Analytical Profiles of Drug Substances

Volume 14

Edited by

Klaus Florey

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PREFACE

The compilation of *Analytical Profiles of Drug Substances* to supplement the information contained in the official compendia is now a well-established activity.

That we are 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 papers 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.

In the preface to the eleventh volume, I announced that we would try to supplement previously published profiles with new data. Unfortunately, most of the original contributors are no longer available to undertake this task, and it has proven difficult to find other volunteers. We shall continue to pursue the updating program, but it will not be as comprehensive as originally envisioned.

Again, I would like to request those who have found these profiles useful to contribute papers of their own. We, the editors, stand ready to receive such contributions.

CONTENTS

CHLORTHALIDONE

Jeff M. Singer, Michael J. O'Hare,
Carl R. Rehm, and John E. Zarembo

Revlon Health Care Group
Tuckahoe, New York

ISBN 0-12-260814-3

INTRODUCTION

Chlorthalidone is an antihypertensive diuretic used in the treatment of edema associated with congestive heart failure. It is the active component in Hygroton®, Regroton® and Demi-Regroton. The drug shows long lasting diuretic actions similar to those of other thiazide diuretics such as chlorothiazide. It is absorbed slowly from the gastrointestinal tract and is excreted largely as unchanged drug. The overall duration of effect is 48 to 72 hours.

ANALYTICAL METHODS FOR ANALYSIS OF CHLORTHALIDONE

1. DESCRIPTION

1.1 Name, Formula, Molecular Weight, Chemical Names

Chlorthalidone is designated by the following names:

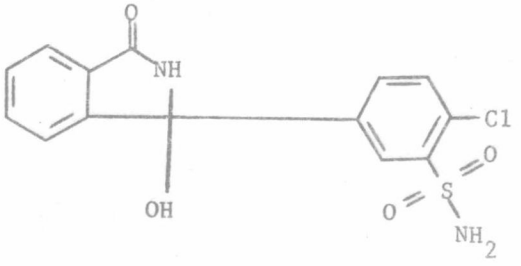
Benzenesulfonamide, 2-Chloro-5-(2,3 dihydro-1-hydroxy-3-oxo-1H-isoindol-1-yl)

2-Chloro-5'-(1-hydroxy-3-oxo-1-isoindolinyl) benzene sulfonamide

and is also known as:

3-Hydroxy-3-(4-chloro-3-sulfamylphenyl) phthalimidine.

The empirical formula is $C_{14}H_{11}ClN_2O_4S$ with a molecular weight of 338.76.



1.2 Trade Names

Hygroton®
Regroton®
Hydro-Long
Hydroton
Igroton

Chlorthalidone is also a component of Regroton® and Demi-Regroton combination products containing Chlorthalidone in combination with reserpine.

1.3 Appearance, Color

Chlorthalidone is a white to yellowish-white crystalline powder.

2. PHYSICAL PROPERTIES

2.2 Spectra

2.1.1 Infrared Spectrum

The infrared absorption spectrum of Chlorthalidone obtained from a potassium bromide dispersion is shown in Figure 1. The spectrum was recorded on a Perkin-Elmer 621 Grating Infrared Spectrophotometer. Table 1 contains the assignments of several of the characteristic absorption bands.

2.1.2 Mass Spectrum

The mass spectrum of Chlorthalidone is presented in Figure 2. A Varian MAT-112 mass spectrometer, operating in the electron impact ionization mode at 70 eV and using a source and probe temperature of 250°C, was used for the analysis. The peak assignments are listed in Table 2. The base peak is at m/z 148. These results are in agreement with the previously published work of Frigerio and Pantarotto (1).

