Instrumental Data for Drug Analysis

Second Edition

Volume 1

Terry Mills III and J. Conrad Roberson

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INSTRUMENTAL DATA FOR DRUG ANALYSIS

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PREFACE

Almost everyone engaged in the analysis of drug-related compounds, whether in the forensic, clinical, or university laboratory, has an accumulation of analytical data and thus has acquired a data base of sorts for the analysis of these compounds. Unfortunately, many of these compilations contain a number of unauthenticated "standards" acquired over a long period of time using various techniques and, perhaps, several generations of instrumentation. Some of the information contained in *Instrumental Data for Drug Analysis* is available in the literature; however, there is no single source that contains timely, quality data of this type presented in a large, easily usable format. This four volume set is the result of our desire to provide each laboratory in our own system with an authentic, up-to-date data base for the instrumental analysis of drugs.

These volumes are neither a text nor a cookbook. They contain no analytical methods. They do provide the trained chemist with a single source of accurate instrumental data on twelve hundred drug-related compounds. We have included what we feel are the six currently most popular analytical techniques: ultraviolet (UV) spectrophotometry, infrared (IR) spectrophotometry, proton nuclear magnetic resonance (NMR) spectrometry, mass spectrometry (MS), gas chromatography (GC), and high pressure liquid chromatography (HPLC). As we felt that the quality of data presented was of paramount importance in a reference source, we generated all of our data in our laboratory under uniform, reproducible conditions using state-of-the-art technology and verified chemical standards.

In the second edition, we have included several new appendixes. A collection of supplemental infrared and nuclear magnetic resonance spectra comprises two of these appendixes. In these appendixes we have included many useful spectra not included in the main text. For those users who do not have the assistance of computer search systems, we have compiled an infrared peak table index. Another new appendix is the molecular formula index. All of the NMR data has been revised using a 300 MHz FTNMR system. The MS data has been replotted in a more readable format.

We hope that this book will be as helpful to all analytical chemists as it is to us.

Terry Mills III
J. Conrad Roberson

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We are grateful to Dr. Larry B. Howard, Director of the Division of Forensic Sciences, and Mr. E.P. Peters, the late Director of the Georgia Bureau of Investigation, for making the facilities of the crime laboratory available for this work.

The authors wish to thank the Hewlett-Packard Company for the use of the H-P 8450A UV-Vis spectrophotometer.

We appreciate the assistance of Ron Haney and Patricia Price for helping with the mass spectral data. We also appreciate the members of the crime laboratory drug identification staff for their help.

Our thanks are expressed to the following suppliers of drug standards: Abbott Laboratories; Adria Laboratories; Beechman Laboratories; Biocraft Laboratories; Brown Pharmaceutical Company; Burroughs Wellcome Company; Ciba Pharmaceutical Company; the Canadian Government; Danbury Pharmacal; Dermik Laboratories; Dista Products Company; Dorsey Laboratories; Drug Enforcement Administration (DEA); E.I. Dupont DeNemours & Company; Elder Pharmaceuticals; Geigy Pharmaceuticals; Graymor Chemical Company; Hoechst-Roussel Pharmaceuticals; Hoffmann-Laroche Inc.; Ives Laboratories; Jacobus Pharmaceutical Company; Janssen Pharmaceutica; Knoll Pharmaceutical Company; Lederle Laboratories; Lilly Research Laboratories; Marion Laboratories; McNeil Pharmaceutical; Mead Johnson Pharmaceutical Division; Merck Sharp & Dohme Research Laboratories; Merrell Dow Pharmaceuticals; Miles Pharmaceuticals; National Institute of Drug Abuse (NIDA); Norwick-Eaton Pharmaceuticals; O'Neal, Jones & Feldman, Inc.; Ortho Pharmaceutical Corporation; Parke-Davis Pharmaceutical Company; Pennwalt Pharmaceutical Division; Pfizer Laboratories Division; William P. Polythress & Company; Reid-Provident Laboratories; A.H. Robins Company; Roerig Pharmaceuticals; Ross Laboratories; Sandoz Pharmaceutical Division; R.P. Scherer Corporation; Schering Corporation; Searle Pharmaceuticals; Sigma Chemical Company; Smith Kline & French Laboratories; E.R. Squibb & Sons, Inc.; Sterling-Winthrop Research Institute; Stuart Pharmaceuticals; Syntex Laboratories; Tutag Pharmaceuticals; United Nations; Upjohn Company; USV Pharmaceutical Corporation; Wallace Laboratories; Warner Lambert Company; Westwood Pharmaceuticals; Winthrop Laboratories; and Wyeth Laboratories.

INTRODUCTION

This reference book consists of chromatographic and spectral data on twelve hundred selected compounds. Each monograph is accompanied by UV, NMR, IR, and MS spectra and tabulation of GC and HPLC data where available. The information on a specific compound should be located by using the alphabetical index, the GC, IR, and MS tables or the UV maxima indexes found in the back of the book.

