# Solid-state Dehydrochlorination and Decarboxylation Reactions. Part 1. Reactions of *p*-Aminosalicylic Acid Hydrochloride and *p*-Aminosalicylic Acid, and Revised Crystal Structure of *p*-Aminosalicylic Acid

By **Chung-Tang Lin, Pik-Yen Siew, and Stephen R. Byrn,*** Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907, U.S.A.

The decomposition of *p*-aminosalicylic acid hydrochloride involves initial dehydrochlorination followed by decarboxylation to give *m*-aminophenol hydrochloride. The solid-state decarboxylation of *p*-aminosalicylic acid (I) presumably follows the same mechanism as the solution reaction (proton electrophilic substitution) since no decarboxylation of several *meta*-substituted salicylic acids was found. In addition, analyses of the crystal packing of (I) revealed several carboxy-protons within 5 Å of the nucleophilic ring carbon atom. A solid-state electrophilic substitution involving one of these protons would be consistent with available data concerning the solid-state reaction of (I).

The crystal structure of (I) [$a$ = 7.209(2), $b$ = 3.786(1), $c$ = 25.109(9) Å, β = 103.22°, space group $P2_1/c$] is reported and the published structure corrected. The structure was solved by direct methods and refined to an $R$ 0.044 for 1 044 observed reflections.

SOLUTION reactions which produce gases are well known and have been extensively studied. Several studies of the reactions of organic solids to produce gases have also been reported. These include the desolvation of crystal solvates,[1] the dehydration of a carbinolamine,[2] the decomposition of explosives including HMX and RDX,[3] the decomposition of solid azo-compounds,[4] the decarboxylation of peroxides,[5] and the decarboxylation of *p*-aminosalicylic [6] and benzoic acids.[7]

The kinetics and mechanism of the decarboxylation of *para*-substituted salicylic acid in solution have been investigated [6] and it was suggested that proton electrophilic substitution was the rate-determining step.[6]

We were interested in determining whether the same mechanism was operative in the solid state. In addition, since studies of the solid-state decarboxylation of *para*-substituted benzoic acids indicated that *para*-substituents OH, $NO_2$, NHMe, and $NMe_2$ decarboxylated while F and Cl did not,[7] we studied some *meta*-substituted (either electron-releasing or -withdrawing group) salicylic acids. We also studied the decarboxylation of sodium *p*-aminosalicylate and *p*-aminosalicylic acid hydrochloride under similar conditions. Unexpectedly, *p*-aminosalicylic acid hydrochloride decarboxylated smoothly to give *m*-aminophenol hydrochloride even though the amino-group is no longer electron donating. In order better to understand this reaction, *meta*-substituted aminosalicylic acid hydrochlorides were also studied.

We also report the revised crystal structure of *p*-aminosalicylic acid and an interpretation of its solid-state decarboxylation in terms of crystal packing.

## EXPERIMENTAL

*p*-Aminosalicylic acid (I) (recrystallized from ethanol), *m*-aminophenol, 5-chlorosalicylic acid, and 3-methylsalicylic acid were from Aldrich Chemical Co. Mixed m.p.s of *p*-aminosalicylic acid and *m*-aminophenol, measured on a Kofler hot-stage, gave lowest m.p. *ca.* 109—111 °C, for an approximate equimolar mixture. All other compounds were prepared as described. N.m.r. spectra were recorded on a Varian EM 360 spectrometer with tetramethylsilane as either internal or external standard. All crystallographic calculations were made by use of the '*X*-Ray' program system.[8]

Accurate cell dimensions were determined from least-squares analysis of the positions of 14 independent reflections, and gave the following crystal data, in agreement with that published previously.[9]

*Crystal Data for* p-*Aminosalicylic Acid* (I).—$C_7H_7NO_3$, $M$ = 153.41, Monoclinic, $a$ = 7.209(2), $b$ = 3.786(1), $c$ = 25.109(9) Å, β = 103.22(3)°, $U$ = 667.14 Å$^3$, $Z$ = 4, $D_c$ = 1.53, $F(000)$ = 320. Cu-$K_\alpha$ radiation, λ = 1.541 8 Å; μ(Cu-$K_\alpha$) = 10.20 cm$^{-1}$. Systematic absences: h0l, l = 2n + 1, 0k0, k = 2n + 1, space group $P2_1/c$ from systematic absences.

