

Analytical Profiles of Drug Substances

Volume 15

Edited by

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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. Such information is scattered through the scientific literature and the files of pharmaceutical laboratories.

I perceived a need to supplement the official compendial standards of drug substances with a comprehensive review of such information, and fifteen 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 articles 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.

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 articles 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.

Klaus Florey

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AMILORIDE HYDROCHLORIDE

David J. Mazzo

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1. Introduction

1.1 Therapeutic Category (1)

Amiloride hydrochloride dihydrate, hereafter referred to as amiloride hydrochloride, is a potassium-conserving diuretic with relatively weak natriuretic and antihypertensive activity. It is not an aldosterone antagonist and, therefore, is effective in the absence of aldosterone. Amiloride hydrochloride is indicated as adjunctive treatment with thiazide diuretics or other kaliuretic-diuretic agents in congestive heart failure or hypertension to aid in the restoration of normal serum potassium levels and/or to prevent the development of hypokalemia. Amiloride hydrochloride is available for oral dosing as tablets, is usually well tolerated, and except for hyperkalemia, has had significant adverse effects reported infrequently (1).

1.2 History

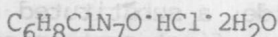
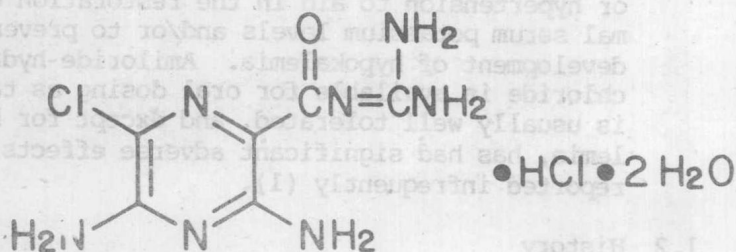
Amiloride hydrochloride, a substituted (pyrazine-carbonyl)guanidine, was first synthesized in the Merck, Sharp and Dohme Research Laboratories (2). The first non-patent literature reference to amiloride appeared in 1966 (3) and the first structure-activity relationship study was published in 1967 (4). Amiloride hydrochloride has gained steadily increasing popularity as a therapeutic drug as well as a pharmacological tool and its actions and effects have been the subject of at least three international symposia (5,6,7). A search of Chemical Abstracts from 1966 to 1985 produced 490 bibliographic citations for works dealing with amiloride hydrochloride.

2. Description

2.1 Chemical Name, Formula, Molecular Weight

The current accepted Chemical Abstracts name for amiloride hydrochloride (MK-870) is 3,5-diamino-N-(diaminomethylene)-6-chloropyrazinecarboxamide monohydrochloride dihydrate. The CAS registry no. is 17440-83-4.

Other names which have been used for amiloride hydrochloride include 3,5-diamino-N-(amino-iminomethyl)-6-chloropyrazinecarboxamide monohydrochloride dihydrate, N-amidino-3,5-diamino-6-chloropyrazinecarboxamide monohydrochloride dihydrate, N-amidino-3,5-diamino-6-chloropyrazinamide monohydrochloride dihydrate, 1-(3,5-diamino-6-chloropyrazinecarboxyl)guanidine monohydrochloride dihydrate, 1-(3,5-diamino-6-chloropyrazinoyl)guanidine monohydrochloride dihydrate, as well as the monohydrochloride dihydrated salts of guanampazine, amipramidin and amipramizide



Molecular Weight: 302.12 g/mole

2.2 Definition

Amiloride Hydrochloride, unless specifically stated otherwise, is defined as the crystalline, monohydrochloride dihydrated salt form of the compound. Its tradename is MIDAMOR®. Amiloride, when referred to, indicates the free base.

2.3 Appearance, Color, Odor

Amiloride hydrochloride is a yellow to greenish yellow crystalline powder which is odorless or practically odorless.

3. Synthesis

Amiloride hydrochloride, essentially a substituted guanidine, has been prepared through a series of synthetic steps beginning with methyl cyanoacetate and urea (4,8-14). The synthetic route is presented in

Figure 1. The starting materials (I and II) are reacted in sodium isopropoxide and subsequently nitrated. The product (III) is reduced to the amino compound (IV), treated with glyoxal to form a pteridine intermediate (V) and hydrolyzed in base which upon acidification gives 3-aminopyrazinoic acid (VI). This substituted pyrazinoic acid is then esterified with methanol (VII) in the presence of sulfuric acid, chlorinated (VIII) and converted to the 5-amino ester with ammonia in DMSO. The product (IX) is then reacted with guanidine to form amiloride which upon reaction with hydrochloric acid in water forms amiloride monohydrochloride dihydrate (X).