CHEMICAL STANDARDS

Every effort was made to secure chemical standards of the highest purity available. Where possible, the data presented in this book were obtained from samples secured as "pure" drug standards from the Drug Enforcement Administration (DEA), Applied Sciences Laboratories, United States Pharmacopeial Convention, Inc., Sigma Chemical Company, or various pharmaceutical companies. When necessary samples were purified by extraction methods followed by recrystallization to constant literature melting points and verified by thin layer chromatography. In almost all cases, the data presented on each compound were obtained from one sample. The sample purity was usually greater than 95% and, in many cases, greater than 99%. Where available, each spectrum generated was confirmed by previously published data.

DRUG MONOGRAPHS

Each monograph chiefly consists of the chemical title, molecular formula and weights, synonyms and trade names, usage, and structure. In most cases the chemical title, which appears above each spectrum, either is listed in the Federal Drug Code, Title 21, or is the most common name. The molecular weights are based on the current acceptable IUPAC convention to the nearest hundredth of a decimal place. The value in parentheses represents the weight using the most abundant naturally occurring isotope of each element.

Generally, the first name listed as the synonym is the uninverted form of the Chemical Abstracts' name. Other alternate names such as common chemical or trivial names follow the Chemical Abstracts listing. The trade names include those that are currently available as listed in the 1986 Physician's Desk Reference (PDR). The major therapeutic actions of the drugs are listed in the use section. The structure presented on each compound is, in most cases, not intended to represent spatial configuration.

GAS CHROMATOGRAPHY

The gas chromatography data are presented in the monographs in the form of Kovats indexes calculated by the following formula

$$I = 100\left(2\frac{\log T_D/T_Y}{\log T_X T_Y} + X\right)$$

where

I = Kovats index
T_D = Retention time of the drug
T_X = Retention time of an even numbered normal hydrocarbon whose carbon number is X
T_Y = Retention time of an even numbered normal hydrocarbon whose carbon number is Y where $Y = X + 2$

and

$T_X \leq T_D \leq T_Y$

Each retention index is presented in the monograph with the temperature at which its T_D, T_X, and T_Y values were measured. All retention times were measured from the time of injection. A Hewlett-Packard 5830A gas chromatograph was used with an 18850A terminal, FID detector, and a 4′ x ¼″ column of 3% OV-1 Chromosorb WHP 80/100 mesh. The carrier gas was nitrogen at a flow rate of 32 ml/min. Large samples of drugs were used (10–100 μg) for injection. At these levels, a moderate change in the amount injected does not change the retention time significantly. To reproduce the results obtained in this book, the same temperature, column packing, carrier gas, gas flow rate, and column length should be used. A table of retention indexes appears in Appendix G.

HIGH PRESSURE LIQUID CHROMATOGRAPHY

High pressure liquid chromatography was carried out on either a Varian 5000 or Varian 6000 HPLC instrument. Most of the samples were chromatographed on a 30 cm x 4 mm SI-10 porous silica column (10 μ particle size) with a 2-in. guard column filled with Porasil A. The remaining samples were run on a 13 cm x 4 mm Lichrosorb NH_2 ($LiNH_2$) column with a 2-in. Co:Pell ODS guard column. The flow rate used was 2 ml/min with a column "dead volume" of 4 ml. A fixed wavelength (254 nm) UV detector was used to detect UV absorbing compounds. A refractive index detector was used for the remaining compounds. The eluted compounds were verified on a Hewlett-Packard 8451A diode array spectrophotometer. The following list of solvents were used

Solvent A: Methanol with 1 % NH OH
Solvent B: Methylene chloride
Solvent C: Cyclohexane
Solvent D: Acetonitrile
Solvent E: Deionized water

All organic solvents were purchased as HPLC grade solvents from Fisher Scientific Company.

The HPLC data are presented in the monographs in the form of Column Packing; Solvent; Retention time in minutes.

ULTRAVIOLET SPECTROPHOTOMETRY

The absorption spectra were obtained with either a Hewlett-Packard 8450A or 8451A diode array spectrophotometer and plotted as a wavelength versus transmittance from 220 nm to 340 nm. Sample solutions were prepared by dissolving an appropriate amount of chemical into the proper solvent. In the printed spectrum, the solvent solutions are represented by a solid line for the $0.2NH_2SO_4$ solu-

tion and by a dashed line for strongly basic solutions. Other solvents, when used, are identified on the individual spectra. A matched pair of Fisher-brand Suprasil ultraviolet cells were used for the reference and sample solutions. The solutions were made basic by the addition of several drops of concentrated sodium hydroxide solution.

A listing of compounds with their respective UV maxima values can be found in Appendix D.

MASS SPECTROMETRY

The mass spectra were acquired on a Hewlett-Packard 5985B GC/MS operating in the electron impact (EI) mode with an electron energy of 70 ev. Unless otherwise noted, the samples were introduced via a 5 % phenylmethyl silicone column into the ms source, which was maintained at 200°C.