*Data Collection.*—Crystals of *p*-aminosalicylic acid are well formed and elongated along the $b$ direction. A crystal *ca.* 0.144 × 0.075 × 0.100 mm$^3$ was sealed in a glass capillary external diameter (0.5 mm) and aligned with its axis parallel to the diffractometer φ axis. Data were collected on a card-driven Picker four-angle diffractometer by use of β-filtered Cu-$K_\alpha$ radiation and a scintillation detector. A θ—2θ scan range of 2.6° with a scan speed of 30 s deg$^{-1}$ was used. Backgrounds were counted for 20 s at each end of the scan range. The reciprocal region *hkl*

[1] See S. R. Byrn and C. T. Lin, *J. Amer. Chem. Soc.*, 1976, **98**, 4004; D. Y. Curtin and I. C. Paul, *Science*, 1975, **187**, 19, and references therein.

[2] S. A. Puckett, I. C. Paul, and D. Y. Curtin, *J. Amer. Chem. Soc.*, 1976, **98**, 786.

[3] See W. C. McCrone and H. Morawetz, in 'Physics and Chemistry of the Organic Solid State,' eds. D. Fox, M. M. Labes, and A. Weissberger, Interscience, New York, 1965, vol. II, p. 725 *et seq.*, and vol. I, p. 287 *et seq.*

[4] A. B. Jaffe, K. J. Skinner, and J. M. McBride, *J. Amer. Chem. Soc.*, 1972, **91**, 8510.

[5] N. J. Karch, E. T. Koh, B. L. Whitsel, and J. M. McBride, *J. Amer. Chem. Soc.*, 1975, **97**, 6729; S. E. Morsi, J. M. Thomas, and J. O. Williams, *J.C.S. Faraday I*, 1975, 1857.

[6] (*a*) S. Kornblum and B. Sciarrone, *J. Pharm. Sci.*, 1964, **53**, 935; (*b*) J. T. Carstensen and P. Pothisiri, *ibid.*, 1975, **64**, 37; (*c*) A. Dobrowsky, *Monatsh.*, 1966, **87**, 574; (*d*) S. R. Byrn, *J. Pharm. Sci.*, 1976, **65**, 1.

[7] J. T. Carstensen and M. N. Musa, *J. Pharm. Sci.*, 1972, **61**, 1172.

[8] '*X*-Ray' program system, Computer Science Centre, University of Maryland, Technical Report TR 192, 1972.

[9] F. Bertinotti, G. Giacomello, and A. M. Liquori, *Acta Cryst.*, 1945, **7**, 808.

and $hkl$ was explored to $2\theta_{max.}$ 133.85°. Of 1 196 independent reflections 1 044 had $F_o > 3\sigma(F_o)$ and were considered observed. A standard reflection measured every 60 reflections decayed only slightly (*ca.* 6%) during data collection. Data were corrected for isotropic extinction but not for absorption.

*Structure Analysis.*—The structure was solved for non-hydrogen atoms by direct methods and refined by full-matrix least-squares to $R$ 0.154, with isotropic temperature factors, and then to $R$ 0.086 with anisotropic temperature factors. Hydrogen atoms were located from a difference map and added to the refinement with isotropic thermal parameters. The final $R$ was 0.044. The weighting scheme used was $1/w = 1 + [(F_o - B)/A]^{1/2}$ with $A = 2.05$ and $B = 7.03$. In the final difference map there were no residual peaks >0.18 eÅ$^{-3}$.