4. Physical Properties

4.1 Infrared Spectrum

The infrared spectrum of amiloride hydrochloride taken in a KBr pellet is shown in Figure 2 (15). A Digilab Model FTS-15C fourier transform infrared spectrophotometer was used to acquire the spectrum. Frequency assignments for some of the characteristic bands are listed in Table I.

Table I
Infrared Spectral Assignments
for Amiloride Hydrochloride

<u>Frequency (cm⁻¹)</u>	<u>Assignment</u>
3250-3500	N-H stretch (NH ₂)
3150	N-H stretch (NH)
1680	C=O stretch
1640	H ₂ deformation mode
1600	H ₂ deformation mode
1240	N-(C ₆ H ₆) stretch
770	C-H out-of-plane mode

The infrared spectrum of amiloride hydrochloride taken in a mineral oil mull is shown in Figure 3 (15).

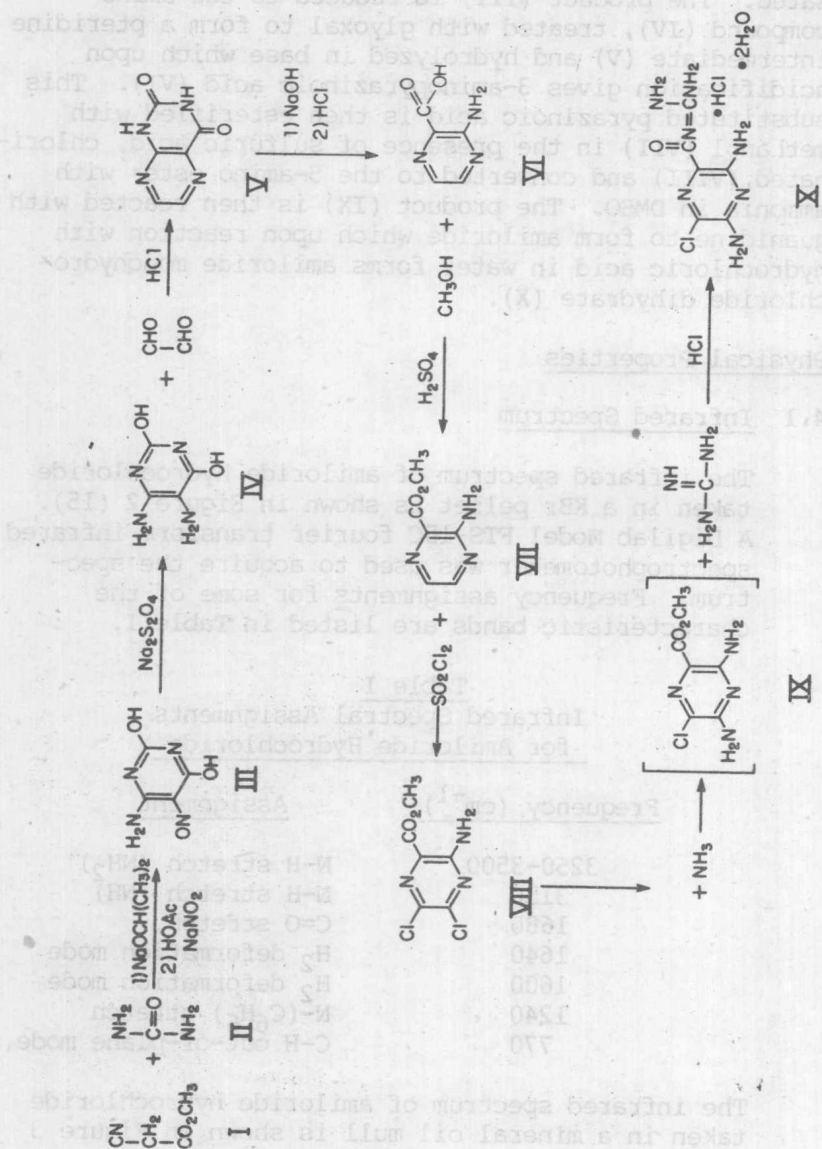


Figure 1. Synthetic route to amiloride hydrochloride

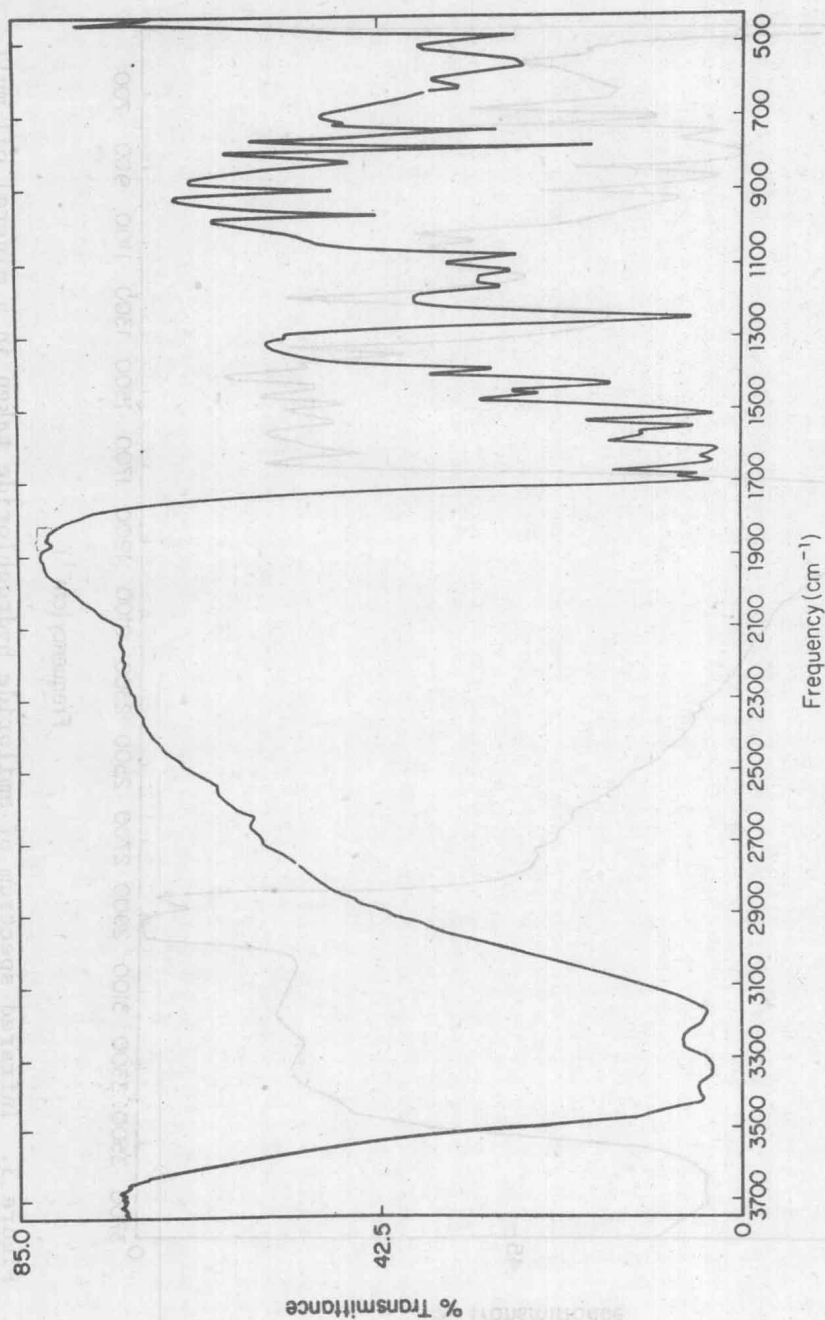


Figure 2. Infrared spectrum of amiloride hydrochloride taken in a KBr pellet.