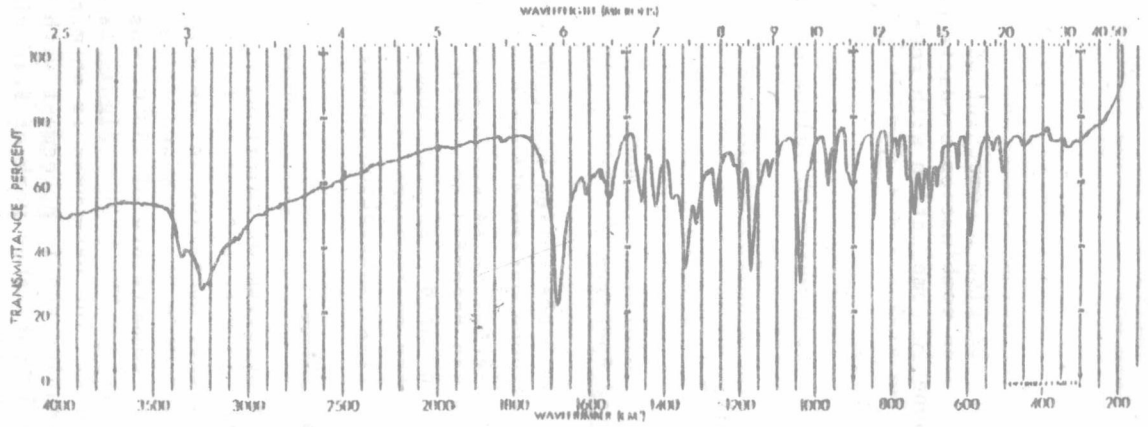


FIGURE 1 INFRARED SPECTRUM OF CHLORTHALIDONE: KBr DISPERSION

INSTRUMENT: PERKIN-ELMER 621

TABLE 1

INFRARED BAND ASSIGNMENTS FOR CHLORTHALIDONE

BAND (cm^{-1})	INTENSITY*	ASSIGNMENT
3350	M	O-H Stretch
3240	M	N-H Stretch
1685	S	$-\underset{\underset{O}{\|}}{C}-NH$ Amide
1345	S	Sulfonamide
1170	S	Sulfonamide
1038	S	O-H bending
595	S	C-Cl Stretch

* M = Medium
S = Strong

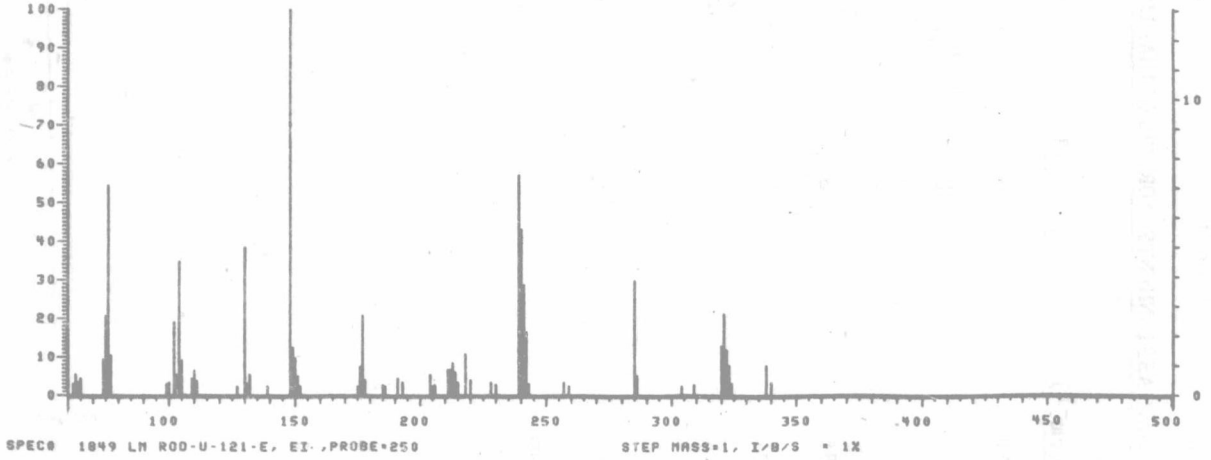
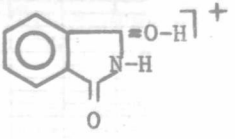
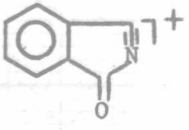
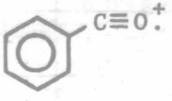
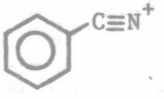