Every effort was made to standardize the sample size and mass spectrometer tuning to ensure consistent spectra throughout this collection. Where it was necessary to manipulate the spectra, e.g., to remove traces of the injection solvent or column background, due care was exercised to avoid distorting the data. Mass calibration was checked several times a day, and the inertness of the interface was demonstrated daily by the analysis of cholesterol, which produced a 386/368 ion ratio of greater than 2:1.

In a few cases, the only appropriate means of introducing a sample was by direct insertion probe, also called solid probe or DIP. These spectra are identified where they occur in the book.

Finally, the mass spectra were plotted on a HP 7550A graphics plotter using a routine written especially for this work. Although prominent ions in each spectrum are labeled, the user should be aware that these masses were selected on the basis of abundance and may not indicate the most significant fragments for each compound.

A cumulative index of the mass spectra, sorted by base peak, is included as Appendix E.

NUCLEAR MAGNETIC RESONANCE SPECTROMETRY

The proton nuclear magnetic spectra were recorded on a General Electric QE-300 Superconducting FTNMR spectrometer operating at 300 MHz. This NMR spectrometer is equipped with a 70.5 KG NB-Ti superconducting magnet, a magnet bore of 44 mm and a dual $^{1}H/^{13}C$ 5-mm probe.

Samples were prepared by dissolving the compound in the appropriate solvent (Aldrich deuterochloroform 99.5 % containing 0.03 % TMS unless otherwise noted on the NMR spectrum). Where possible, the sample concentration was maintained at a level judged to be the best compromise between solute interactions and instrument response. In some instances, low solubility or low sample concentration (less than 5 mg of compound was available in many instances) has resulted in spectra showing high noise level or trace contamination. All spectra were observed at a constant thermostated probe temperature. Sample solutions were equilibrated to the probe temperature before the spectra were recorded. Most spectra were recorded at a spinning rate of 15 to 25 rps, 32 acquisitions with quadrature phase detection, observed frequency of 300.151851 MHz, spectral width of 6024 Hz, 32768 data size resolution, no line broading, and a pulse width of 2.33 μsec (30 deg). Most spectra include 0.03 % TMS as a reference. Precautions were taken in handling all NMR solvents to minimize contamination with atmospheric moisture.

Spectra of the various Aldrich NMR solvents used can be found in Appendix A.

The nuclear magnetic resonance spectra presented in this book as well as Carbon-13 and standard APT (Attached Proton Test) experimental data are available in computer library form from General Electric NMR Instrument Division.

INFRARED SPECTROPHOTOMETRY

The infrared spectra were produced using a Nicolet 170SX Fourier Transform Infrared spectrometer. This infrared spectrometer is equipped with a laser-referenced Michelson interferometer with

an absolute wavenumber accuracy specified better than ± 0.01 cm^{-1}. As many grating and prism spectrophotometers are currently in use, the constant spectral resolution was kept at 4 cm^{-1} by collecting 64 one-second scans (4096 data points/scan). Because the FT-IR spectrometer is a single beam instrument, some of the spectra may have small absorption bands due to CO_2 present in the sample chamber when the data were collected. This doublet can be found at 2360 cm^{-1} and 2340 cm^{-1}.

Unless otherwise stated, the compounds were prepared for spectral analysis by using potassium bromide (KBr) pellets. The KBr powder was oven dried and then kept in a desiccator. Every effort was made to remove water; however, as many times both the sample as well as the KBr were hygroscopic, water bands may have appeared in some of the spectra. It must be noted that spectra reproducibility may be difficult to regulate without careful weighing of both the KBr and the sample. In addition, there may be KBr interactions with the sample, especially amine compounds. Although these complications exist, KBr pellets generally give much better resolution than other techniques. Each spectrum was expanded to give full scale presentation of the data. Representative peaks as listed on each spectrum are intended to aid the user. They were determined by a Peak-Picker Program and should be used only for approximate values. A cumulative index of the infrared spectra, sorted by prominent peaks identified by a computer program with an accuracy of ± 0.1 cm^{-1}, is included in Appendix F. Example of a blank KBr pellet at various transmittance values can be found in Appendix A.

The infrared spectra presented in this book are also available in computer library form from Nicolet Instrument Corporation, Bomem, Inc., Brucker/IBM Instrument Corporation, Digilab Instrument Corporation, Analect Instruments, Mattson Instruments, and Perkin-Elmer Corporation.

