

Analytical Profiles of Drug Substances

Volume 5

Edited by
Klaus Florey

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**The Squibb Institute for Medical Research
New Brunswick, New Jersey**

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*Compiled under the auspices of the
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PREFACE

Although the official compendia list tests and limits for drug substances related to identity, purity, and strength, 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. 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 and Control Section, Academy of Pharmaceutical Sciences, has undertaken a cooperative venture to compile and publish Analytical Profiles of Drug Substances in a series of volumes of which this is the fifth.

The concept of Analytical Profiles is taking hold not only for compendial drugs but, increasingly, in the industrial research laboratories. Analytical Profiles are being prepared and periodically updated to provide physico-chemical and analytical information of new drug substances during the consecutive stages of research and development. Hopefully, then, in the not too distant future, the publication of an Analytical Profile will require a minimum of effort whenever a new drug substance is selected for compendial status.

The cooperative spirit of our contributors had made this venture possible. All those who have found the profiles useful are earnestly requested to contribute a monograph of their own. The editors stand ready to receive such contributions.

Klaus Florey

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BENDROFLUMETHIAZIDE

Klaus Florey and Frank M. Russo-Alesi

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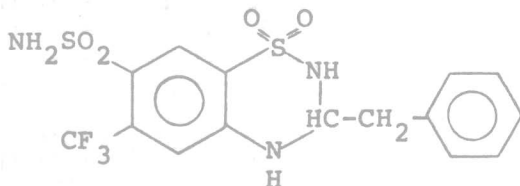
1. Description

1.1 History

Bendroflumethiazide belongs to the class of thiazide diuretics. Its synthesis was first reported by Holdrege, Babel and Cheney¹ in 1959 and its diuretic activity was first described in 1960 almost simultaneously by Lund and Kobinger¹⁶ and by Kennedy, Buchanan and Cunningham².

1.2 Name, Formula, Molecular Weight

Bendroflumethiazide (also bendrofluazide, benydroflumethiazide, and benzylhydroflumethiazide) is 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3,4-dihydro-3-(phenyl methyl)-6-trifluoromethyl-1,1-dioxide or 3-Benzyl-3,4-dihydro-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1 dioxide [73-48-3].



Mol. Wt. 421.41

1.3 Appearance, Color, Odor

White or slightly off-white, uniform free flowing crystalline powder; slight floral odor.

2. Physical Properties

2.1 Infrared Spectrum

The infrared spectrum of bendroflumethiazide is given in Figure 1¹.

2.2 Nuclear Magnetic Resonance

The 60 MHz proton magnetic resonance spectrum in d_4 -methanol containing tetramethylsilane as an internal reference (Figure 2) is assigned as follows²³:

