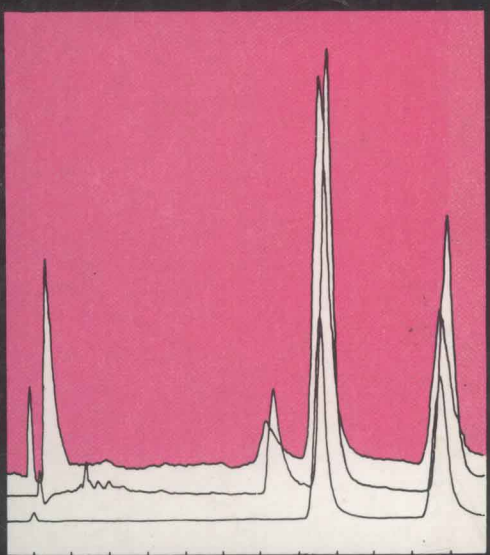
Analysis of Drugs and Metabolites by Gas Chromatography-Mass Spectrometry

Volume 3

Antipsychotic, Antiemetic, and Antidepressant Drugs



Benjamin J. Gudzinowicz
Michael J. Gudzinowicz

ANALYSIS OF DRUGS AND METABOLITES BY GAS CHROMATOGRAPHY–MASS SPECTROMETRY

VOLUME 3

Antipsychotic, Antiemetic, and Antidepressant Drugs

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

MARCEI 'KER, INC. d Basel

Library of Congress Cataloging in Publication Data (Revised)

Gudzinowicz, Benjamin J
Analysis of drugs and metabolites by gas chromatography--mass spectrometry.

Includes bibliographical references and indexes.
CONTENTS: v. 1. Respiratory gases, volatile anesthetics, ethyl alcohol, and related toxicological materials.--v. 2. Hypnotics, anticonvulsants, and sedatives.--v. 3. Antipsychotic, antienetic, and antidepressant drugs.
1. Drugs--Analysis. 2. Gas chromatography. 3. Mass spectrometry. 4. Drug metabolism. I. Gudzinowicz, Michael J., joint author. II. Title.
[DNLM: 1. Drugs--Analysis. 2. Chromatography, Gas. 3. Spectrum analysis, Mass. QV25 G923a]
RS189. G83 615'.1901 76-56481
ISBN: 0-8247-6586-9

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

Current printing (last digit):
10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA

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

VOLUME 3: Antipsychotic, Antiemetic, and Antidepressant Drugs

IN PREPARATION

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

CONTENTS OF OTHER VOLUMES

OTHER VOLUMES IN PREPARATION

CONTENTS

Chapter 1

ANTIPSYCHOTIC AND ANTIEMETIC DRUGS: PHENOTHIAZINE, BUTYROPHENONE, AND THIOXANTHENE DERIVATIVES

In the category comprising drugs with antipsychotic (psychosedative) and antiemetic activity belong for the most part the neuroleptic phenothiazine, butyrophenone, and thioxanthene derivatives. As noted by Jucker [1], "the great success of chlorpromazine and reserpine has resulted in tremendous interest in phenothiazine derivatives and reserpine analogues. In the last few years, thousands of new phenothiazine compounds have been synthesized and tested pharmacologically and to some extent clinically; this has resulted in the development of a considerable number of practically applicable drugs. . . . The success of phenothiazine derivatives in the treatment of psychic disturbances suggested substitution of the phenothiazine tricyclic system with analogous three-ring systems. A series of thioxanthene derivatives resulted. Their activity is strongly reminiscent of the phenothiazine neuroleptics with antidepressant activity." Although substituted butyrophenones have been used as major tranquilizers, particularly in psychiatry, the tranquilizing (so-called neuroleptic) butyrophenones are used also in anesthesiology in combination with some potent narcotic analgesic [2].

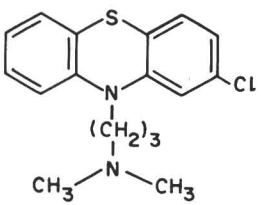
I. PHENOTHIAZINE DERIVATIVES

Of the three drug species noted above, the largest single group is comprised of phenothiazine derivatives. Since the introduction in 1952 of the

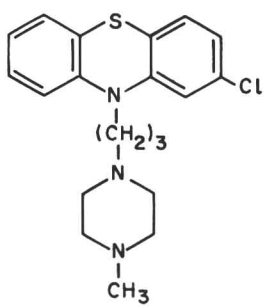
first synthetic tranquilizer, chlorpromazine, the phenothiazines synthesized can be divided into three main subdivisions: (1) compounds resembling chlorpromazine that contain a three-carbon chain grouping attached to the nitrogen of the phenothiazine nucleus, (2) compounds that contain a piperazine ring on the three-carbon chain, and (3) compounds that have a piperidine group on the side chain. Within themselves, all groups differ only by the nature of the substituent at the 2-position of the phenothiazine nucleus, as illustrated in Table 1.1, which contains the structures of some of the more common phenothiazine therapeutic agents.

