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

Contributing Editors

Norman W. Atwater
Glenn A. Brewer, Jr.
Lester Chafetz
Boen T. Kho
Gerald J. Papariello
Bernard Z. Senkowski

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AFFILIATIONS OF EDITORS AND CONTRIBUTORS

H. Y. Aboul-Enein, USV Pharmaceuticals, Tuckahoe, New York, now: Riyadh University, Riyadh, Saudi Arabia

G. D. Anthony, Searle and Company, Chicago, Illinois

N. W. Atwater, Searle and Company, Chicago, Illinois

J. I. Bodin, Carter-Wallace Inc., Cranbury, New Jersey

G. A. Brewer, The Squibb Institute for Medical Research, New Brunswick, New Jersey

D. E. Cadwallader, School of Pharmacy, University of Georgia, Athens, Georgia

L. Chafetz, Warner-Lambert Research Institute, Morris Plains, New Jersey

A. R. Chamberlin, Stanford Research Institute, Menlo Park, California

Z. L. Chang, Searle and Company, Chicago, Illinois

A. P. K. Cheung, Stanford Research Institute, Menlo Park, California

E. M. Cohen, Merck, Sharp and Dohme, West Point, Pennsylvania

J. P. Comer, Eli Lilly and Company, Indianapolis, Indiana

R. D. Daley, Ayerst Laboratories, Rouses Point, New York

K. Florey, The Squibb Institute for Medical Research, New Brunswick, New Jersey

S. A. Fusari, Parke, Davis and Company, Detroit, Michigan

G. G. Gallo, Gruppo LePetit, Milan, Italy

R. Gomez, Hoffmann-LaRoche, Inc., Nutley, New Jersey

R. B. Hagel, Hoffmann-LaRoche, Inc., Nutley, New Jersey

D. D. Hong, The Sterling-Winthrop Research Institute, Rensselaer, New York

E. H. Jensen, The Upjohn Company, Kalamazoo, Michigan

J. H. Johnson, Hoffmann-LaRoche, Inc., Nutley, New Jersey

H. W. Jun, School of Pharmacy, University of Georgia, Athens, Georgia

B. T. Kho, Ayerst Laboratories, Rouses Point, New York

P. Lim, Stanford Research Institute, Menlo Park, California

J. P. McDonnell, Salsbury Laboratories, Charles City, Iowa

E. A. MacMullan, Hoffmann-LaRoche, Inc., Nutley, New Jersey

A. F. Michaelis, Sandoz Pharmaceuticals, East Hanover, New Jersey

S. M. Miller, Wyeth Laboratories, Philadelphia, Pennsylvania

N. G. Nash, Ayerst Laboratories, Rouses Point, New York

C. E. Orzech, Ayerst Laboratories, Rouses Point, New York

G. J. Papariello, Wyeth Laboratories, Philadelphia, Pennsylvania

A. Post, Smith, Kline and French Laboratories, Philadelphia, Pennsylvania

P. Radaelli, Gruppo LePetit, Milan, Italy

J. A. Raihle, Abbott Laboratories, North Chicago, Illinois

R. J. Rucki, Hoffmann-LaRoche, Inc., Nutley, New Jersey

B. C. Rudy, Schering-Plough, Corp., Bloomfield, New Jersey

F. Russo-Alesi, The Squibb Institute for Medical Research, New Brunswick, New Jersey

B. Z. Senkowski, Hoffmann-LaRoche, Inc., Nutley, New Jersey

C. M. Shearer, Wyeth Laboratories, Philadelphia, Pennsylvania

F. Tishler, Ciba-Geigy, Summit, New Jersey

R. J. Warren, Smith, Kline and French Laboratories, Philadelphia, Pennsylvania

E. H. Waysek, Hoffmann-LaRoche, Inc., Nutley, New Jersey

L. L. Wearley, Searle and Company, Chicago, Illinois

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 degredation 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

CONTENTS

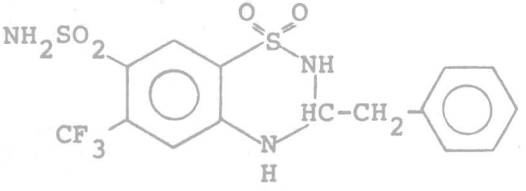
1. Description

1.1 History

Bendroflumethiazide belongs to the class of thiazide diuretics. Its synthesis was first reported by Holdrege, Babel and Cheney[1] in 1959 and its diuretic activity was first described in 1960 almost simultaneously by Lund and Kobinger[16] and by Kennedy, Buchanan and Cunningham[2].