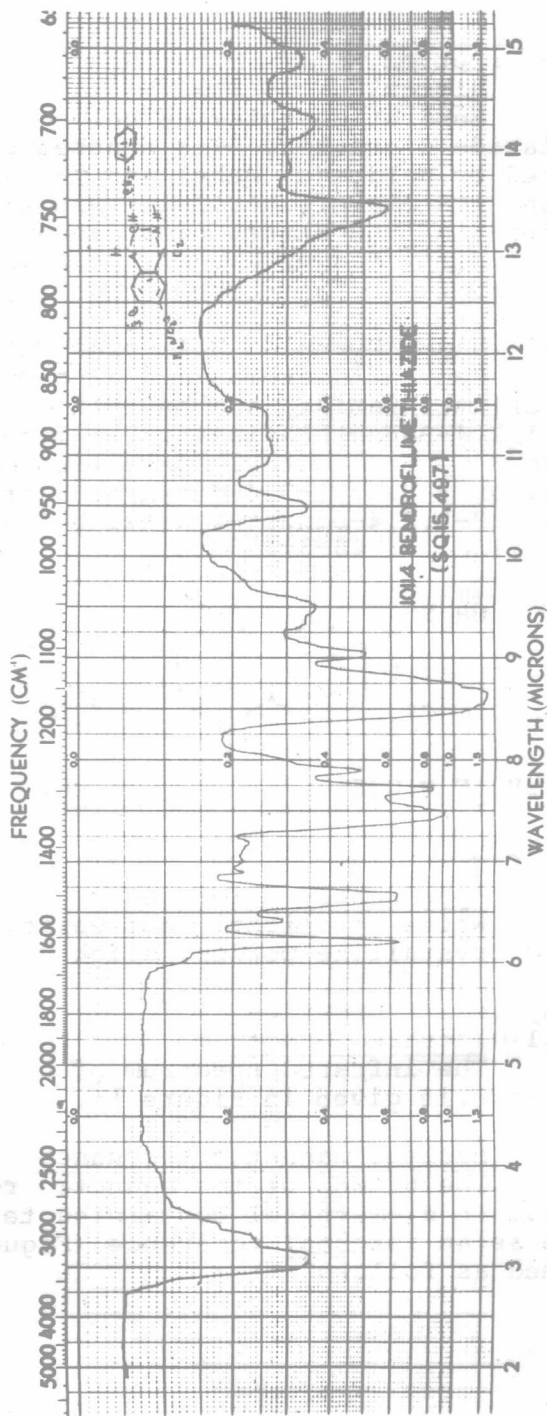


Figure 1. Infrared Spectrum of Bendroflumethiazide (batch #15); KBr, MeOH.
Instrument: Perkin-Elmer 621.

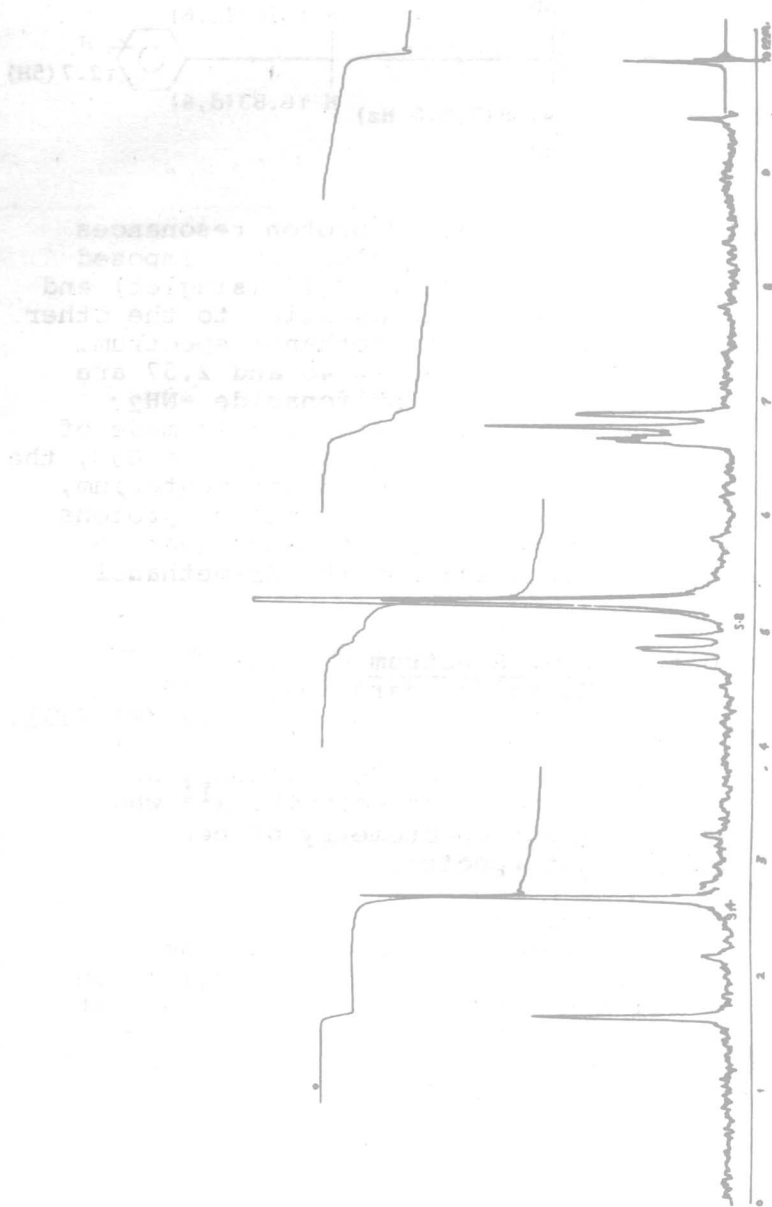
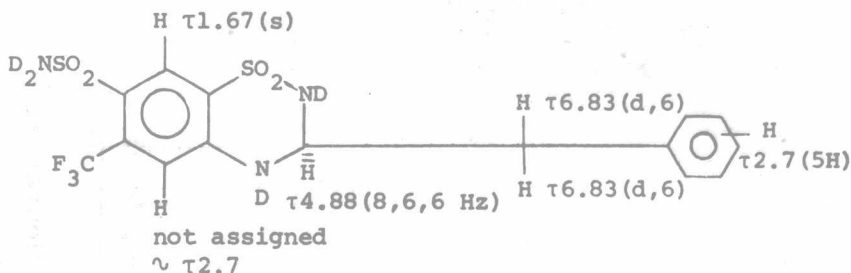


