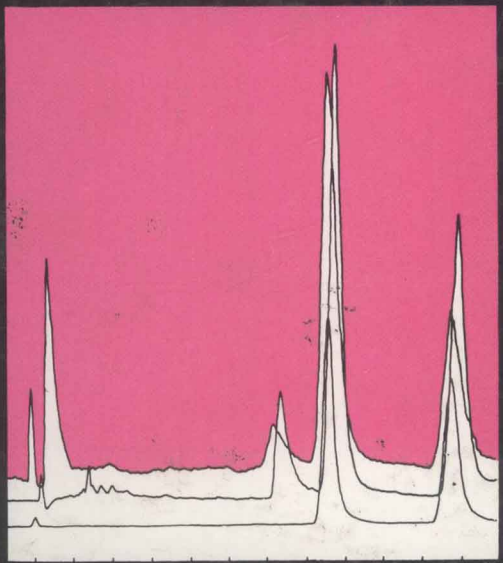
Analysis of Drugs and Metabolites by Gas Chromatography-Mass Spectrometry

Volume 2

Hypnotics, Anticonvulsants, and Sedatives



Benjamin J. Gudzinowicz
Michael J. Gudzinowicz

ANALYSIS OF DRUGS AND METABOLITES BY GAS CHROMATOGRAPHY–MASS SPECTROMETRY

VOLUME 2

Hypnotics, Anticonvulsants, and Sedatives

Benjamin J. Gudzinowicz
Department of Pathology
Rhode Island Hospital
Providence, Rhode Island

Michael J. Gudzinowicz
Center in Toxicology
Department of Biochemistry
School of Medicine
Vanderbilt University
Nashville, Tennessee

With the Assistance of

Horace F. Martin
Department of Pathology, Rhode Island Hospital
Providence, Rhode Island
and
Division of Biological and Medical Sciences
Brown University, Providence, Rhode Island
and

James L. Driscoll
Department of Pathology, Rhode Island Hospital
Providence,

M[illegible]ER, INC., [illegible]ne [illegible]d Basel

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Analysis of Drugs and Metabolites by Gas Chromatography–Mass Spectrometry

ANALYSIS OF DRUGS AND METABOLITES
BY GAS CHROMATOGRAPHY-MASS SPECTROMETRY

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

VOLUME 2: Hypnotics, Anticonvulsants, and Sedatives

IN PREPARATION

VOLUME 3: Antipsychotic, Antiemetic, and Antidepressant Drugs

VOLUME 4: Central Nervous System Stimulants

VOLUME 5: Analgesics, Local Anesthetics, and Antibiotics

OTHER VOLUMES IN PREPARATION

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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OTHER VOLUMES IN PREPARATION

Analysis of Drugs and Metabolites by Gas Chromatography–Mass Spectrometry

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Chapter 1

HYPNOTICS, ANTICONVULSANTS, AND SEDATIVES: BARBITURATE COMPOUNDS

Until recently (that is, the past ten years), gas chromatography found its greatest applicability in two major fields: the chemical and petroleum industries. Except for a relatively small number of analytical methods established for low-boiling materials of clinical interest and determined with conventional temperature-limited, insensitive instrumentation, very few complex pharmaceutical-medical-toxicological materials were amenable to analysis by gas chromatography. With the advent of more sensitive detection systems and sophisticated equipment, gas chromatography's latent potential was, so to speak, unleashed, permitting this technique to be applied to the determination of complex, high-boiling, high-molecular-weight materials of biological significance.

For example, in the field of psychopharmacology--the treatment of patients with emotional or mental disorders with psychoactive drugs--gas chromatography has provided the analyst with an appropriate tool for the separation of a large variety of drugs grouped as psychoactivators (psychostimulants, psychomotor stimulants, and psychic energizers), psychoinhibitors (hypnotics, sedatives, muscle relaxants, and tranquilizers), and psychomimetics, and the mass spectrometer has permitted their unequivocal identification through the use of "fingerprint" mass spectra derived from a specific mode of ionization and single or multiple ion (mass fragmentography) detection.

Since the "drug scene" is dynamic and local with respect to both time and place [1] and the drug subculture is constantly experimenting with

several drugs in combination to enhance the state of intoxication [2], Finkle [1] notes in his status report on forensic toxicology of drug abuse that heavy responsibilities accrue to chemists and toxicologists who provide analyses of blood and urine samples for drugs and narcotics and interpret results to physicians, nurses, probation officers, police, and the courts. Clinical chemists must now be concerned not only with therapeutic monitoring, analyzing biologic materials, and testing for the presence of unknown drugs, but must possess a current knowledge of the drugs of abuse since the drugs encountered may be in legal or illegal use, therapeutic or nontherapeutic, and used alone or in combination with others [2-4].