CONTENTS

Drug Data
Acebutolol-Doxapram

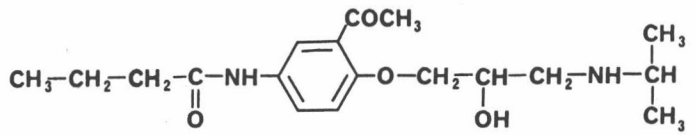
2

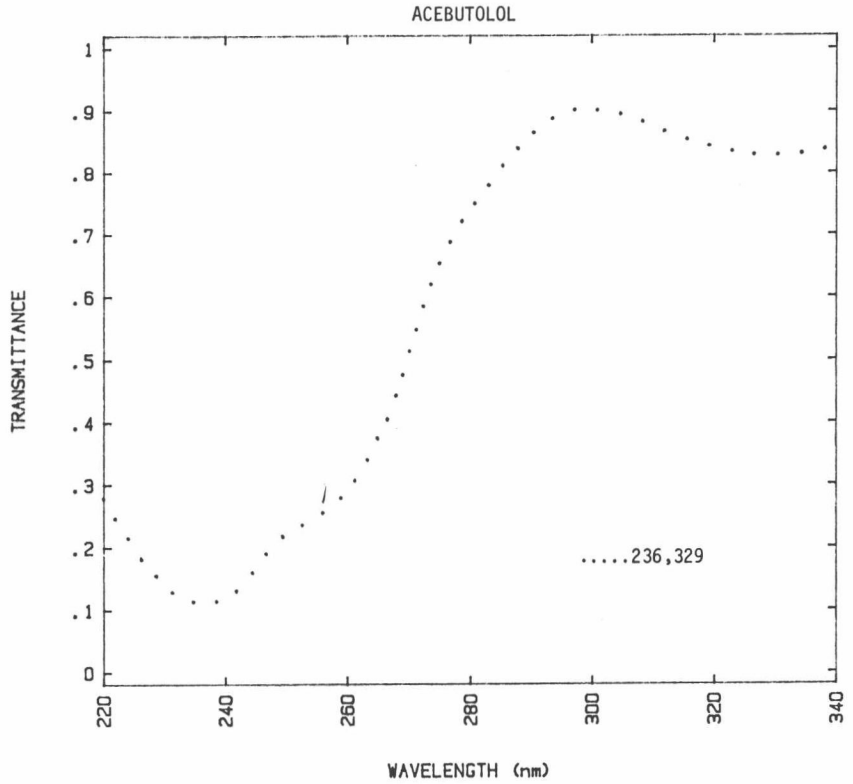
ACEBUTOLOL

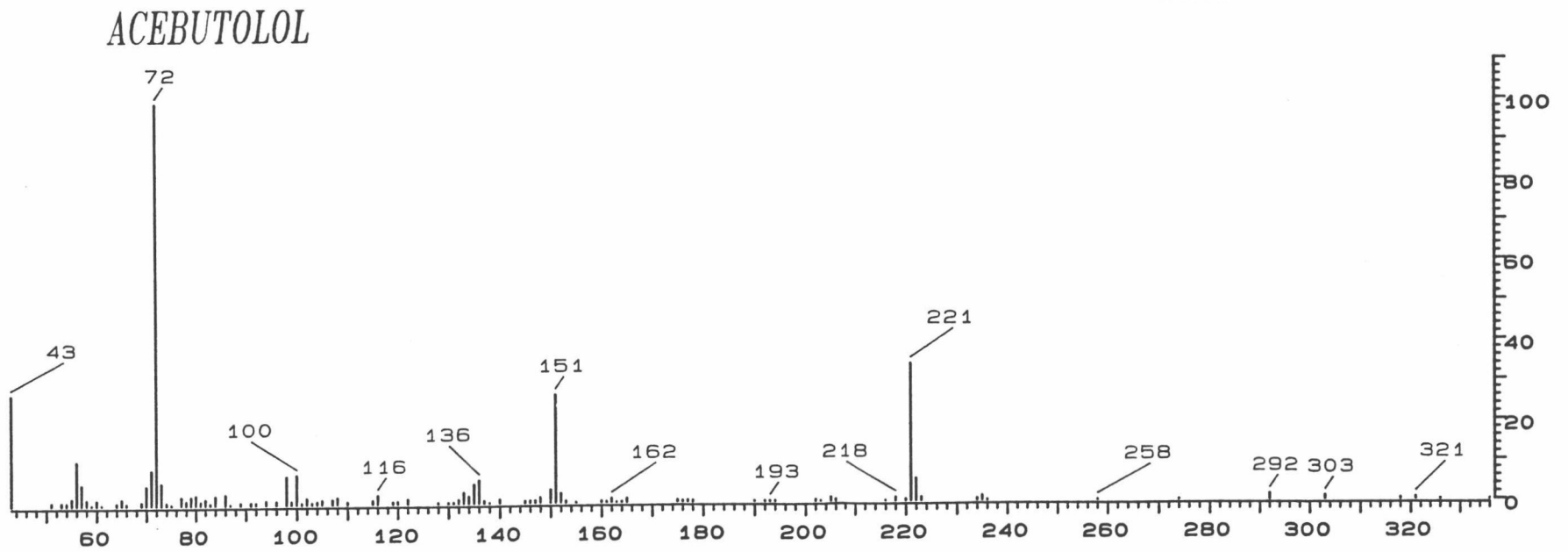
$C_{18}H_{28}N_2O_4$