Preliminary attempts to fit positional and thermal parameters from ref. 9 to our experimental data resulted in enormous shifts in the parameters during least-squares refinement. The result showed a random structural model with $R$ 0.65. However, a fair trend of agreement between $F_o$ and $F_c$ was found for the $0kl$ reflections. The $y$ and $z$ co-ordinates of ref. 9 differ from the final parameters by only 1 σ and the two sets of atomic positions can be brought into coincidence by reflection through a mirror plane at $x = 1/4$ (see Figure 1).* Superposition of the (010) projection

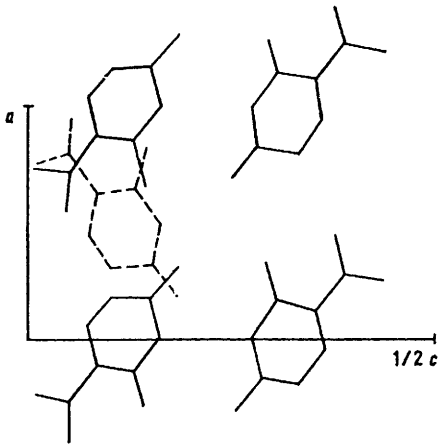



FIGURE 1 Superposition of the structure given in ref. 8 (dotted line) projected on (010) over a portion of the unit cell of the present structure (full lines)

of the Fourier map shown in ref. 9 with an (010) projection of the co-ordinates from our data ruled out the possibility that these workers [9] made an error in publishing their co-ordinates (see Figure 1). Comparison of the $F_o$ from ref. 9 with ours showed good agreement for many selected reflections.

Observed and calculated structure factors and thermal parameters are deposited as Supplementary Publication No. SUP 22240 (3 pp., 1 microfiche).†

*Optical Goniometry of* p-*Aminosalicylic Acid.*—*p*-Aminosalicylic acid crystallizes 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 angles calculated from unit-cell dimensions 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 precession photography. The $hk0$ net was in approximately reflecting position on the precession camera when the face-assigned indices (001) were approximately normal to the $X$-ray beam. Figure 2 shows a

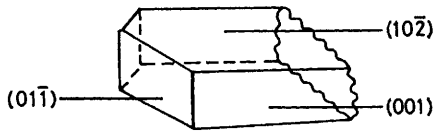



FIGURE 2 Schematic diagram of crystals of *p*-aminosalicylic acid in habit I

schematic drawing of habit I with the assigned faces. The end faces of habit II did not have the indices (01$\bar{1}$) but precession photography and optical goniometry showed that (001) and (10$\bar{2}$) were its two largest faces.

*3-Amino-5-chlorosalicylic Acid* (IX).—This compound was prepared by a method similar to that described in the literature.[10,11] 5-Chlorosalicylic acid (10 g) was stirred with concentrated nitric acid (100 ml) at room temperature for 8 h. The filtered solution was cooled in a freezer overnight, and yellow needle crystals (7 g) were collected. Recrystallization from water gave yellow needles (m.p. 165—167 °C). The n.m.r. spectrum (deuterioacetone) showed a peak (δ 8.2) which indicated that they were 5-chloro-3-nitrosalicylic acid. Further reaction with nitric acid gave 4-chloro-2,6-dinitrophenol, m.p. 80 °C.

An aqueous solution of 5-chloro-3-nitrosalicylic acid was added to a small amount of sodium hydroxide. The yellow solution became red and an excess of an aqueous solution of sodium hydrosulphite was added, with stirring, until the red solution became clear light yellow. The solution was then cooled in a refrigerator overnight and the suspended solid identified as (IX) by n.m.r. and elemental analysis. The n.m.r. spectrum in trifluoroacetic acid showed two doublet peaks (δ 7.5—7.6 and 7.8—7.9) (Found: C, 44.70; H, 3.15; Cl, 19.1; N, 7.30. Calc. for $C_7H_6ClNO_3$: C, 44.8; H, 3.2; Cl, 18.93; N, 7.47%). The hydrochloride was obtained by reaction with hydrochloric acid.

*5-Amino-3-methylsalicylic Acid* (VIII).—As described in ref. 12, 3-methylsalicylic acid (5 g) was dissolved in acetic acid (50 ml) and cooled in an ice-bath. After equilibration, concentrated nitric acid (50 ml) was added slowly with stirring during 1 h and a brown solid (3 g) was collected. Recrystallization from aqueous alcohol solution gave yellow needle crystals (m.p. 200—202 °C) of 3-methyl-5-nitrosalicylic acid which reacted with nitric acid to give 2-methyl-4,6-dinitrophenol (m.p. 85 °C). The n.m.r. spectrum (deuterioacetone) showed one singlet (δ 2.4) and two doublet peaks (δ 8.3—8.4 and 8.7—8.8).

