Analytical Profiles of Drug Substances

Volume 11

Edited by

Klaus Florey

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PREFACE

It is now well over a decade that I perceived the need to supplement the official compendial standards of drug substances with a comprehensive review of pertinent physical, chemical, and analytical data and methods. Ten years ago the first volume of *Analytical Profiles of Drug Substances* was published under the auspices of the Pharmaceutical Analysis and Control Section of the APhA Academy of Pharmaceutical Sciences. That we were able to publish one volume per year is a tribute to the diligence of the editors to solicit monographs and even more so to the enthusiastic response of our authors, an international group associated with pharmaceutical firms, academic institutions, and compendial authorities. I would like to express my sincere gratitude to them for making this venture possible.

I am pleased to report that five years ago a companion series entitled *Pharmacological and Biochemical Properties of Drug Substances* was initiated by Morton E. Goldberg under the auspices of the section on Pharmacology and Toxicology, APhA Academy of Pharmaceutical Sciences. So far, three volumes have been published.

Over the years, we have had queries concerning our publication policy. Our goal is to cover all drug substances of medical value and, therefore, we have welcomed any monographs of interest to an individual contributor. We also have endeavored to solicit profiles of the most useful and used medicines, but many in this category still need to be profiled.

Starting with this, the eleventh volume, we shall also supplement previously published profiles with new data as we can find volunteers to write such supplements. In this volume, five of the original profiles in Volume 1 have been updated.

The goal to cover and update all drug substances of medical value with comprehensive monographs is still a distant one. I estimate that only about a quarter of such compounds have been profiled so far. We would very much like to accelerate

the rate of publication and hope that even more authors can be encouraged to write profiles. All those who have found these profiles useful are requested to contribute monographs of their own. We, the editors, stand ready to receive such contributions.

Klaus Florey

CONTENTS

PROFILE SUPPLEMENTS

AMINOPHYLLINE

Kailas D. Thakker and Lee T. Grady

ISBN 0-12-260811-9

1. Description

1.1 Nomenclature

1.11 Chemical Name

Aminophylline is chemically known as 1H-purine-2,6-dione,3,7-dihydro-1,3-dimethyl-, compound with 1,2-ethanediamine (2:1).[1]

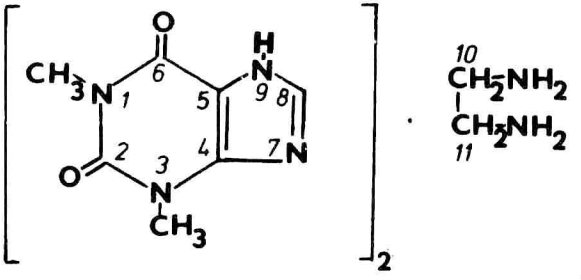
1.12 Adopted Names

Aminophylline was also known as theophylline ethylenediamine and euphylline.[1]

1.13 Trade Names

Aminophylline is known as carena; inophylline; metaphylline; theophyldine; aminocardol; ammophylline; cardiocilina; cardophyllin; phylcardin; tefamin; cardiomin; grifomin; minaphil; peterphylline; stenovasan; theodrox; diophylline; genophylline; phyllindon and theolamine.[1]

1.2 Formula, Molecular Weight, and Composition:



Anhydrous:	$C_{16}H_{24}N_{10}O_4$	420.44
Dihydrate:	$C_{16}H_{28}N_{10}O_6$	456.44
Theophylline		85-87%
Ethylenediamine		12-15%

1.3 Appearance, Color and Odor

Aminophylline is available in the anhydrous form or as the dihydrate. The dihydrate occurs as white or slightly yellowish granules or powder. It has a faint ammoniacal odor and a bitter taste.[1]

2. Physical Properties

2.1 Spectral

2.11 Infrared

The infrared spectrum of aminophylline in mineral oil mull, obtained on a Beckman 4250 spectrophotometer, is shown in Figure 1.[2] It is generally consistent with the reported infrared spectrum of theophylline.[3,4] The stretches for $-NH_2$ in ethylenediamine and -NH in theophylline appear as a broad band (combined with the mineral oil signal) in the region of 3.0-4.0 μM. Other signals are in the same vicinity as those for theophylline. The fingerprint region beyond 8.5 μM is distinctive and can be used for identification.

2.12 Ultraviolet

Spectral characteristics of aminophylline solutions in the ultraviolet region were reported by Andrade and Inacio.[5] Absorption maxima occurred at 243-5 nm [$E^{1\%}_{1cm}$ = 170] and at 273-5 [$E^{1\%}_{1cm}$ = 500] in pH 9.5 borate buffer.