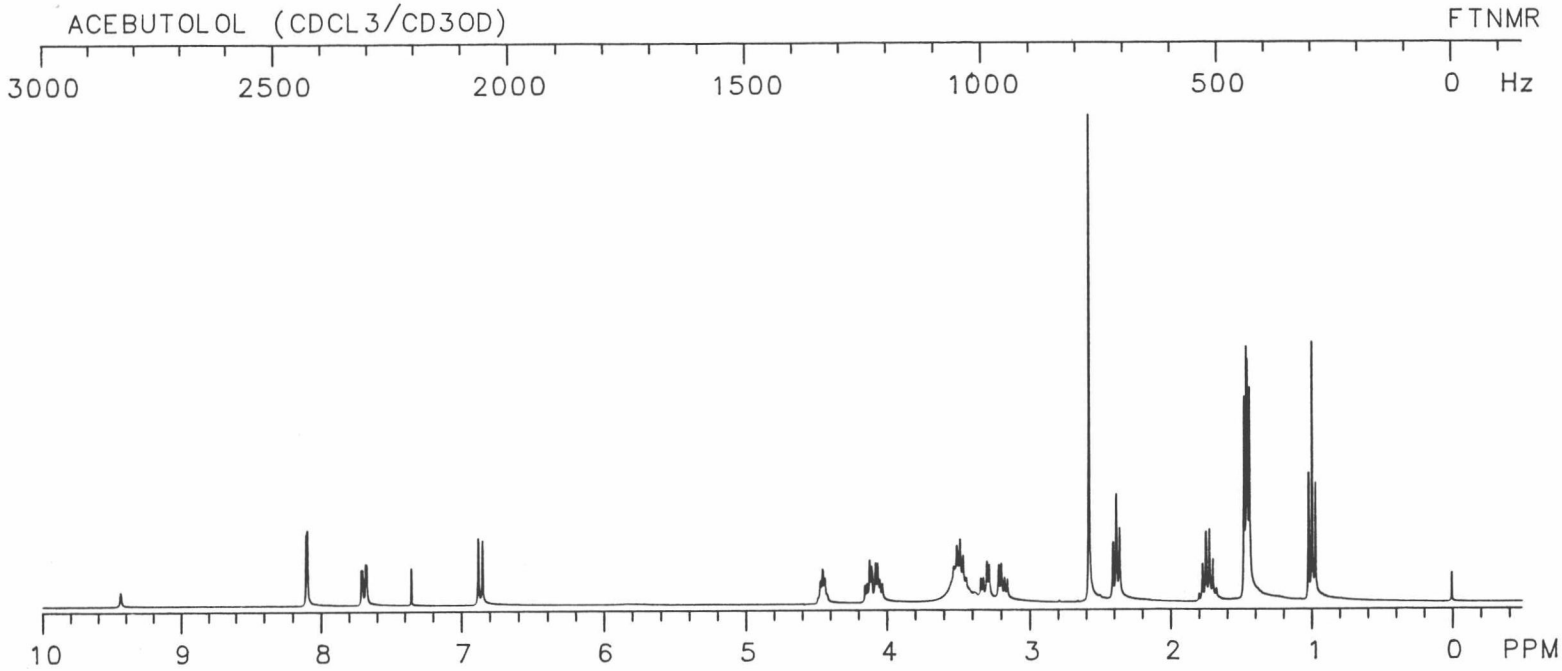
Molecular weight: 336.43 (336.21)
Synonyms: N-[3-acetyl-4-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]-phenyl]butanamide
Trade names: Neptall, Prent, Secadrex, Sectral