An aqueous solution of 3-methyl-5-nitrosalicylic acid was added to a small amount of sodium hydroxide, when the yellow solution became red. An excess of aqueous sodium hydrosulphite was then added with stirring until the red solution became clear and light yellow, and the solution cooled in a refrigerator overnight. The suspended solid was identified as (VIII) by n.m.r. and elemental analysis. The n.m.r. spectrum (trifluoroacetic acid) showed one singlet

* In ref. 9, $B$ was reported as obtuse; however, the atom parameters appeared to refer to a unit cell with $B$ acute.

† See Notice to Authors No. 7 in *J.C.S. Perkin II*, 1977, Index issue.

[10] Beilstein's Handbuch Der Organische Chemie, Verlag Chemie, vol. IX, 1929, p. 120.

[11] Ref. 10, vol. XIV, 1929, p. 578.

[12] Ref. 10, vol. X, 1929, p. 224.

(δ 2.4) and two doublet peaks (δ 7.5—7.6 and 7.8—7.9) (Found: C, 57,2; H, 5.4; N, 8.3. Calc. for $C_8H_9NO_3$: C, 57.49; H, 5.39; N, 8.38%). The hydrochloride salt was obtained by reaction with concentrated hydrochloric acid.

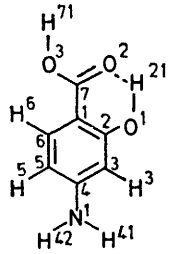
*Sodium* p-*Aminosalicylate*.—The equivalent molar amount of (I) was dissolved in aqueous sodium hydroxide solution. After cooling the solution in a refrigerator needle crystals were formed (Found: C, 47.8, H, 3.6; H, 7.9. Calc. for $C_7H_6NNaO_3$: C, 48.01; H, 3.43; N, 7.91%).

*Solid-state Decomposition Reactions*.—Reactions were run either in an oil-bath, a sand-bath, or on a Zeiss microscope equipped with a camera and a Mettler FP 5 hot-stage. The single-crystal reactions were run by sealing the crystal between two cover slides with Hi-Vac grease. In the large-scale reactions the compound was placed in a small closed vial and heated at constant temperature in air. After a certain time the remainder of the material was analysed by use of n.m.r., u.v., or i.r. spectroscopy.

The extent of decomposition of a given weight of *p*-aminosalicylic acid hydrochloride was estimated by washing the remainder of the material with water. Since any *m*-aminophenol hydrochloride present would dissolve in water while *p*-aminosalicylic acid hydrochloride would not, the weight of the dried insoluble solid allowed calculation of the extent of decomposition.

## RESULTS AND DISCUSSION

*Crystal Structure of* p-*Aminosalicylic Acid* (I).—The structure is different from that reported in ref. 9 (see



(I) Showing crystallographic atom numbering system

Figure 1) before the advent of modern computers. Tables 1 and 2 list the bond lengths and angles in (I)

TABLE 1

Bond lengths (Å) in *p*-aminosalicylic acid (I), 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) |

and Table 3 atom positions. Intramolecular contacts and angles involving the O(1)–H(21) · · · O(2) hydrogen bond are also included. Table 4 compares the desig-

TABLE 2

Bond angles (°) in *p*-aminosalicylic acid (I), 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) | 118.0(2) |
| O(2)–C(7)–C(1) | 123.1(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) | 125(2) | | |

TABLE 3

Final atomic positions (× $10^4$; for H × $10^3$) for *p*-aminosalicylic acid (I), with standard deviations in parentheses