TABLE 1.1

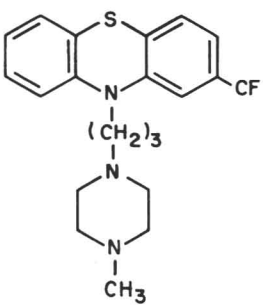
Structures of Some Phenothiazine Drugs



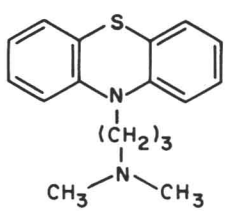
Chlorpromazine



Prochlorperazine

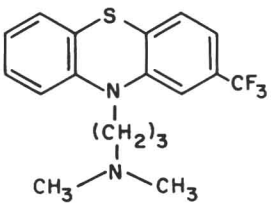


Trifluoperazine

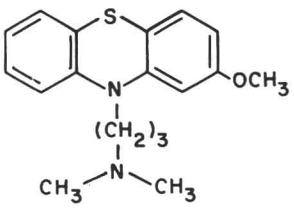


Promazine

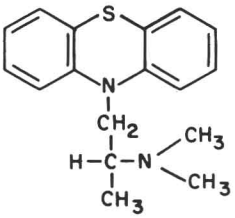
TABLE 1.1 (continued)



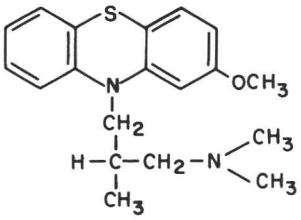
Triflupromazine



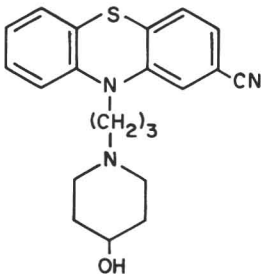
Methoxypromazine



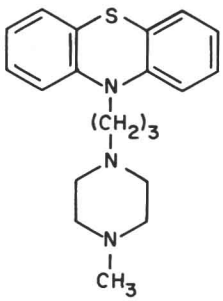
Promethazine



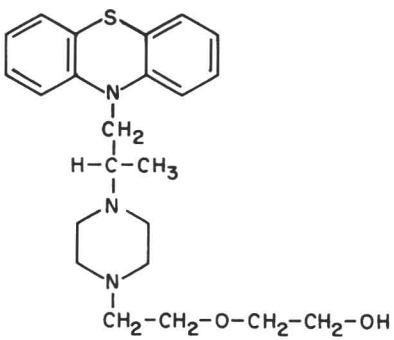
Methotrimeprazine
(Levomepromazine)



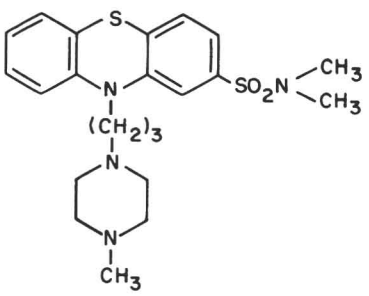
Propericiazine



Perazine

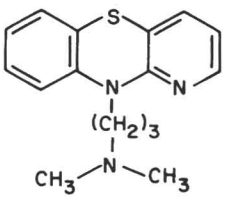


Dixyrazine

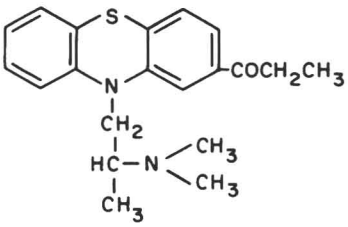


Thioproperazine

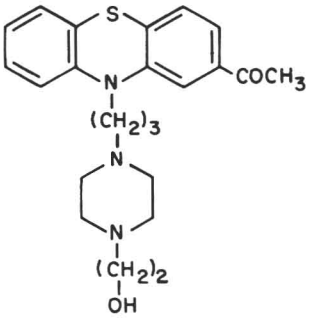
TABLE 1.1 (continued)