FIGURE 2 MASS SPECTRUM OF CHLORTHALIDONE, ELECTRON IMPACT IONIZATION
INSTRUMENT: VARIAN MAT-112

TABLE 2

MASS SPECTRUM OF CHLORTHALIDONE

PEAK #	MASS #	REL. INT.	ASSIGNMENT
1	340	2.4	$M^+ + 2$=(indicates 1 chlorine)
2	338	6.5	M^+ (Molecular ion)
3	321	14.6	$M^+ - OH\cdot$
4	285	27.4	$M^+ - H_2O - Cl$
5	239	67.9	$M^+ - H_2O - SO_2NH_2$
6	177	19.0	Not Assigned
7	148	100.0	
8	130	36.4	
9	104	43.7	
10	102	18.0	

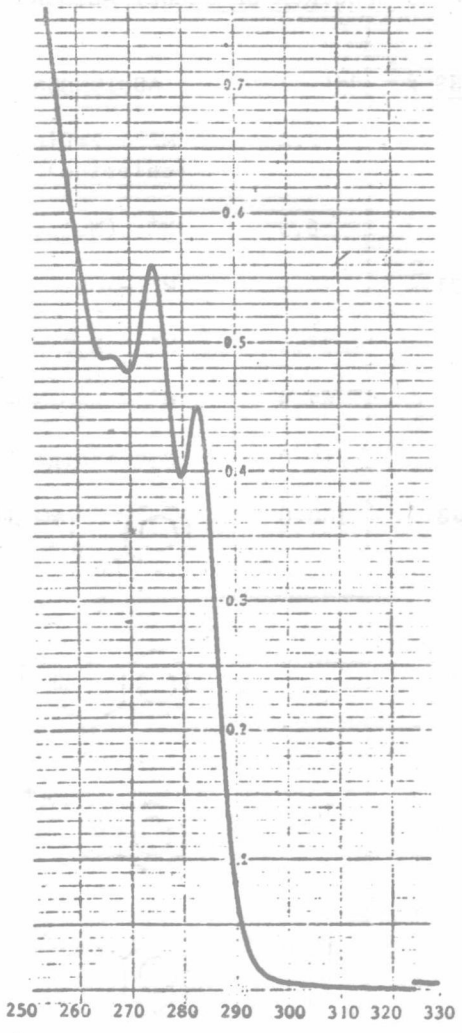


FIGURE 3 ULTRAVIOLET SPECTRUM OF CHLORTHALIDONE
INSTRUMENT: CARY 219

2.1.3 Ultraviolet Absorption Spectrum

A Cary 219 Spectrometer was used to record the ultraviolet spectrum of Chlorthalidone in dilute HCl/methanol, 1:50 (v:v). The spectrum in Figure 3 shows an aromatic multiplet with maxima at 266 nm (a=4.73), 275 nm (a=5.40) and 283 nm (a=4.33).

2.1.4 Nuclear Magnetic Resonance Spectrum

The proton spectrum shown in Figure 4 was obtained on a JEOL FX 90Q NMR Spectrometer using DMSO-d_6. The band assignments are referenced to a TMS internal standard and are listed in
Table 3. Singlets occur at 9.38 ppm and 7.20 ppm due to protons "a" and "b" respectively. Protons "a", "b" and "e" are exchangeable with the addition of D_2O. A doublet due to the proton assigned as "d" occurs at 8.11 ppm.

Multiplets at 7.63-7.20 ppm and 7.63-7.48 ppm are due to the protons assigned as "c" and "e". The additional peaks in the spectrum are due to solvents.

The completely proton decoupled 22.5 MHz ^{13}C spectrum in DMSO-d_6 has also been recorded and is shown in Figure 5; DMSO-d_6 was used as a reference. Chemical shifts and multiplicities are compiled in Table 4. The signal at 168.4 ppm has been assigned to the amide carbon, C-7; the signal at 86.8 ppm has been assigned to the hydroxylated carbon, C-8. The remaining peaks, occurring within the range 149.8 - 122.7 ppm are due to the aromatic carbons.