Analytical Profiles of Drug Substances

Volume 10

Edited by

Klaus Florey

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New Brunswick, New Jersey

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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 tenth.

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 physiochemical 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 has made this venture possible. It is gratifying to note that increasingly profiles are being written not only in industrial laboratories but also in academic institutions worldwide.

All those who have found the profiles useful are requested to contribute a monograph of their own. The editors stand ready to receive such contributions.

The goal to cover all drug substances with comprehensive monographs is still a distant one. It is up to our perseverance to make it a reality.

Klaus Florey

CONTENTS

AMINOSALICYLIC ACID

Mahmoud M. A. Hassan, Ahmad I. Jado, and Muhammad Uppal Zubair

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1. DESCRIPTION

1.1 Nomenclature

1.1 1 Chemical Names

a. 4-Amino-2-hydroxybenzoic acid.

b. 4-Aminosalicylic acid.

c. Benzoic acid, 4-Amino-2-hydroxy.

The CAS Registry No. is [65-49-6].

1.1 2 Generic Name

p-Aminosalicylic acid.

1.1 3 Trade Names

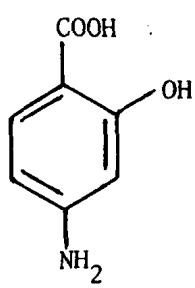
Apas, Apacil, Deapasil, Hellipidyl, PAS,. PAS-C, Pamcyl, Pamisyl, Parasil, Pasorbic, Pasolac, Parasalicil, Parasalindon, Pasnodia, Propasa, Rezipas, Sanipirol-4, Para-Pas, Pasem.

1.2 Formulae

1.2 1 Empirical

$C_7 H_7 NO_3$

1.2 2 Structural



1.2 3 Wiswesser Line Notation

ZR CQ DVQ

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1.3 Molecular Weight

153.13

1.4 Elemental Composition

C,54,90%; H, 4.61%; N, 9.5%; O, 31.34%.

1.5 Appearance, Color, Taste, Odor

White, or yellowish white, bulky powder or crystals darkens on exposure to light and air, odorless or has slight acetous odor.

2. Physical Properties

2.1 Crystal Properties

2.1 1 X-Ray Diffraction

Crystal data

Monoclinic, a = 7.209 (2), b = 3.786 (1), c_o = 25.109 (9) A°, B = 103.22 (3)°, U = 6.67.14 $A^{\circ 3}$, Z = 4, D_c = 1.53, F (000) = 320. Cu-Ka radiation, λ = 1.5418 A°; μ (Cu-Ka) = 10.20cm^{-1}. Systematic absences = h01, l = 2n + 1, 0k0, k = 2n + 1, space group $P2_1/C$ from systematic absences (1).

Optical goniometry

It crystallises from ethanol in at least two habits. The interfacial angles of habit I were measured with a Huber two circle optical goniometer and compared with angels calculated from unit-cell dimentions for all faces having Miller indices between (and including) +2 and -2. A unique set of assignments for the faces was obtained and confirmed by precision photography. The h k o net was in approximately reflecting position on the precession camera when the face-assigned indices (001) were approximately normal to X-ray beam. Fig. 1 shows a schematic drawing of habit I with assigned faces. The end faces of habit II did not have the indices (011) but precession photography and optical goniometry showed that (001) and (10$\bar{2}$) were its two largest faces.

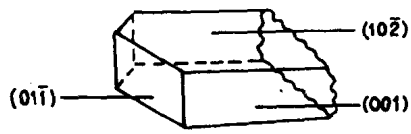
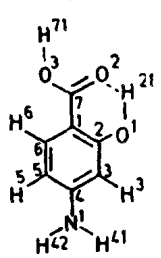


Fig. 1 : Schematic diagram of crystals of p-Aminosalicylic acid in habit I.

Crystal Structure

Two different crystal structures have been reported for p-aminosalicylic acid. Structure II has been reported before the advent of modern computers (2) while structure I has been developed very recently (1). Table 1 and 2 list the bond lengths and angels and Table 3 atom positions. Intramolecular contacts and angels involving the O(1)-H(21)...O(2) hydrogen bond are also included. Data for p-aminosalicylic acid are consistant with the idea that resonance structure (Ib) and (Ic) contribute significantly to its structure.



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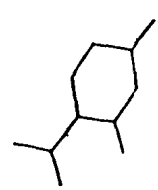
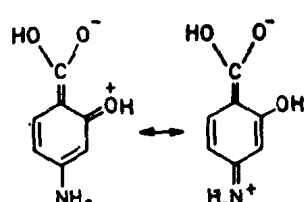


II



(Ib) (Ic)

Table 1

Bond lengths (A) in p-aminosalicylic acid (1), with standard deviations in parentheses. Intramolecular contacts involving the O(1)-H(21)...O(2) hydrogen bond are included.