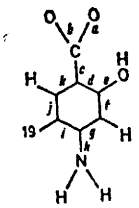
| | *x* | *y* | *z* |
|---|---|---|---|
| O(1) | 6 882(2) | 3 539(4) | 1 641.0(5) |
| O(2) | 5 572(2) | 1 178(4) | 651.0(5) |
| O(3) | 7 438(2) | 1 345(4) | 58.2(5) |
| N(1) | 13 290(3) | 7 453(5) | 2 111.6(8) |
| C(1) | 8 718(2) | 3 353(5) | 946.6(6) |
| C(2) | 8 539(2) | 4 138(5) | 1 483.1(6) |
| C(3) | 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) | 985(3) | 602(6) | 223(1) |
| H(5) | 1 319(3) | 595(6) | 110(1) |
| H(6) | 1 064(2) | 354(5) | 47(1) |

TABLE 4

Comparison of the designated * bond lengths in *p*-aminosalicylic acid (I), salicylic acid (II), and *p*-aminobenzoic acid (III)

| Bond | (III) † | (II) ‡ | (I) |
|---|---|---|---|
| *a* | 1.242 | 1.234 | 1.243 |
| *b* | 1.304 | 1.307 | 1.311 |
| *c* | 1.460 | 1.457 | 1.447 |
| *d* | 1.402 | 1.404 | 1.414 |
| *e* | | 1.358 | 1.361 |
| *f* | 1.371 | 1.381 | 1.371 |
| *g* | 1.396 | 1.379 | 1.392 |
| *h* | 1.380 | | 1.364 |
| *i* | 1.396 | 1.384 | 1.406 |
| *j* | 1.380 | 1.365 | 1.362 |
| *k* | 1.396 | 1.394 | 1.400 |

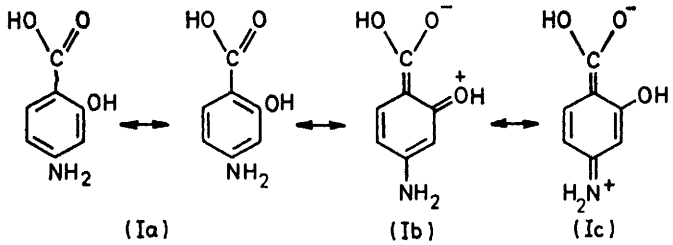
* Bond lengths are designated as:



† The mean of two crystallographically independent molecules from ref. 14.

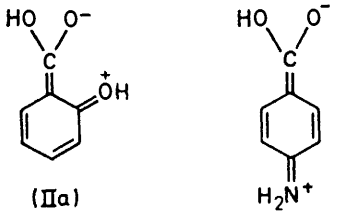
‡ From ref. 13.

nated bond lengths in *p*-aminosalicylic acid with those in salicylic acid [13] and *p*-aminobenzoic acid.[14]



(Ia) (Ib) (Ic)

Data for *p*-aminosalicylic acid are consistent with the idea that resonance structures (Ib) and (Ic) contribute



(IIa) (IIIa)

significantly to the structure of (I). If they do so then bond *j* (Table 4) would be the shortest ring carbon–carbon bond, and bonds *d*, *k*, and *i* should be the longest. This is seen to be so.

idea that resonance structures (IIa) and (IIIa) are important contributors to their structures. In salicylic acid bonds *d*, *f*, *i*, and *k* are longer than bonds *g* and *j* (see Table 4). In *p*-aminobenzoic acid bonds *f* and *j* are shortest while *d*, *g*, *i*, and *k* are longer.

The ring carbon–carbon bond lengths can be best explained in terms of resonance hybrids and this series of compounds appears to provide excellent evidence for resonance theory as applied to aromatic compounds.

The ring C–C–C bond angles particularly at carbon atoms C(1) and C(4) [117.4(1) and 118.7(1)°] deviate significantly from 120°. This deviation may be related to the bond-length distortions introduced by contributions of resonance structures (Ib) and (Ic).

The bond lengths and angles associated with the O(1)–H(21) • • • O(2) hydrogen bond suggest that this bond in (I) is at least as strong as that in salicylic acid (II) [9] but perhaps slightly weaker than that in 3,6-dichloro-2,5-dihydroxyterephthalate (IV).[15] The O • • • O distances for (I), (II), and (IV) are 2.607, 2.620, and 2.532 Å. The shortened O • • • O distance in the terephthalate (IV), could be due to buttressing caused by the *meta*-chloro-substituents. The H • • • O distances and O–H • • • O angles are almost identical in (I) (1.71 Å and 147°) and (II) [9] (1.704 Å and 146°).