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].



$C_{15}H_{14}F_3N_3O_4S_2$ 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 1[1].

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 follows[23]:

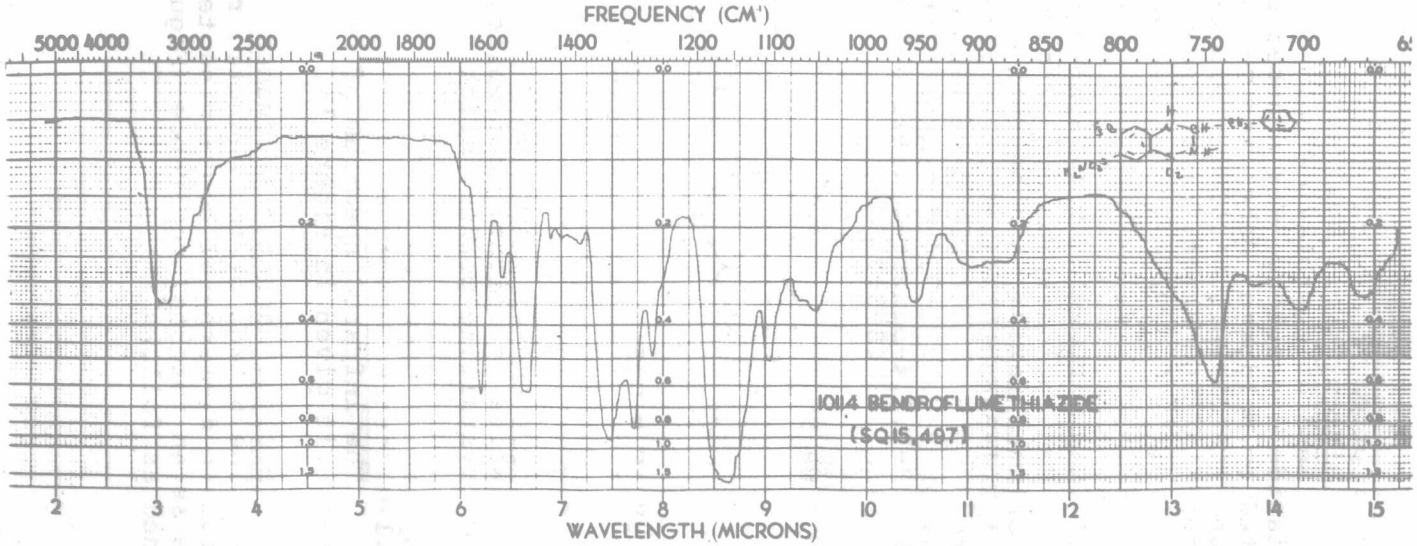


Figure 1. Infrared Spectrum of Bendroflumethiazide (batch #15); KBr, MeOH. Instrument: Perkin-Elmer 621.