Figure 2 shows the ultraviolet spectrum of aminophylline in water obtained on a Beckman 5260 recording spectrophotometer.

2.13 Nuclear Magnetic Resonance

2.13.1 Proton NMR

An 80 MHz proton magnetic resonance spectrum of aminophylline in d_6-dimethyl sulfoxide, obtained on a Varian FT-80A,[6] containing tetramethylsilane as an internal reference, is shown in Figure 3. It is similar to the reported (60 MHz) proton NMR of theophylline.[3] The assignments, based on assignments of theophylline protons, are shown in Table I.

2.13.2 Carbon-13 NMR

The 20 MHz proton-noise decoupled ^{13}C spectrum of aminophylline in d_6-dimethyl sulfoxide, obtained on a Varian FT-80A is shown in Figure 4.[6] The assignments are shown in Table II. These are based on assignments of dimethyluracil and 1-methylhypoxanthine.[7]

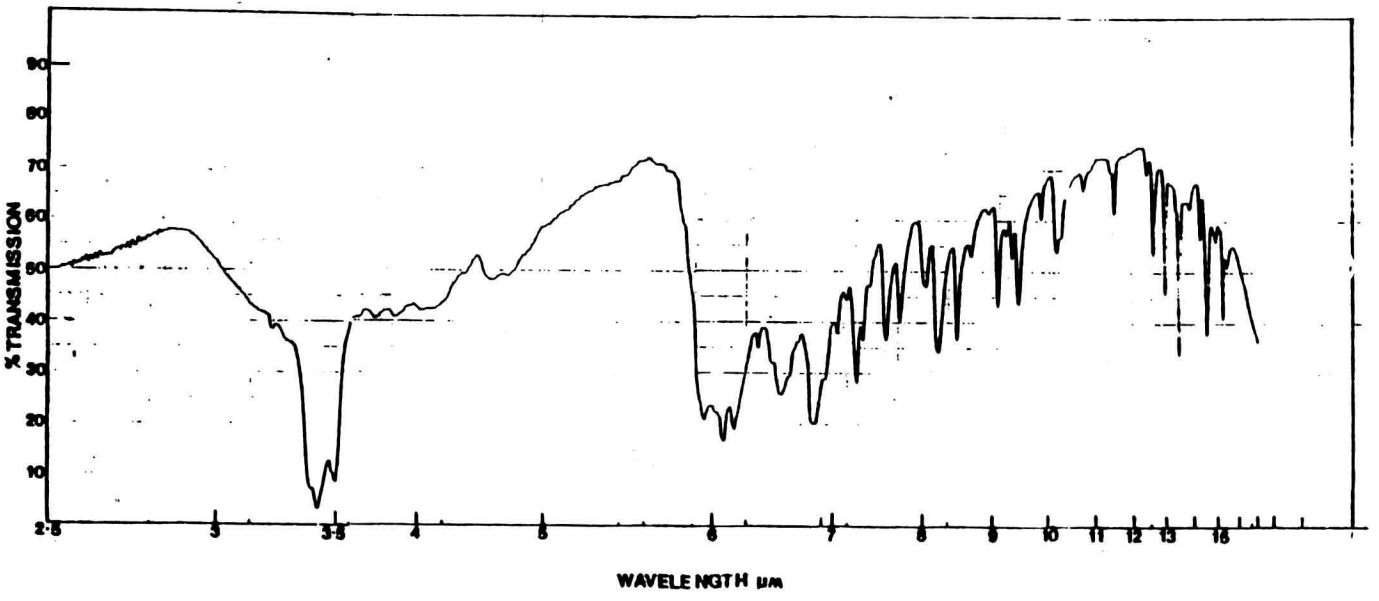


Fig. 1. IR Spectrum of Aminophylline

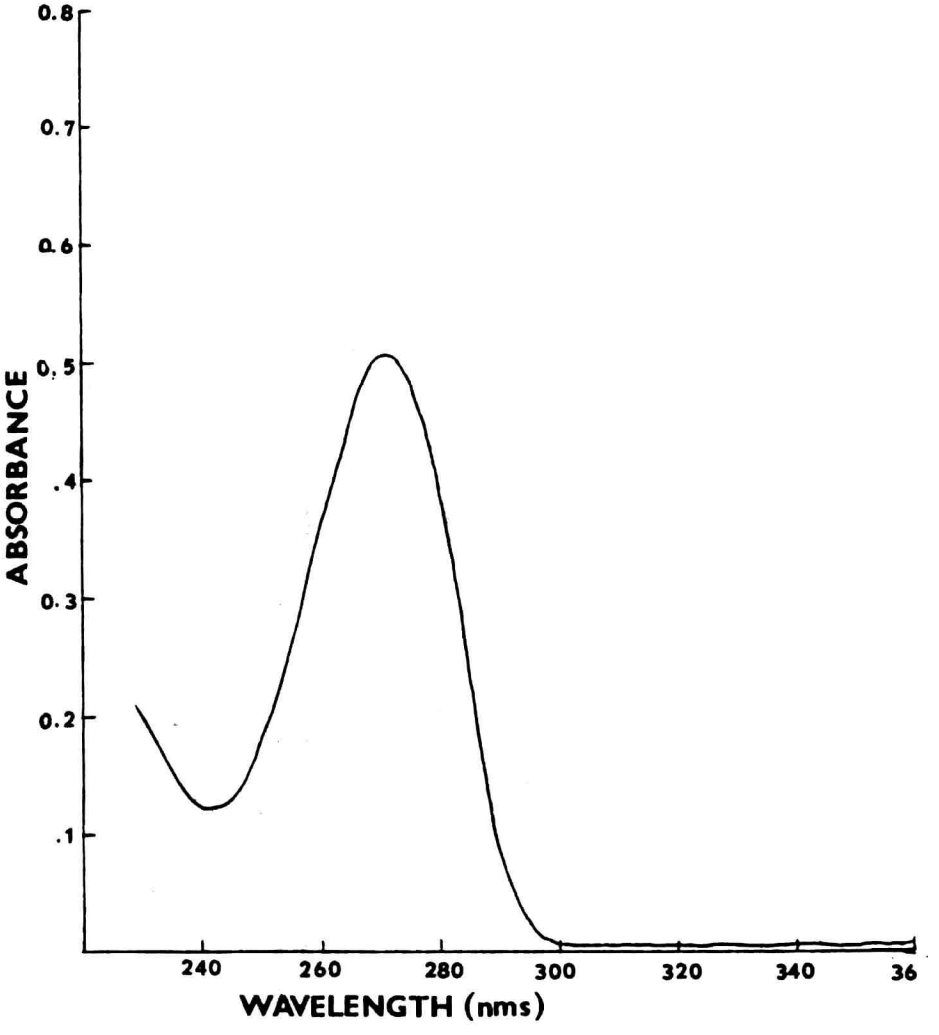


Fig. 2. UV Spectrum of Aminophylline

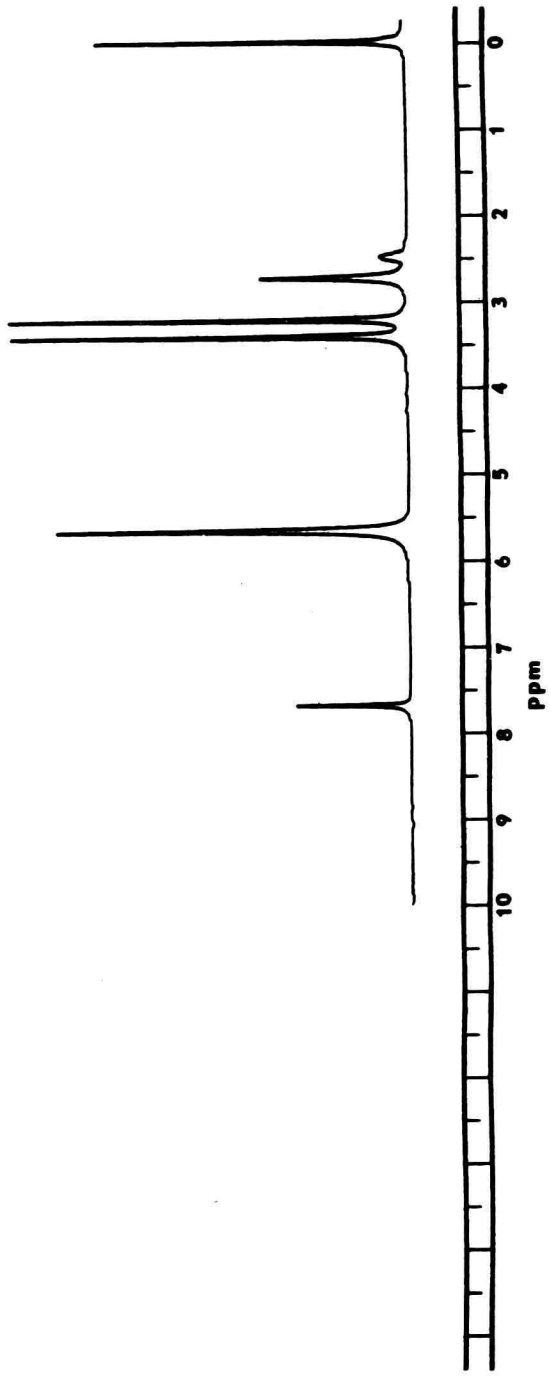


Fig. 3. ^{1}H NMR of Aminophylline

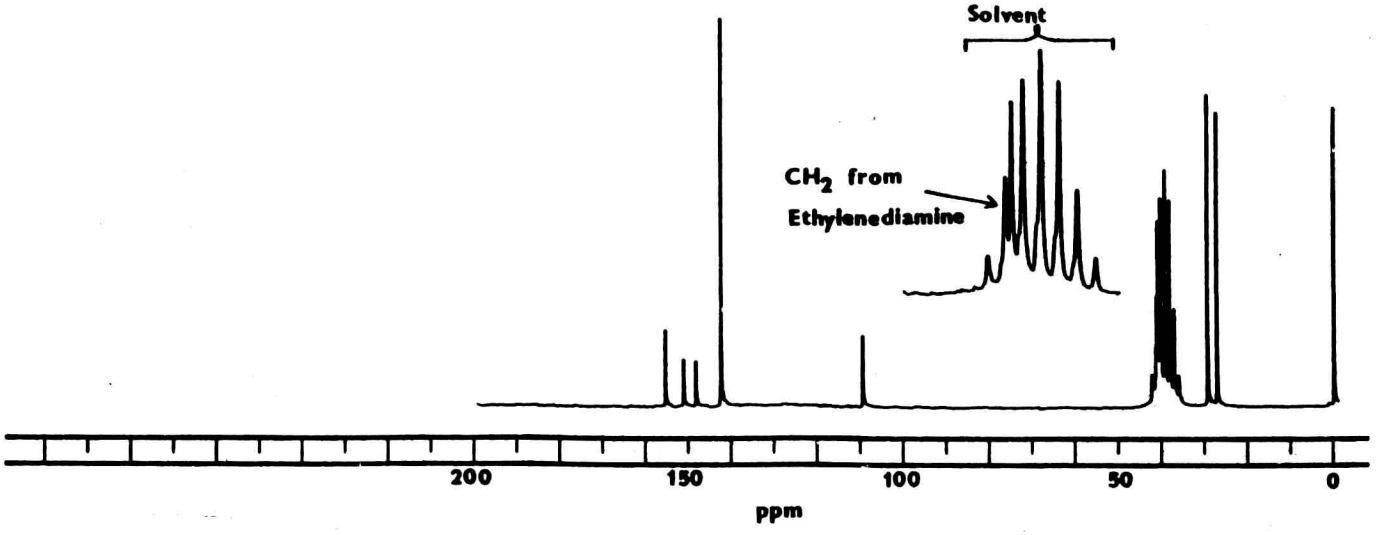


Fig. 4. ^{13}C NMR of Aminophylline

Table I

Proton Assignment	Proton Position (see structure)	Chemical Shift (ppm)
$-CH_2-$	10,11	2.75
$-N-CH_3-$	1	3.23
$N-CH_3-$	3	3.42
$N-H^a$	7	5.67
C-H	8	7.71

[a]Intensity of signal is proportional to the concentration. This proton may be delocalized in the ring.

Table II

Carbon Assignment	Carbon Position (see structure)	Chemical Shift
$N-CH_3$	1	29.7
$N-CH_3$	3	27.5
C=C	5	109.6
C=C	4	148.5
N-C-N	8	142.7
-C=O	2	151.4
N-C=O-N	6	155.6

$-CH_2$ on ethylenediamine is buried in the solvent signal as shown in Figure 4.

2.2 Other Properties

2.21 Differential Scanning Calorimetry and Melting Point

The thermogram of aminophylline[2] shows two endothermic transitions, one at 120° and another at 272°C. The first transition reflects the melting point of aminophylline; the second transition reflects the melting point of theophylline. Theophylline is known to sublime on melting.[2]

2.22 Solubility

Aminophylline is soluble in water