Use: Beta-Adrenergic blocker
HPLC: Si-10; 20A:80B; 7.9
GC: 2185; 250°C









PEAK LISTING

#	HT	PPM
1	24	.96
2	53	.99
3	26	1.01
4	43	1.43
5	49	1.45
6	52	1.45
7	42	1.47
8	15	1.72
9	14	1.74
10	15	2.35
11	22	2.38
12	99	2.57
13	13	3.48
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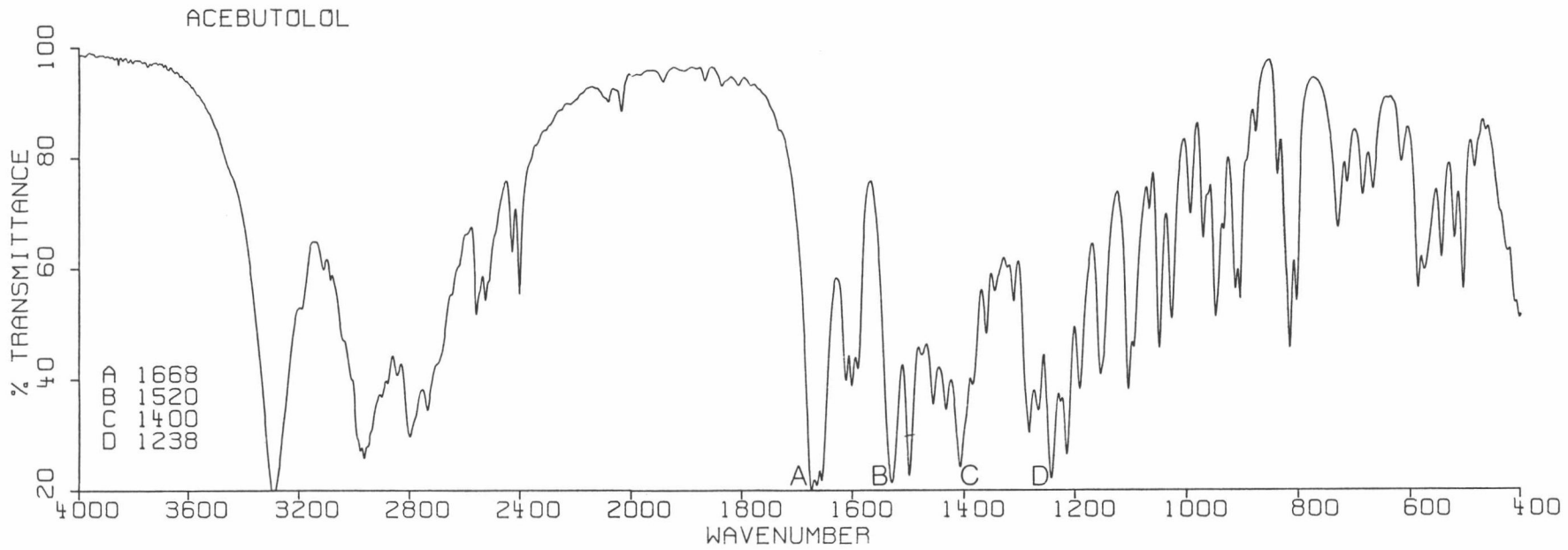
15	13	6.87
16	15	8.09
17	14	8.10



