ANALYTICAL PROFILES OF DRUG SUBSTANCES

Vol. 2

Edited by

KLAUS FLOREY

Analytical Profiles of Drug Substances

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FOPEWORD

The concept for gathering together and publishing pertinent information on the physical and chemical properties of various official and new drug substances had its origin with the members of the Section on Pharmaceutical Analysis and Quality Control of the Academy of Pharmaceutical Sciences. More than two years of consideration preceded the authorization of this ambitious project by the Executive Committee of the Academy in the Spring of 1970. The immediate and virtually spontaneous enlistment of the first group of contributors to this work attested to its importance and the wisdom of pursuing its publication.

By coincidence, the delegates to the sesquicentennial anniversary meeting of the United States Pharmacopeial Convention, Inc., in Washington, D.C. on April 8-10, 1970, adopted the following resolution:

> Whereas widespread interest has been expressed in the inclusion of additional information about physical and chemical properties of drugs recognized in the United States Pharmacopeia
>
> *Be It Resolved* that the Board of Trustees consider publishing in the Pharmacopeia, or in a companion publication, information on such attributes as solubilities, pH and pK values, spectra and spectrophotometric constants, and stability data, pertaining to pharmacopeial drugs.

The U.S.P.C. Board of Trustees unanimously approved the resolution in principle on June 4, 1970 and authorized the Director of Revision to include in the U.S.P. monographs such physical-chemical information as he deemed proper and also to cooperate with the Academy of Pharmaceutical Sciences to secure the publication of other physical-chemical data.

It was my privilege to be the President of the Academy during the period when *Analytical Profiles* was under consideration. It is my unusual and unique honor as President of the Academy and Director of U.S.P. Revision to assist in the institution and dedication of this first volume. I trust that it will serve immeasurably in providing the scientific community with an authoritative source of information on the properties of many of our important drug compounds.

January 1971

Thomas J. Macek

PREFACE

Although the official compendia define a drug substance as to identity, purity, strength, and quality, they normally do not provide other physical or chemical data, nor do they list methods of synthesis or pathways of physical or biological degradation and metabolism. At present such information is scattered through the scientific literature and the files of pharmaceutical laboratories.

For drug substances important enough to be accorded monographs in the official compendia such supplemental information should also be made readily available. To this end the Pharmaceutical Analysis Section, Academy of Pharmaceutical Sciences, has started a cooperative venture to compile and publish *Analytical Profiles of Drug Substances* in a series of volumes of which this is the second. It is also planned to revise and update these profiles at suitable intervals.

Our endeavor has been made possible through the encouragement we have received from many sources and through the enthusiasm and cooperative spirit of our contributors. For coining the term Analytical Profile we are indebted to Dr. James L. Johnson of the Upjohn Company.

We hope that this, our contribution to the better understanding of drug characteristics, will prove to be useful. We welcome new collaborators, and we invite comment and counsel to guide the infant to maturity.

Klaus Florey

CONTENTS

AMPICILLIN

Eugene Ivashkiv

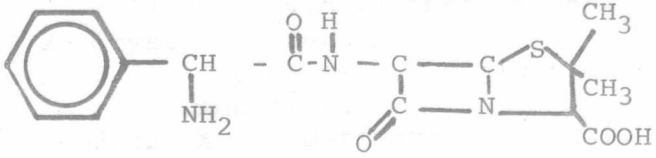
Table of Contents

1. Description

1.1 Name: Ampicillin

Ampicillin[1,2,3] is designated by Chemical Abstracts as D-(2-amino-2-phenyl-acetamido)-3,3-dimethyl-oxo-4-thia-1-azabicyclo [3.2.0] heptane-2-carboxylic acid. Ampicillin is also known as 6[D(-)-α-aminophenylacetamido] penicillanic acid, D(-)-α-aminobenzylpenicillin[4] and α-aminobenzylpenicillin[5].

1.2 Formula and Molecular Weight



$C_{16}H_{19}N_3O_4S$ 349.41

1.3 Isomers

The presence of a symmetric C atom in the side chain provides optical isomer[6]. The D-isomer, D(-)-α-aminobenzylpenicillin, is more active than the L-isomer, L(-)-α-aminobenzyl-penicillin[7]. The synthesis of ampicillin epimer has been reported[8,9].

1.4 Hydrates

It has been reported that ampicillin can exist in anhydrous[10-13], monohydrate[14,15] sesquihydrate[16] and trihydrate[17,18] forms. Austin, et al.[19] postulate that ampicillin exists in anhydrous or trihydrate forms only. Refer to section 2.21.

1.5 Salts

Potassium and sodium salts of ampicillin[20-29], human lysozyme ampicillin salt[30], 2-nitro-1,3-indandione salt[31], and the ampicillin salt of kanamycin[32] have been prepared.

1.6 Appearance, Color and Odor

Ampicillin is a free-flowing, white crystalline powder. It has an odor characteristic of penicillins.

2. Physical Properties

2.1 Spectra

2.11 Infrared Spectra

Substituted monocyclic β-lactams in solution show carbonyl absorption within the range 5.68-5.78μ[33]. When the β-lactam ring is fused to a thiazolidine ring, the carbonyl absorption occurs in the range 5.62-5.65μ. Morin and co-workers[34] have noted rough correspondence between the frequencies of the β-lactam carbonyl absorption and the biological activities of a series of penicillin derivatives.

The infrared spectra of penicillin analogues have been discussed[35]. The infrared spectrum of ampicillin trihydrate was measured on a Perkin-Elmer Model 21 double-beam spectrophotometer[36]. The infrared absorption of penicillin derivatives has been recorded and discussed[37]. Figure 1 and Figure 2 are the spectra of the Squibb Primary Reference Substances of ampicillin trihydrate and anhydrous ampicillin recorded as mineral oil mull and potassium bromide pellets with a Perkin-Elmer Model 21 spectrophotometer. Interpretation of the spectrum of ampicillin trihydrate has been reported[38] and is given in Table 1.