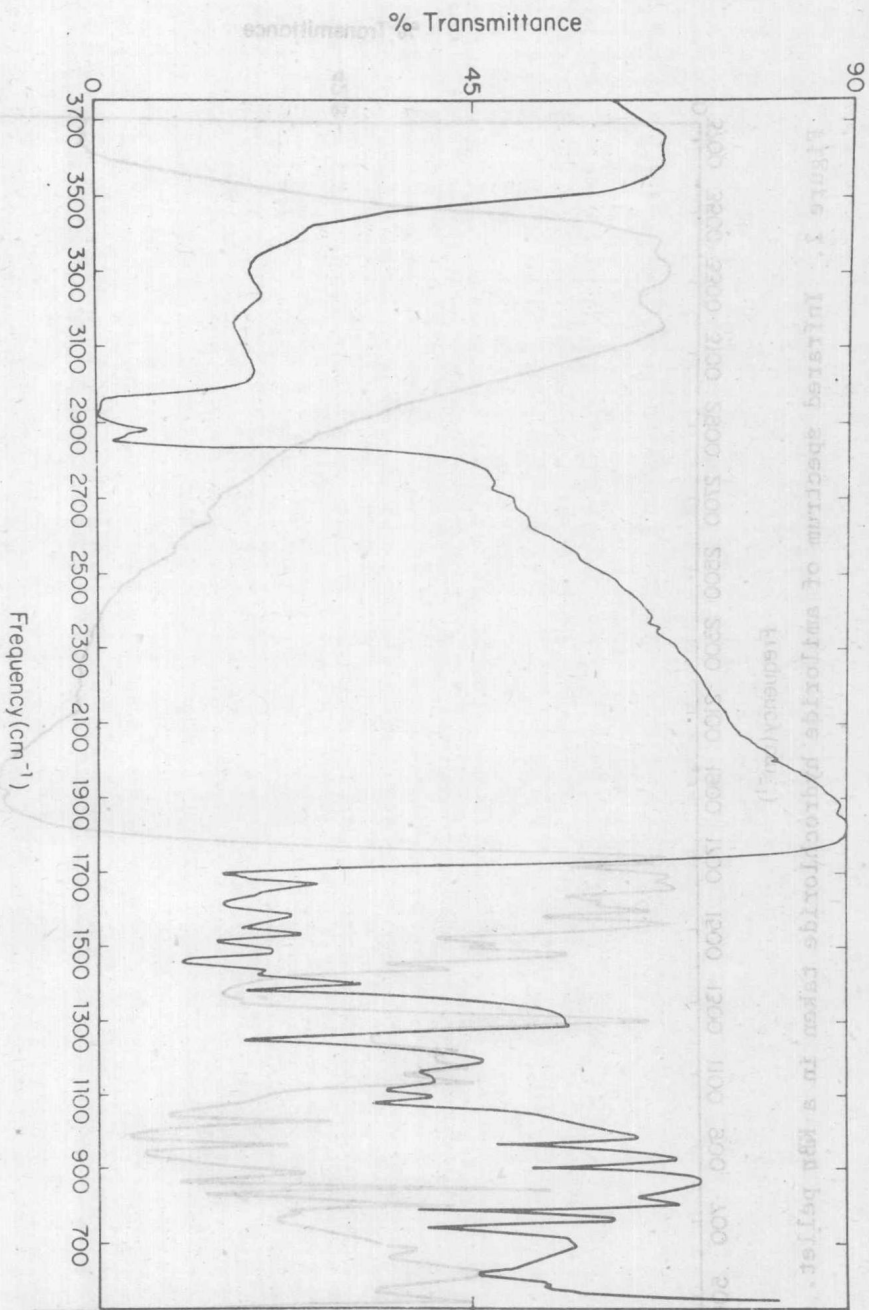


Figure 3. Infrared spectrum of amiloride hydrochloride taken in a mineral oil mull.

4.2 Nuclear Magnetic Resonance Spectrum (16)

4.2.1 Proton NMR Spectrum

The proton magnetic resonance spectrum of amiloride hydrochloride was obtained using a JEOL(USA) C-60HL spectrometer. The spectrum was acquired from a 1.0 M drug solution in fully deuterated dimethylsulfoxide (d_6 -DMSO). The spectrum is shown in Figure 4 and the spectral assignments are listed in Table II (17).

Table II

Proton NMR Spectral Assignments
for Amiloride Hydrochloride

(ppm) (a)	Integral (mm)	Relative No. Protons	Assignments
3.8	52	4.4 (b)	H ₂ O
7.4	48.5	4.1	Aromatic -NH ₂
7.7			
9.8			
11.1	57 (c)	4.9	N—H

Notes:

- All protons are bound to nitrogen or oxygen (H₂O), therefore chemical shift will be strongly dependent upon sample concentration, temperature and/or solution pH.
- This signal includes a small contribution due to water originally present in the d_6 -DMSO.
- The total integral resulting from these signals is reported since the appearance of the spectrum suggests intermediate kinetic exchange between the two types of sites.