRY

VOLUME 7

Natural, Pyrolytic, and Metabolic Products of Tobacco and Marijuana

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Analysis of Drugs and Metabolites by Gas Chromatography–Mass Spectrometry

ANALYSIS OF DRUGS AND METABOLITIES
BY GAS CHROMATOGRAPHY-MASS SPECTROMETRY

VOLUME 1: Respiratory Gases, Volatile Anesthetics, Ethyl Alcohol, and Related Toxicological Materials

VOLUME 2: Hypnotics, Anticonvulsants, and Sedatives

VOLUME 3: Antipsychotic, Antiemetic, and Antidepressant Drugs

VOLUME 4: Central Nervous System Stimulants

VOLUME 5: Analgesics, Local Anesthetics, and Antibiotics

VOLUME 6: Cardiovascular, Antihypertensive, Hypoglycemic, and Thyroid-Related Agents

VOLUME 7: Natural, Pyrolytic, and Metabolic Products of Tobacco and Marijuana

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Dedicated to

HELEN L. GUDZINOWICZ
a devoted and understanding wife and mother

PREFACE

In the past two decades, remarkable progress has been made in the analysis of drugs, pharmaceuticals, and related toxicological materials. In great measure, these notable advances can be attributed to technological advancements in two specific types or areas of analytical instrumentation; namely, gas chromatography and integrated gas chromatography-mass spectrometry.

Since James and Martin revealed to the scientific community their gas chromatographic technique which permitted the separation of fatty acid mixtures into their individual components, the rapid growth of gas chromatography has been very evident. This remarkable progress can be directly correlated with the improvements that we have witnessed over the years in gas chromatographic stationary phase, carrier gas, column, and temperature- and pressure-controlling technology. Furthermore, it has assumed a position of even greater analytical significance since the advent of highly specific, rapid, sensitive detection systems.

On the other hand, the integrated GC-MS analytical system is rather unique and exceptional in that it combines the mass spectrometer's unexcelled identification potential with the gas chromatograph's separation capabilities. Although the integration of GC and MS was first reported in 1957 by Holmes and Morrell, it nevertheless remained a dormant, costly, and seemingly unappreciated technique until 1970. Since then, with improved instrumentation at a more reasonable price and newly developed operating techniques, numerous publications have appeared in the literature showing its applicability to a wide variety of difficult analytical problems, thus opening up new horizons for analytical research in toxicology, biochemistry, pharmacology, forensics, medicine, etc. To be able to monitor a drug, its persistence and metabolic fate in biological fluids of man via mass fragmentography at picogram concentration levels provides the researcher with a tool of immeasurable significance.

Because much has been written over the years about the analysis of drugs and their metabolites by either or both techniques, the objectives of these volumes are several-fold: (1) to compile from existing literature in a chronological manner the various GC and/or GC-MS procedures available for the analysis of specific drugs and their metabolites, (2) to describe with as much detail as possible all procedures (qualitative and quantitative) in order that they might be reproduced faithfully in one's laboratory, and (3) to indicate, wherever possible, not only the results, precision, accuracy, and limits of detection achieved by a given procedure, but also its applicability to pharmacokinetic studies. For this reason, in addition to the text, which is well referenced in each section, many illustrations of actual applications and tables of data for each instrumental technique are included as aids to the analyst for his greater appreciation and understanding of the limitations as well as potentials ascribed to each method. As stated in the past, from an analytical chemist's point of view, it is hoped that this deliberately combined visual and factual approach will find acceptance by the reader who would otherwise rely only on his interpretation of the written word relative to some published procedure.

Without wishing to be repetitious, in retrospect it must be again stated that this volume really represents the end result of many tedious and arduous investigations by numerous eminent scientists whose research efforts have appeared in the literature throughout the world. We are indeed humbly indebted to them, and to those journals, publishers, and organizations that granted special copyright permission to the authors.

Benjamin J. Gudzinowicz
Michael J. Gudzinowicz

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Chapter 1

NATURAL, PYROLYTIC, AND CARCINOGENIC PRODUCTS OF TOBACCO

The natural, pyrolytic, and carcinogenic products of tobacco will be discussed in Chapter 1 of this volume, and the natural constituents of marijuana and products isolated and identified as smoke by-products in Chapter 2.

With regard to the so-called active ingredients of tobacco and marijuana, Jaffe [1], in his discussion of drug addiction and drug abuse, noted that:

> Next to caffeine, nicotine (tobacco) is the substance most widely used for its effects on mood. That some persons develop a considerable psychological dependence on the smoking of tobacco is a matter of common experience. Some investigators feel that in chronic smokers distinct withdrawal phenomena follow the abrupt cessation of smoking. It is now generally accepted that the smoking of tobacco is linked to cardiovascular, pulmonary, and neoplastic disease. The inability of many persons to give up smoking in spite of these serious consequences makes it logical to include tobacco-using behavior as another form of compulsive drug use. There is already a vast literature on the pharmacological effects of chronic cigarette use, and technics for modifying the patterns of compulsive tobacco use are under study.

In addition to the above, the carcinogenic nature of tobacco smoke components is extremely important to personal health. Consequently, the GC and/or GC-MS conditions required to separate and identify such carcinogenics will be discussed in this chapter. Furthermore, GC methods for the analysis of polynuclear aromatics from sources other than tobacco smoke

having potential carcinogenic activity using both packed and capillary columns, will be included.