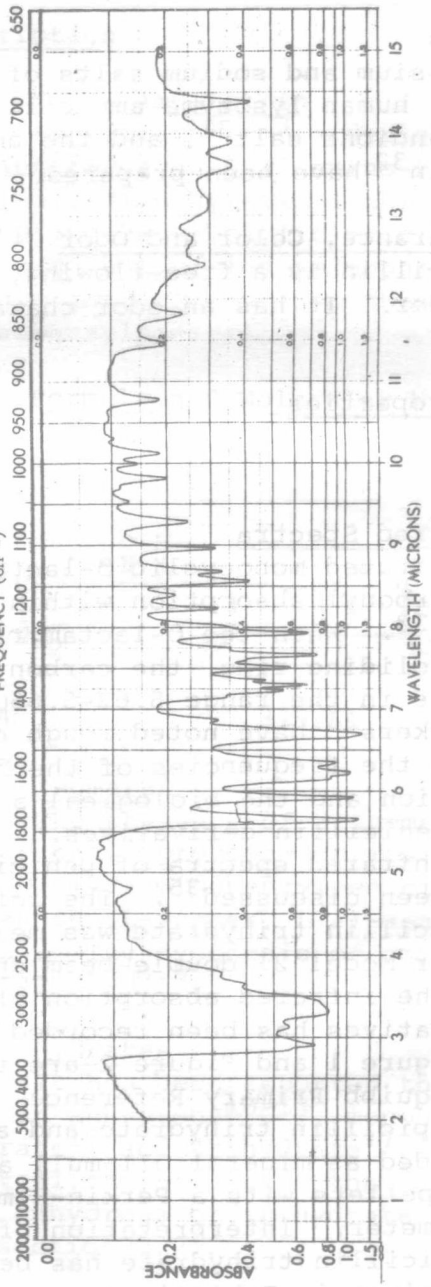


Figure 1. Infrared Spectrum of Ampicillin Trihydrate Squibb Reference Standard.

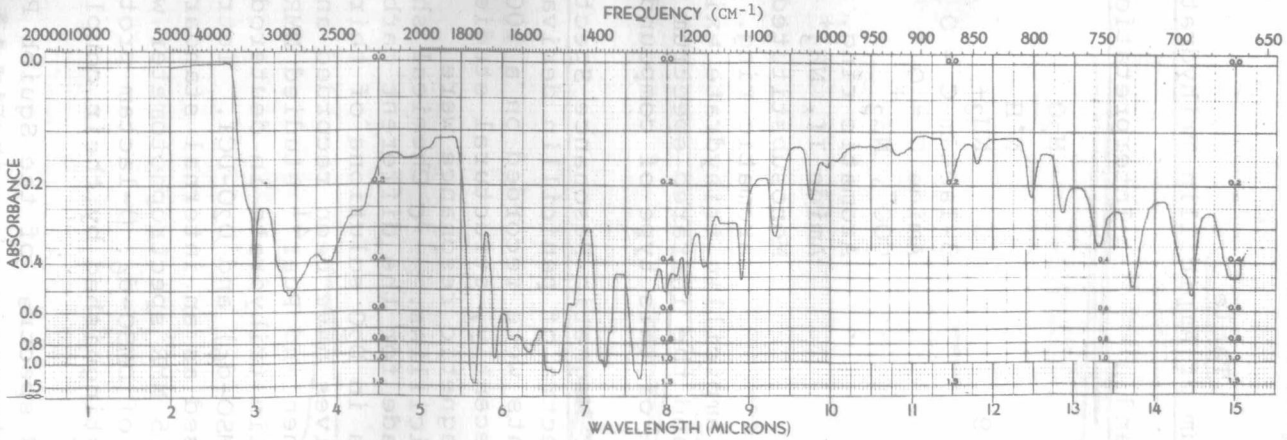


Figure 2. Infrared Spectrum of Anhydrous Ampicillin Squibb Reference Standard.

Table I
Infrared Spectrum of Ampicillin Trihydrate

IR Absorption Band, μ	Interpretation
2.9	H_2O
3.1	N·H
weak bands 3.5-4.8	NH_3+
5.65	β-lactam C = O
5.90	Amide C = O
6.2 and 6.35	COO^-, NH_3^+
6.7	Aromatic ring, Amide II, NH_3^+
14.4	Monosubstituted aromatic ring.

In the solid form, ampicillin trihydrate exists as the zwitterion and the infrared spectrum shows absorptions typical of this type of compound[38].

2.12 Nuclear Magnetic Resonance Spectra

NMR spectra of penicillin derivatives in different solvents were recorded on a 100 MHz spectrometer[39]. Recently, structural studies with ^{13}C nuclear magnetic resonance were reported[40] for penicillins. ^{13}C Chemical shift assignments were made for the different carbon atoms. NMR spectra in D_2O solutions of thirteen penicillin derivatives have been recorded and interpreted[37]. Cohen and Puar[41] studied NMR spectra of ampicillin trihydrate in deuterodimethylsulfoxide (DMSO-d_6) and D_2O-DCl. Tetramethylsilane was used as an internal standard. The Varian XL-100-15 NMR spectrophotometer was used. In the case of DMSO-d_6, β-lactam protons could be easily distinguished by their coupling pattern.

The NMR spectra of the Squibb Primary Reference Substance are given in Fig. 3 and Fig. 4. The assignments are reported in Table II.