4

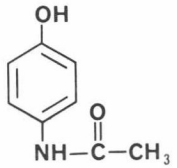
ACETAMINOPHEN

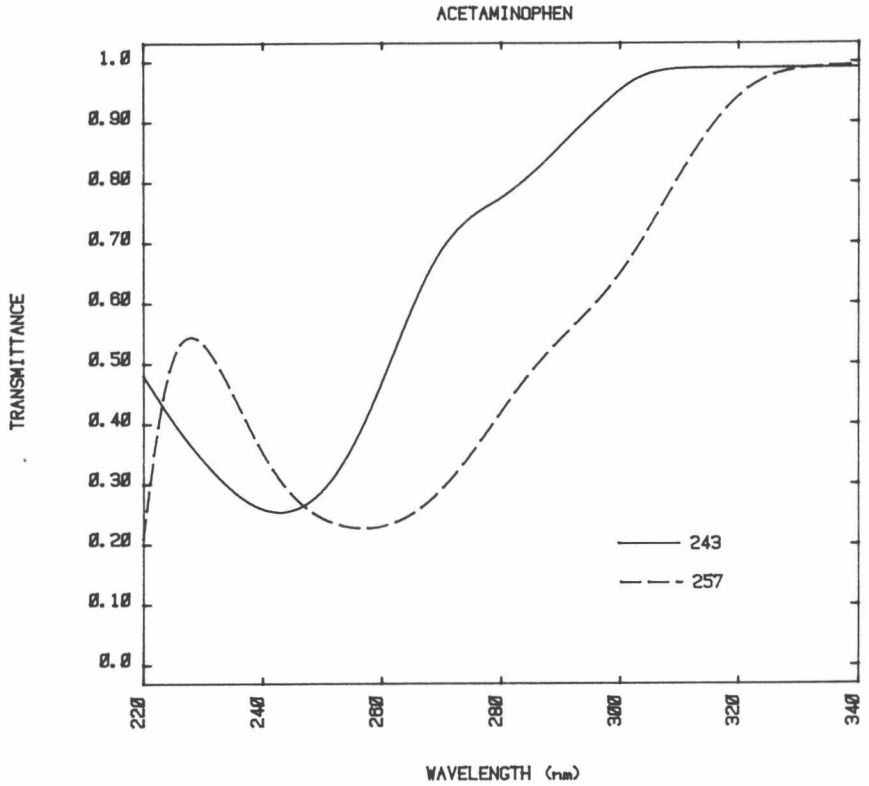
$C_8H_9NO_2$

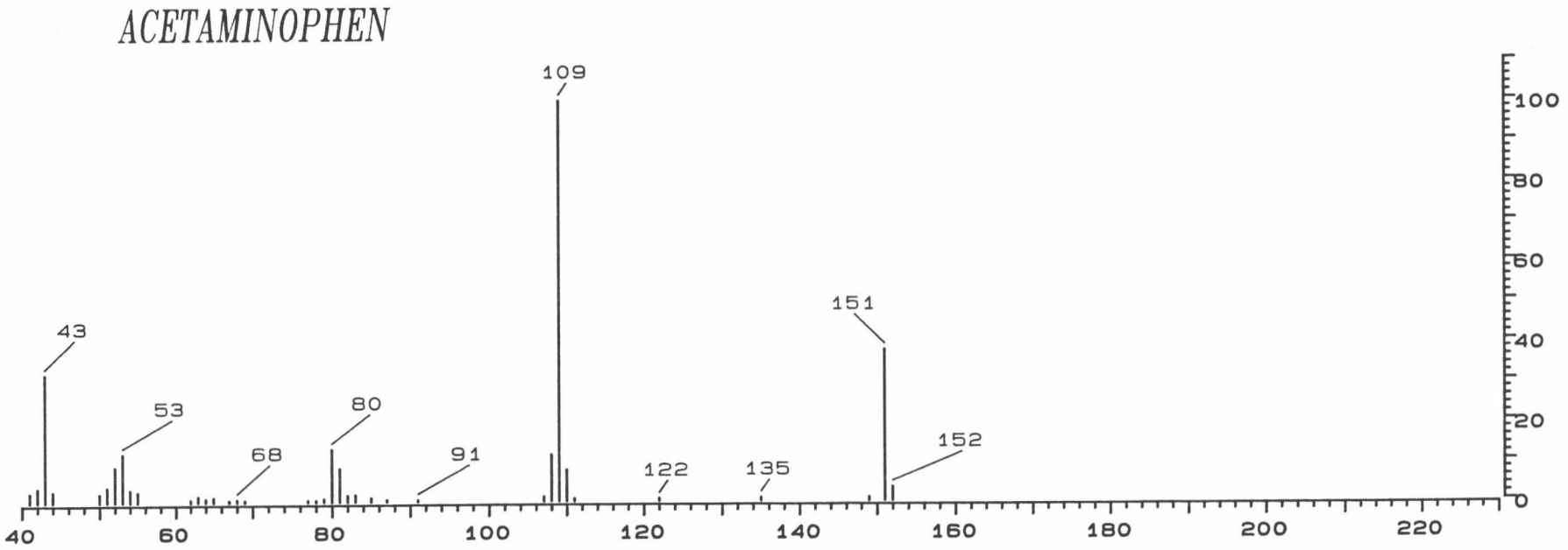
Molecular weight: 151.16 (151.06)
Synonyms: N-(4-Hydroxyphenyl)acetamide; paracetamol