In Chapter 2, the pharmacology, absorption, metabolism, and excretion of delta-9-tetrahydrocannabinol (Δ^9-THC), the major psychoactive ingredient of marijuana, will be explored, as well as the GC/GC-MS analysis of its natural and pyrolytic products. With regard to marijuana use, Jaffe notes that "the remarkable similarity between the descriptions of the subjective effects of Δ^9-THC and those of LSD is the basis for the classification of the former as a psychedelic agent. Yet cannabis has sedative effects not seen with LSD, does not produce the sympathomimetic effects characteristic of other psychedelics, induces a low order of tolerance compared to the high degree seen with LSD, and exhibits no cross-tolerance with LSD. These features indicate a distinctly different mechanism of action."

I. CHEMICAL COMPOSITION OF TOBACCO LEAF

In 1968, Stedman [2] prepared a comprehensive review of the constituents of tobacco and tobacco smoke, surveying only those compounds for which claims of identity appear to be reasonably justified. The various constituents found in tobacco leaf in this 1968 survey are listed in Table 1.1. The list of known components in tobacco and smoke has risen since 1959 from about 400 to more than 1200, not including the individual components in complex substances such as the brown pigments and resins, which, at that time, had not been resolved. In the following text, the GC and/or GC-MS analysis of some of these organics that have been reported in the literature will be discussed, with special emphasis directed to the determination of nicotine and related alkaloids in tobacco leaf.

A. Nicotine and Other Tobacco Alkaloids

In Figure 1.1 are shown the structures of nicotine and related tobacco alkaloids. The metabolites of nicotine formed by oxidation, demethylation, and pyridine-N-methylation are illustrated in Figure 1.2.

As early as 1958, Quin [3] reported preliminary results clearly indicating the usefulness of gas chromatography in the study of tobacco alkaloids. Using a Perkin-Elmer model 154-B gas chromatograph equipped with a thermal conductivity detector and 1-m by 6-mm-o.d. U-shaped glass columns packed with polyglycol liquid stationary phases (20% by weight) coated on alkali-washed Firebrick, the retention times of the various compounds studied are listed in Table 1.2. As noted by Quin, the polyglycol columns exhibited good selectivity for the alkaloids, making possible the

TABLE 1.1

Chemical Composition of Tobacco Leaf[a]

1. Alkanes
   - Normal C_8-C_{35}
   - Iso C_{27}-C_{34}
   - Anteiso C_{28}, C_{30}, C_{32}, C_{34}
2. Isoprenoid hydrocarbons
   - α-Carotene
   - β-Carotene
   - Neo-β-carotene
   - Neophytadiene
   - Phytoene
   - Phytofluene
3. Sterols
   - Campesterol
   - Cholesterol
   - Ergosterol
   - β-Sitosterol
   - Stigmasterol
4. Monoterpenes
   - Borneol
   - 1-Linalool
5. Diterpenes
   - 3,8,13-Duvatriene-1,5-diol (α-,β-)
   - 4,8,13-Duvatriene-1,3-diol (α-,β-)
   - 12α-Hydroxy-13-epimanoyl oxide
   - α_2-Levantanolide
   - Levantenolide (α-,β-)
   - α-5,8-Oxido-3,9,13-duvatrien-1-ol
   - α-5,8-Oxido-3,9(17),13-duvatrien-1-ol
   - β-5,8-Oxido-3,9(17),13-duvatrien-1-ol
6. Triterpenes
   - β-Amyrin
7. Tetraterpenes
   - Cryptoxanthin
   - Flavoxanthin
   - Lutein
   - Neoxanthin
   - Violaxanthin
   - Xeaxanthin

(continued)

TABLE 1.1 (continued)

8. Trisesquiterpene
   Solanesol
9. Related isoprenoids
   6,8-Dihydroxy-11-isopropyl-4,8-dimethyl-14-oxo-4,9-pentadecadienoic acid
   Hexahydrofarnesylacetone
   Solanochromene
   Solanone
   Tocopherols
   Vitamin K_1 (2-methyl-3-phytyl-1,4-naphthoquinone)
10. Alcohols
    a. Aliphatic
       1-Docosanol
       1-Eicosanol
       Ethyl alcohol
       1-Heneicosanol
       1-Heptadecanol
       Methanol
       3-Methyl-1-pentanol
       1-Nonadecanol
       1-Octadecanol
       1-Tricosanol
    b. Aromatic
       Benzyl alcohol
       β-Phenethyl alcohol
    c. Polyols
       Diethylene glycol
       Glycerol
       Propylene glycol
       Triethylene glycol
    d. Cyclic
       Furfuryl alcohol
       Inositol
       Menthol
11. Esters
    β-Amyrenyl esters
    Benzyl acetate
    Dibutyl phthalate
    Di(2-ethylhexyl) phthalate
    Dipropyl phthalate
    Ethyl acetate
    Ethyl butyrate

TABLE 1.1 (continued)

Ethyl caproate
Ethyl isovalerate
Ethyl β-methylvalerate
Ethyl propionate
Ethyl valerate
Glycerides
Methyl and ethyl esters of higher fatty acids
Methyl salicylate
β-Phenethyl acetate
Solanesyl esters
Steryl esters
Undecyl acetate

12. Aldehydes
Acetaldehyde
Acrolein
p-Anisaldehyde
Benzaldehyde
Butyraldehyde
Crotonaldehyde
Formaldehyde
Furfural
Glycolaldehyde
Glyoxal
5-Hydroxymethylfurfural
Isobutyraldehyde
Isovaleraldehyde
Mesoxaldialdehyde
5-Methylfurfural
Methylglyoxal
Methylreductone
Propionaldehyde
Reductone
m-Tolualdehyde
Valeraldehyde

13. Ketones
Acetone
2-Butanone
4-Methyl-2-pentanone
Methyl α-pyrryl ketone
2-Pentanone

14. Quinones
9,10-Anthraquinone

(continued)

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