With regard to lists of drugs considered to be among the most commonly abused chemical substances, Froede [2] indicates on the basis of his data that this category is quite variable, depending on the availability of substances, fads, geographic locations, user preference, communication, desired effects, and relative affluence of users. On the other hand, although there are over 10,000 chemical substances and compounds available to the physician, the toxicologist is essentially concerned with fewer than 50 in actual toxicological analysis [1,5,6], including alcohol, barbiturates, benzodiazepine compounds, glutethimide, propoxyphene, methadone, carbamates, diphenylhydantoin, and the opium alkaloids. In Tables 1.1

TABLE 1.1

Predominant Drugs of Abuse[a,b]

1.	Alcohol
2.	Marijuana
3.	Barbiturates
4.	Amphetamines
5.	Opiates
6.	Synthetic narcotics
7.	Phencyclidine (PCP)
8.	Lysergic acid diethylamide (LSD)
9.	Cocaine
10.	Tranquilizers

[a]From Froede [2], courtesy of the American Association of Clinical Pathologists.

[b]In order of alleged frequency of usage. Alcohol has always been at the top of the list. The popularity of remaining drugs may vary according to geographic area, availability and cost.

TABLE 1.2

Depressants[a]

Barbiturates[b]

Commonly abused barbiturates:

- Secobarbital (Seconal)
- Pentobarbital (Nembutal)
- Amobarbital (Amytal)
- Amo-secobarbital (Tuinal)
- Butalbital (Sandoptal)
- Phenobarbital (Luminal)

Opiates and Synthetic Narcotics

Commonly abused opiates:

- Morphine
- Diacetylmorphine (heroin)
- Hydromorphone (Dilaudid)
- Ethylmorphine
- Methadone (Dolophine)
- Codeine
- Meperidine (Demerol)

Nonbarbiturate Hypnotics

Obtainable by prescription only:

- Methaqualone (Quaalude, Sopor)
- Methaqualone, chlorinated (Mecloqualone)
- Trichloroacetaldehyde (chloral hydrate)
- Ethclorvynol (Placidyl)
- Glutethimide (Doriden)
- Methyprylon (Noludar)
- Flurazepam (Dalmane)

Obtainable "over the counter:"

- Scopolamine, methapyrilene, salicylamide (Sominex)
- Scopolamine, methapyrilene (Sleep-Eze)
- Scopolamine, methapyrilene (Sleep-Tite)
- Scopolamine, belladonna (Asthmador)

Analgesics

- Pentazocine HCL (Talwin)
- Propoxyphene HCL (Darvon, SK-65, Progresic-65)
- Propoxyphene napsylate (Darvon N)
- Salicylates

[a]From Froede [2], courtesy of the American Society of Clinical Pathologists.

[b]Recently there has been a considerable increase in the abuse of the "barbs." This has been attributed to the shortage of the opiates, the availability of barbiturates, and a preference for their effects.

TABLE 1.3

Tranquilizers[a]

Major--phenothiazines
Chlorpromazine (Thorazine)
Prochlorperazine (Compazine)
Trifluoperazine (Stelazine)
Thioridazine (Mellaril)
Minor--benzodiazepines
Diazepam (Valium)
Chlordiazepoxide (Librium)
Oxazepam (Serax)
Carbamates
Meprobamate (Miltown, Equanil)
Ethinamate (Valmid)

[a]From Froede [2], courtesy of the American Society of Clinical Pathologists.

through 1.6 are listed many of the common drugs of abuse which, in many instances, have been successfully chromatographed and will be discussed in subsequent volumes of this series. Because of the large variety of compounds of different chemical classes involved, no single method can be provided for their analysis. It is possible, however, to adopt basic principles regarding the isolation of drugs and their metabolic products from biological media which can be extremely useful when faced with samples containing unknown components. In such situations, general isolation techniques suitable for screening programs are necessary. This type of situation presents a more complex analytical problem than that involving a known, specific compound for which a procedure has been fully developed and evaluated (for example, the selection of the optimum conditions for isolation; the derivative that most suitably enhances the parent compound's volatility for subsequent chromatographic analysis; the best, as well as the most sensitive, specific detection system for quantitation, etc.). For many of the reasons cited above, in this chapter we will first consider (before looking at specific barbiturate procedures) general isolation methods that have been proposed as being suitable for screening purposes.

TABLE 1.4

Stimulants[a,b]

Amphetamine group
Amphetamine (Benzedrine, "Bam")
Dextroamphetamine (Dexedrine)
Methamphetamine (Methadrine, Desoxyn, "Bam")
Amphetamine equivalents
Phenmetrazine (Preludin)
Phendimetrazine (Plegine)
Methylphenidate (Ritalin)
Phentermine (Ionamin)
Antidepressants--MAO inhibitors (monoamine oxidase inhibitors)
Amitriptyline (Elavil)
Nortriptyline (Aventyl)
Imipramine (Tofranil)
Phenelzine sulfate (Nardil)
Other stimulants
Cocaine
Procaine, lidocaine
Caffeine
Ephedrine HCL
Phenyloxazolidine (Pemoline)

[a]From Froede [2], courtesy of the American Society of Clinical Pathologists.

[b]A wide variety of stimulants are available either as a single drug or in combination with other stimulants or depressants.