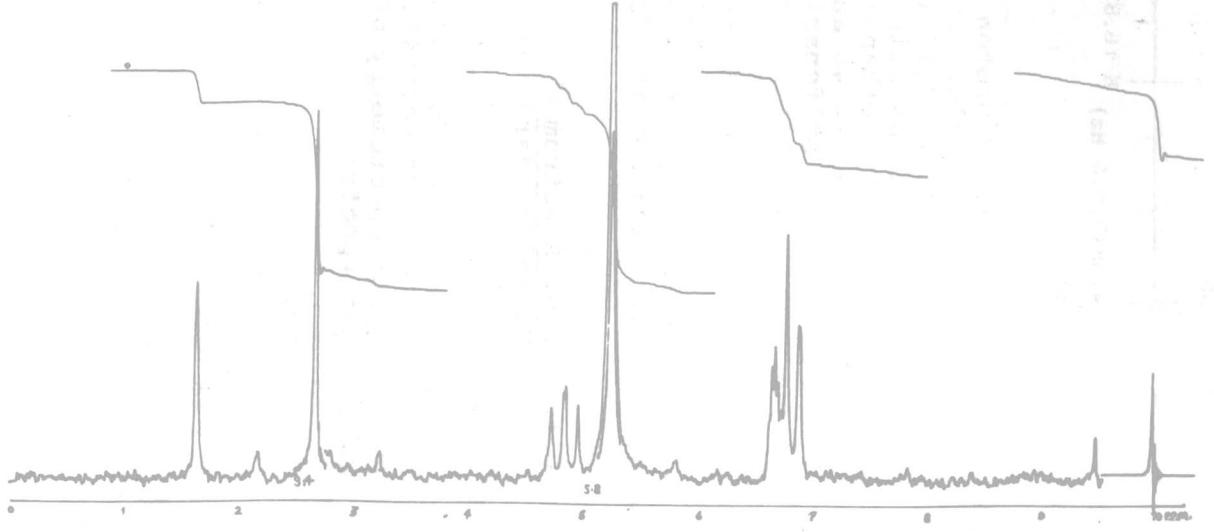
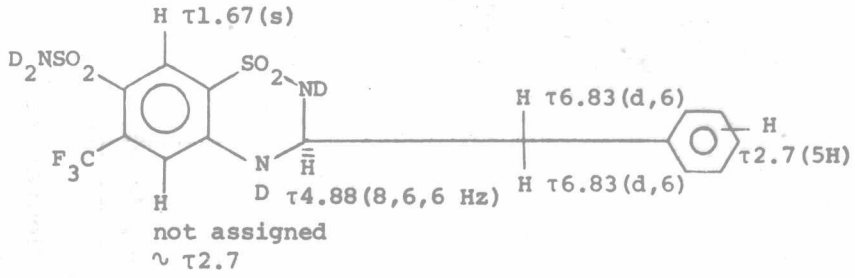


Figure 2. NMR Spectrum of Bendroflumethiazide (batch 15) in deuterated methanol (Instrument: Perkin Elmer R12B)



In d_6-DMSO (Figure 3), the NH proton resonances were observed near τ1.75 (singlet, superimposed with aryl proton), τ2 (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 τ2.45 and 2.57 are tentatively assigned to the sulfonamide $-NH_2$ protons. No preference of assignment is made of the other two -NH protons. On addition of D_2O, the -NH protons are rapidly exchanged for deuterium, resulting in the disappearance of the NH protons and sharpening of the proton resonance near τ5 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 mμ (E^1_1 745), 273 mμ (E^1_1 565) and 326 mμ (E^1_1 96)[13]. This agrees with measurements by Pilsbury and Jackson[15] and by Kracmar and Lastovkova[14] 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:

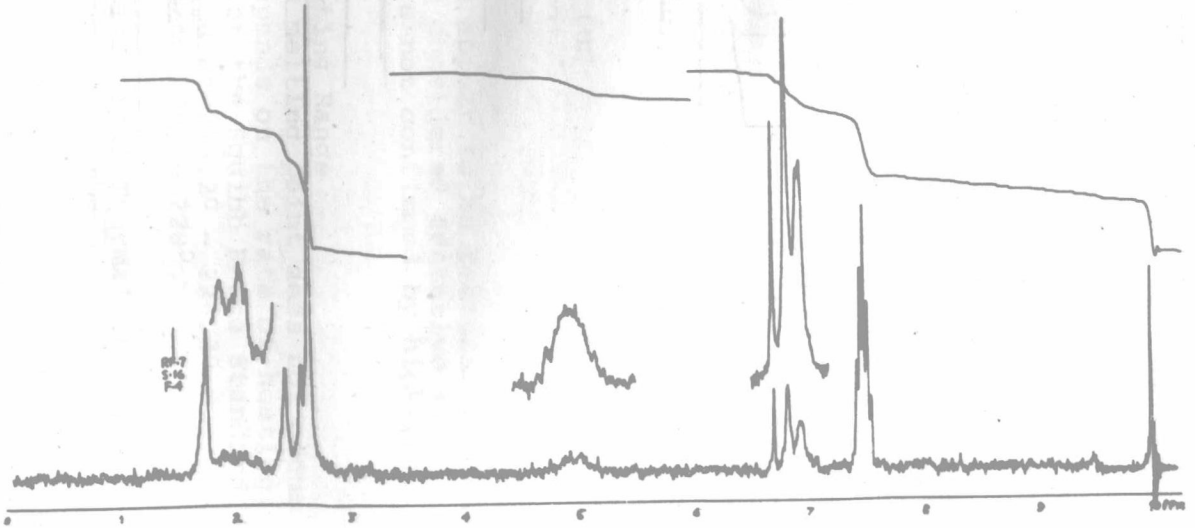


Figure 3. NMR Spectrum of Bendroflumethiazide (batch 15) in deuterated DMSO (Instrument: Perkin-Elmer R12B)

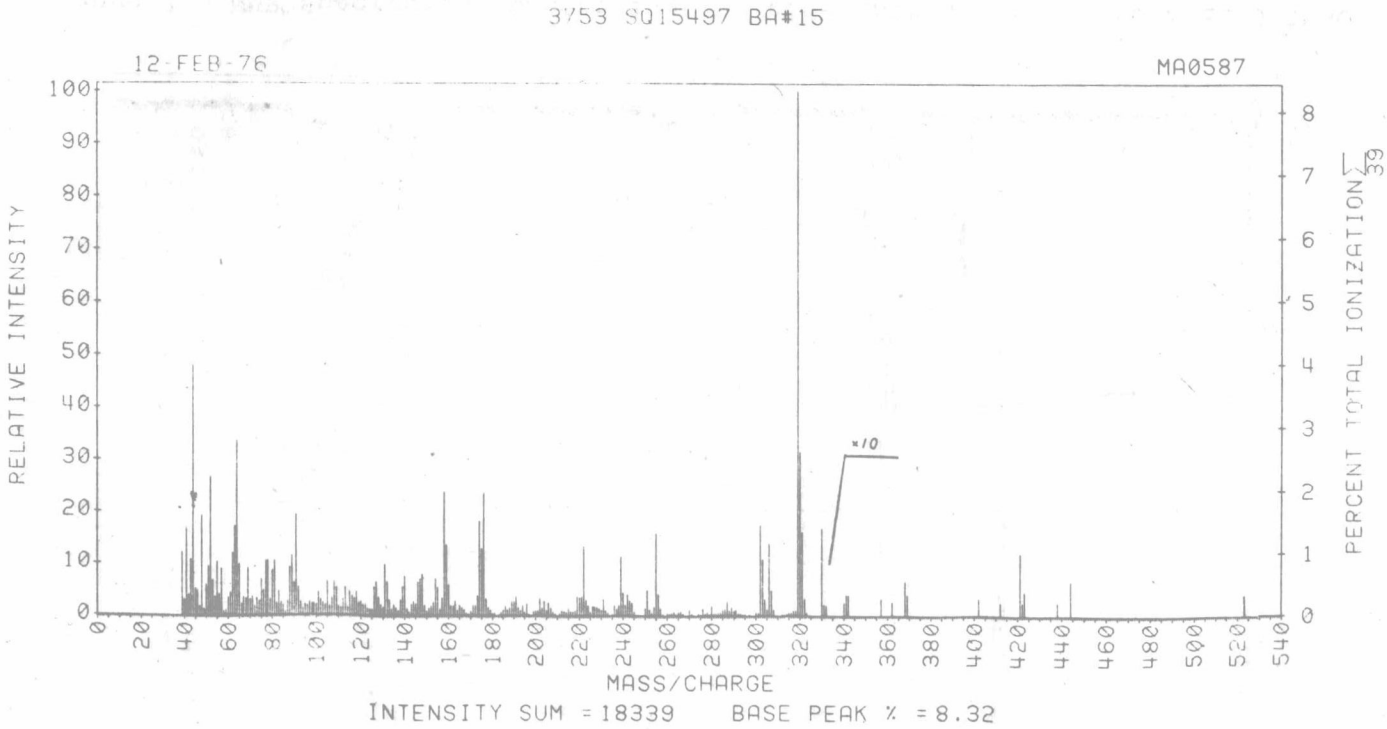


Figure 4. Low Resolution Mass Spectrum of Bendroflumethiazide (Instrument: AEI MS9)