Figure 2. NMR Spectrum of Bendroflumethiazide (batch 15) in deuterated methanol (Instrument: Perkin Elmer R12B)



In d_6 -DMSO (Figure 3), the NH proton resonances were observed near τ 1.75 (singlet, superimposed with aryl proton), τ 2 (broad), 2.45 (singlet) and 2.57 (singlet) (Figure 3) in addition to the other protons assigned from the d_4 -methanol spectrum. The higher field singlets at τ 2.45 and 2.57 are tentatively assigned to the sulfonamide $-\text{NH}_2$ protons. No preference of assignment is made of the other two $-\text{NH}$ protons. On addition of D_2O , the $-\text{NH}$ protons are rapidly exchanged for deuterium, resulting in the disappearance of the NH protons and sharpening of the proton resonance near τ 5 which now appears like that of the d_4 -methanol spectrum.

2.3 Ultraviolet Spectrum

Squibb House Standard (batch #15) in methanol exhibited three maxima at 208 $\text{m}\mu$ ($\text{E}_1^{1.745}$), 273 $\text{m}\mu$ ($\text{E}_1^{1.565}$) and 326 $\text{m}\mu$ ($\text{E}_1^{1.96}$)¹³. This agrees with measurements by Pilsbury and Jackson¹⁵ and by Kracmar and Lastovkova¹⁴ who discuss the U.V. spectrophotometry of benzothiadiazines and present spectra.

2.4 Mass Spectrum

The low resolution mass spectrum (Figure 4) shows only a very weak molecular ion (M^+) of m/e 421 and a base peak of m/e 319 that could arise by a double proton rearrangement, which is not a common fragmentation pathway. The assignment of some of the fragment ions is shown below:

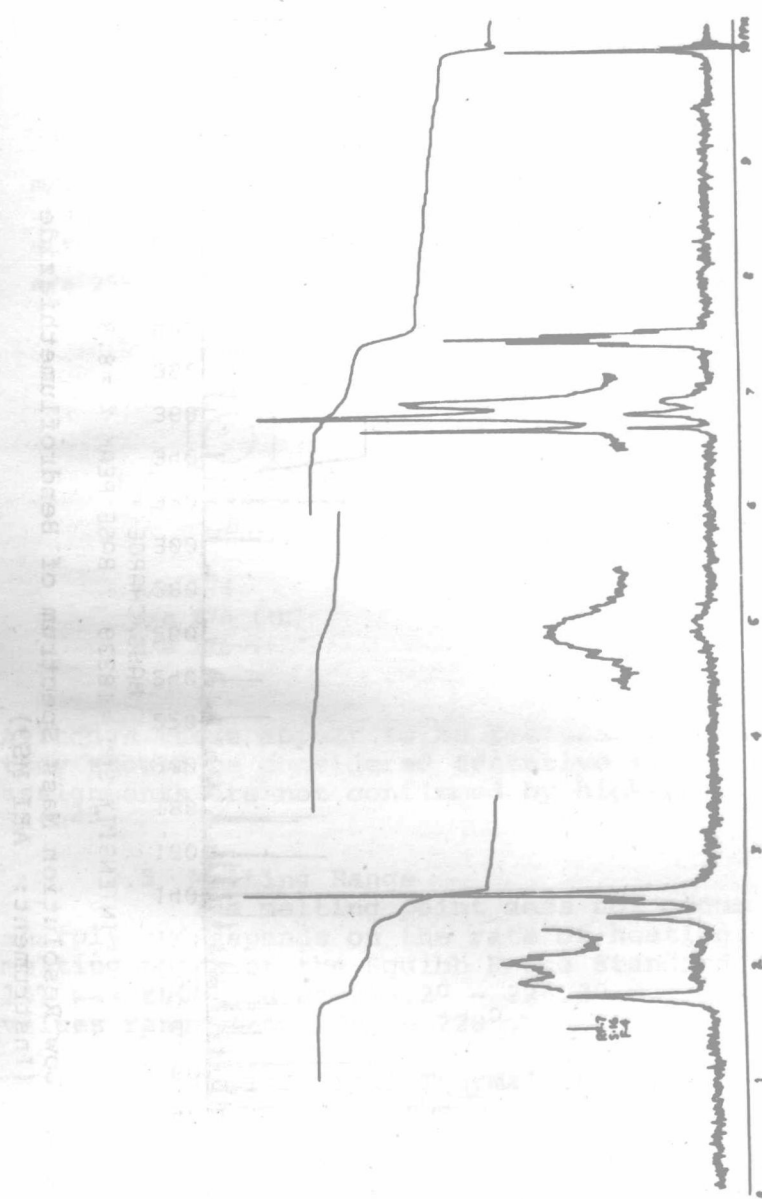


Figure 3. NMR Spectrum of Bendroflumethiazide (batch 15) in deuterated DMSO
(Instrument: Perkin-Elmer R12B)

3753 S015497 BA#15

12 FEB 76

MA0587

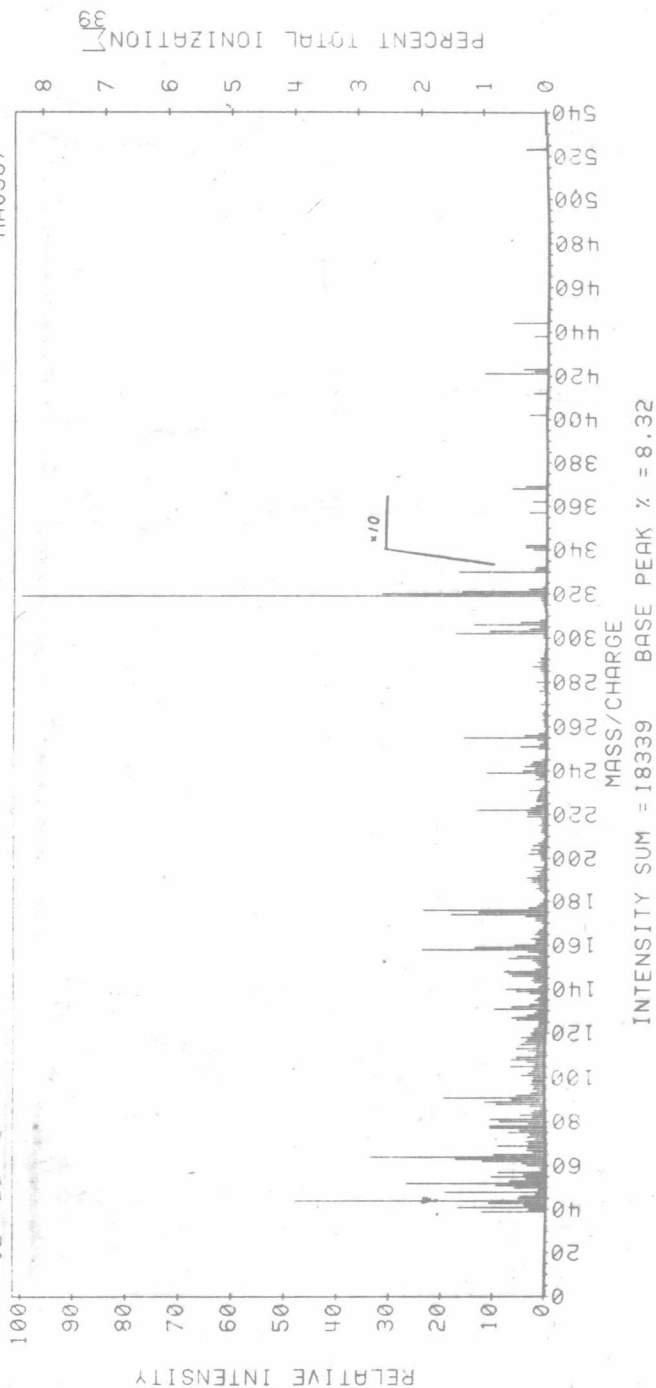


Figure 4. Low Resolution Mass Spectrum of Bendroflumethiazide
(Instrument: AEI MS9)