O(1)-C(2)	1.361(2)	C(1)-C(2)	1.414(2)
O(2)-C(7)	1.243(2)	C(1)-C(6)	1.400(3)
O(3)-C(7)	1.311(2)	C(1)-C(7)	1.447(2)
O(2)...O(1)	2.620(2)	C(2)-C(3)	1.371(2)
N(1)-C(4)	1.364(2)	C(3)-C(4)	1.392(3)
O(1)-H(21)	0.98(3)	C(4)-C(5)	1.406(3)
O(3)-H(71)	0.95(3)	C(5)-C(6)	1.362(2)
O (2)...H(21)	1.73(3)	C(3)-H(3)	0.98(2)
N-H(41)	0.91(3)	C(5)-H(5)	0.98(2)
N-H(42)	0.83(3)	C(6)-H(6)	0.94(2)

Table 2

Bond angles(°) in p-aminosalicylic acid (1), with estimated standard deviations in parentheses. Angles involving the O(1)-H(21)...O(2) hydrogen bond are included.

O(2)-C(7)-O(3)	121.1(1)	O(1)-C(2)-C(3)	118.2(2)
O(2)-C(7)-C(1)	123(2)	C(2)-C(3)-C(4)	121.1(2)
O(3)-C(7)-C(1)	115.8(2)	C(3)-C(4)-C(5)	118.7(1)
C(7)-C(1)-C(2)	120.8(2)	C(3)-C(4)-N(1)	120.7(2)
C(7)-C(1)-C(6)	121.7(2)	C(5)-C(4)-N(1)	120.6(2)
C(2)-C(1)-C(6)	117.4(1)	C(6)-C(5)-C(4)	120.1(2)
C(1)-C(2)-O(1)	121.3(1)	C(1)-C(6)-C(5)	122.0(2)
C(1)-C(2)-C(3)	120.6(2)		

H(71)-O(3)-C(7)	113(2)	H(41)-N(1)-C(4)	120(2)
H(21)-O(1)-C(2)	107(2)	H(42)-N(1)-C(4)	115(2)
O(2)...H(21)-O(1)	147(3)	H(5)-C(5)-C(4)	119(1)
C(7)-O(2)...H(21)	100(1)	H(5)-C(5)-C(6)	121(1)
H(3)-C(3)-C(2)	118(1)	H(6)-C(6)-C(1)	119(1)
H(3)-C(3)-C(4)	121(1)	H(6)-C(6)-C(5)	119(1)
H(41)-N(1)-H(42)			

Table 3

Final atomic positions ($x10^4$; for H $x\ 10^3$) for p-amino-salicylic acid (I), with standard deviations in parentheses.

	x	y	z
O(1)	6 882(2)	3 539(4)	1 641.0(5)
O(2)	5 572(2)	1 178(4)	651.0(5)
O(3)	7 438(2)	1 345(4)	58.2(5)
N(1)	13 290(3)	7 453(5)	2 111.6(8)
C(1)	8 718(2)	3 353(5)	946.6(6)
C(2)	8 539(2)	4 138(5)	1 483.1(6)
C(3)	10 041(3)	5 531(5)	1 860.5(7)
C(4)	11 784(2)	6 175(5)	1 728.6(7)
C(5)	11 966(3)	5 457(5)	1 193.8(7)
C(6)	10 474(2)	4 058(5)	819.9(7)
C(7)	7 136(2)	1 880(5)	547.1(6)
H(21)	601(4)	241(9)	133(1)
H(71)	637(4)	37(8)	-19(1)
H(41)	1 316(4)	789(8)	246(1)
H(42)	1 427(4)	782(8)	200(1)
H(3)	958(3)	602(6)	223(1)
H(5)	1 319(3)	595(6)	110(1)
H(6)	1 064(2)	354(5)	47(1)

2.1 2 Melting Range

The melting point of 4-aminosalicylic acid is uncertain (3) : 135°-140° with decomposition (4), 148° (dec.)(5), 149-151°(dec.)(6). 150-151° with effervescence (7,8), 139-141°(dec.) (9) and 220° (dec.)(10,11) have been reported. Seaman et al (3) have concluded that the most nearly correct melting point is about 240° and the melting point is not a good criterion of purity.

2.2 Solubility

1 g in about 600 ml of water and about 21 ml of alcohol; slightly soluble in ether; practically insoluble in benzene. Solubility is increased with alkaline salts of alkali metals ($NaHCO_3$) and in weak nitric acid, the amine salts of hydrochloric and sulphuric acids are insoluble. The aqueous solutions have a pH of about 3.2 and when heated the acid decomposes (12).