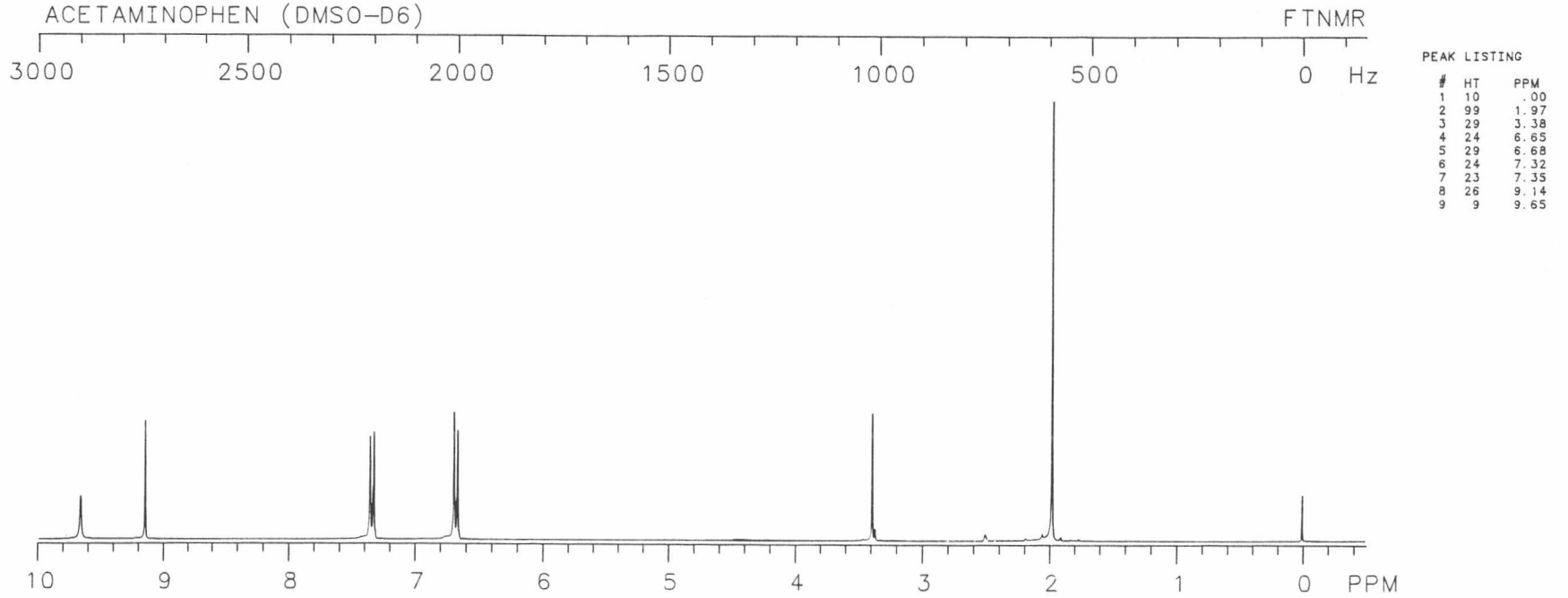
Trade names: Tylenol, Datril, APAP

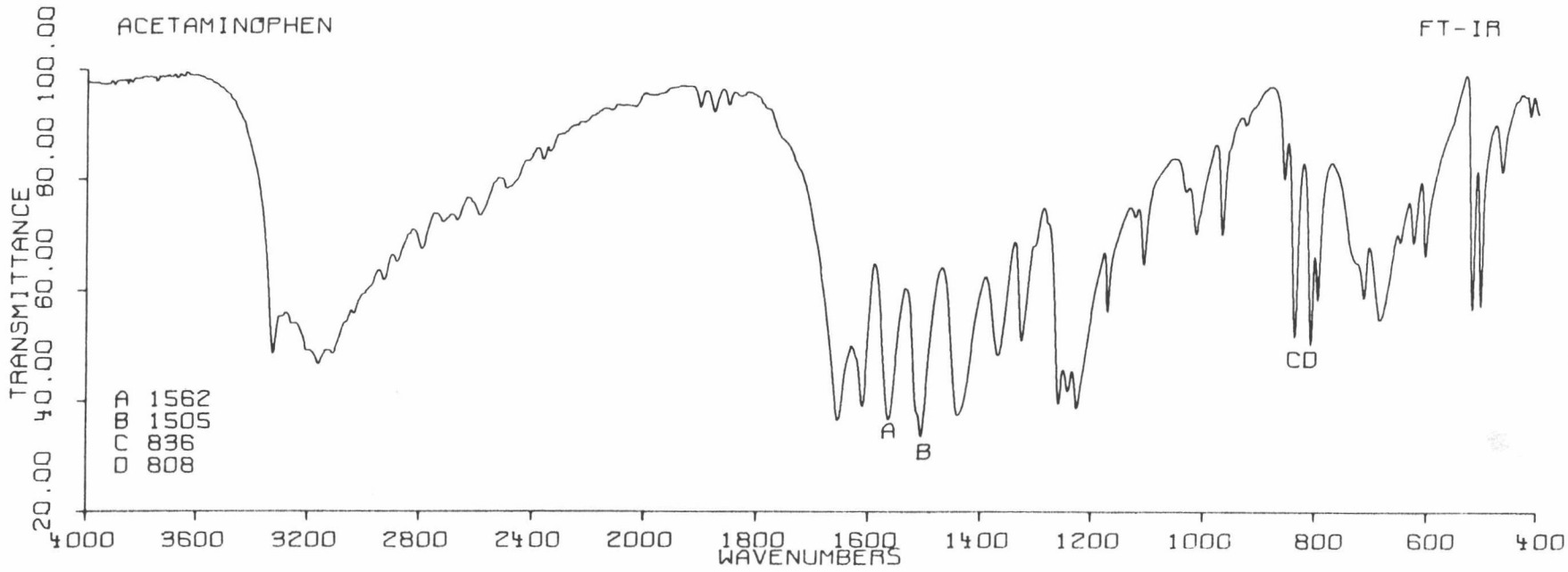
Use: Analgesic, antipyretic
HPLC: Si-10; 5A:95B; 5.5
GC: 1768; 200°C








ACETAMINOPHEN (DMSO-D6)
FTNMR
3000
2500
2000
1500
1000
500
0 Hz
10
9
8
7
6
5
4
3
2
1
0 PPM
PEAK LISTING
HT PPM
1 10 .00
2 99 1.97
3 29 3.38
4 24 6.65
5 29 6.68
6 24 7.32
7 23 7.35
8 26 9.14
9 9 9.65


ACETAMINOPHEN
FT-IR
TRANSMITTANCE
20.00 40.00 60.00 80.00 100.00
A 1562
B 1505
C 836
D 808
A
B
CD
4000
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400
WAVENUMBERS

ACETANILIDE

C_8H_9NO

Molecular weight: 135.17 (135.07)
Synonyms: N-Phenylacetamide; acetylaminobenzene

Trade names:

Use: Antipyretic, analgesic
HPLC: Si-10; 2A:98B; 5.0
GC: 1404; 140°C