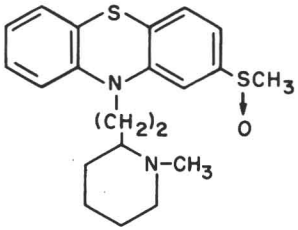
Prothipendyl



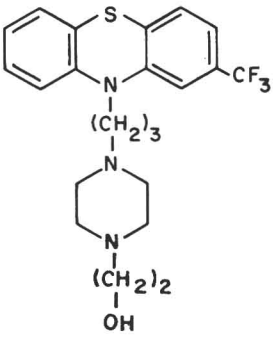
Propiomazine



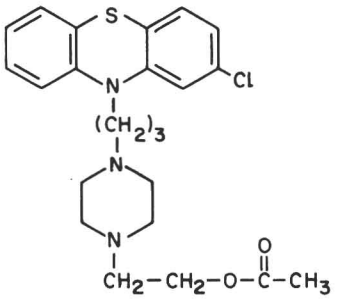
Acetophenazine



Mesoridazine

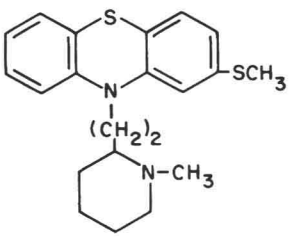


Fluphenazine

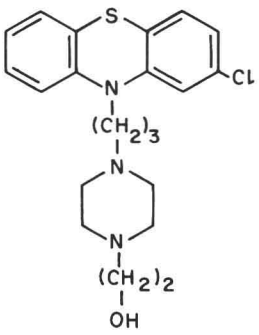


Thiopropazate

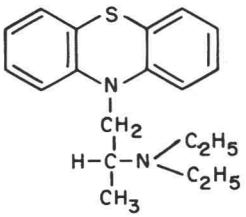
TABLE 1.1 (continued)



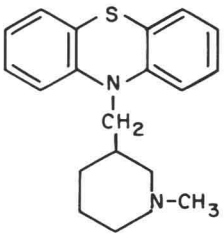
Thioridazine



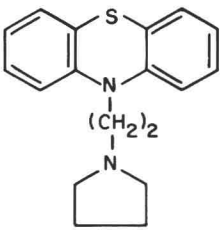
Perphenazine



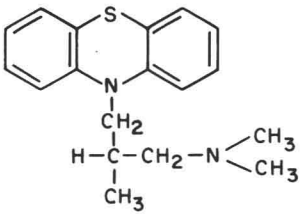
Ethopropazine



Mepazine

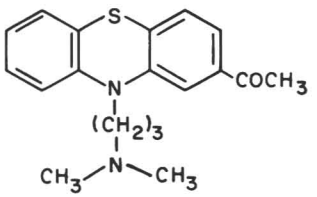


Pyrathiazine

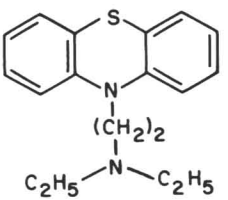


Trimeprazine

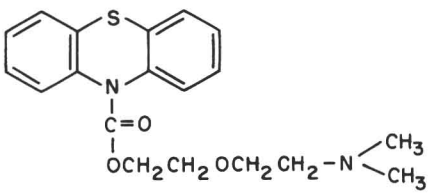
TABLE 1.1 (continued)



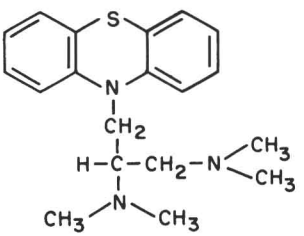
Acetopromazine



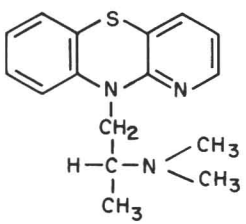
Diethazine



Dimethoxanate



Aminopromazine



Isothipendyl

In recent years, gas chromatography has assumed a position of greater analytical significance for both the detection and quantitative determination of complex compounds of pharmacological importance. Relative to the analysis of psychoactive phenothiazines, the normal methods for determining these drugs and their metabolites in biological media, that is, urine, blood, and feces, have been based on a variety of analytical techniques such as paper chromatography [3-9], fluorescence [10,11], ^{14}C and ^{35}S labeling [12], electrophoresis [13-15], color reactions [16], and electron spin resonance [17]. In most instances, the methods are nonspecific, insensitive to low concentrations, or time consuming.