2.3 Identification

1. p-Aminosalicylic acid gives an intense orange-brown color when reacted with potassium ferricyanide in alkaline solution (13).

2. It gives a green color which changes first to orange and then to orange-red on reaction with hexamine and sulphuric acid at room temperature (14).

2.4 Spectral Properties

2.4 1 Infrared Spectrum

The infrared spectrum of 4-aminosalicylic acid is recorded as a nujol mull on Unicam SP 1025 Spectrophotometer and is shown in Fig. 2. The assignments for the characteristic bands in the infrared spectrum listed in Table 4.

Table 4

Frequency cm^{-1}	Assignment
3520	NH_2
3400	NH_2, OH
1630	bonded C = 0
890	isolated C-H out of plane deformation.
820 800 770	C-H out of plane deformation.

Other characteristic finger print bands are:

1305, 1230, 1200, 1170, 1110, 970, 725 and 690 cm^{-1}. Other values for PAS in potassium bromide disc (15) are, 3571, 3448, 3030, 1667, 1613, 1515, 1449, 1299, 1220, 1190, 1163, 813 and 775.

2.4 2 Ultraviolet Spectrum (UV)

UV spectrum of PAS in ethanol was scanned using Cary, 219 spectrophotometer ; from 400 to 200 nm(16), three maxima and two minima were observed. The maxima are located at 235, 274 and 303 nm.

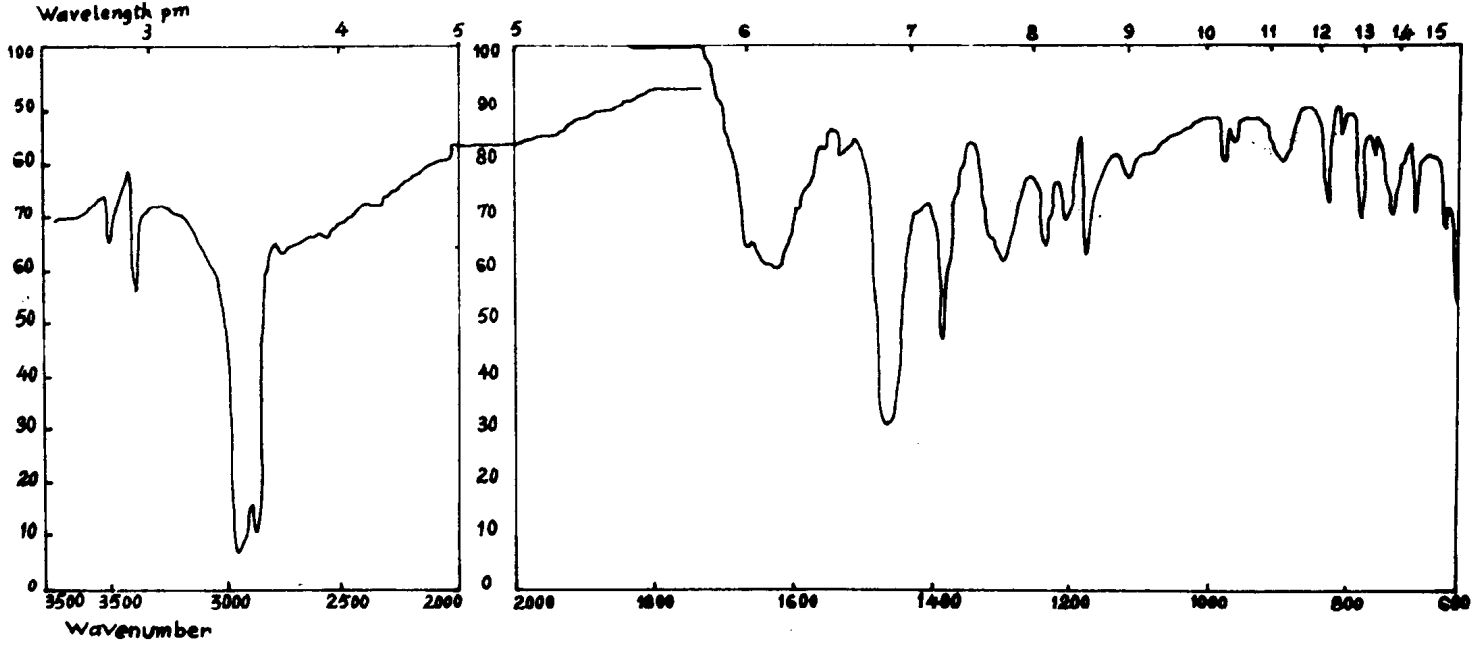


Fig. 2 : Infrared Spectrum of p-Aminosalicylic acid in Nujol.

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