Analysis of the best planes in (I) indicated that the plane involving the ring carbon atoms C(1)—(6), was not

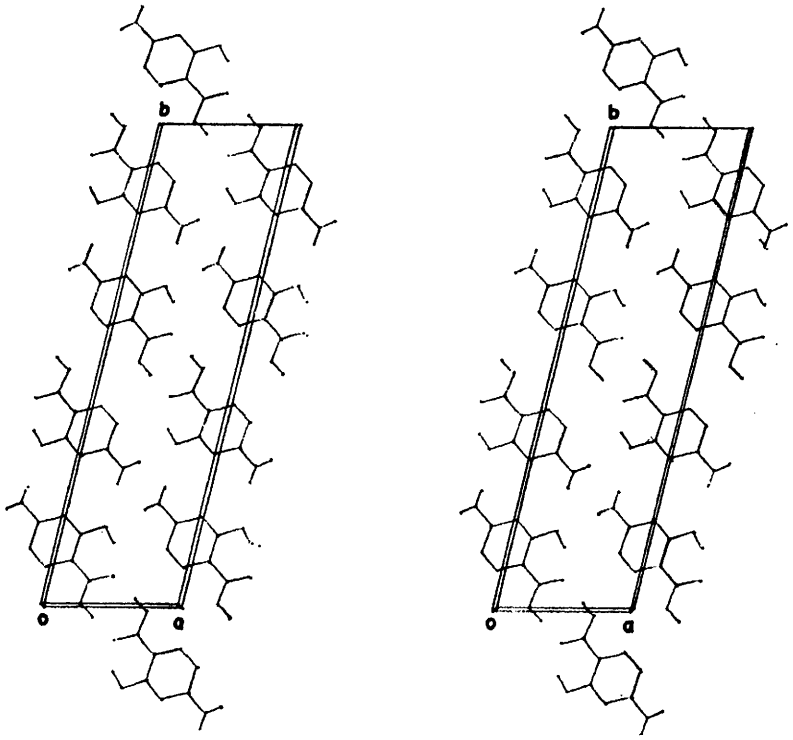



FIGURE 3 Stereoscopic packing drawing of *p*-aminosalicylic acid (I)

Furthermore, the data for salicyclic acid (II) [13] and *p*-aminobenzoic acid (III) [14] are consistent with the

statistically planar ($\chi^2$ 37.16; probability that such a set of atoms would be planar, 0.005) and the deviations of

[13] M. Sundaralingham and L. H. Jensen, *Acta Cryst.*, 1965, **18**, 1053.

[14] T. F. Lai and R. E. Marsh, *Acta Cryst.*, 1967, **22**, 885.

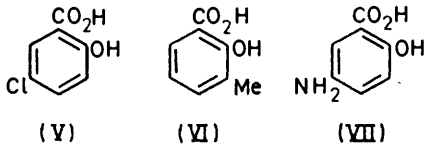
[15] S. R. Byrn, D. Y. Curtin, and I. C. Paul, *J. Amer. Chem. Soc.*, 1972, **94**, 890.

the ring atoms from their best plane ranged from 0.001 to 0.010 Å. This is perhaps related to the contribution of quinoid resonance structures (Ib) and (Ic) to the structure of (I). The atoms C(7), O(1), and N(1) were 0.008, −0.002, and 0.167 Å from this best plane, and the carboxy-group made an angle of 1.5° with it. The angle between the carboxy and ring plane in salicylic acid was 1.1°.[9]

*Crystal Packing.*—Figure 3 shows the packing of *p*-aminosalicylic acid, and Table 5 lists the important intermolecular contacts involving both the non-hydrogen atoms and the hydrogen atoms involved in hydrogen bonds.

The crystal packing is dominated by hydrogen bonding (see Figure 3). The acid groups are dimerized, as are salicylic and *p*-aminobenzoic acid and many others. At least one of the amino-hydrogen atoms is hydrogen-bonded to O(1), with H(41) being involved in a much stronger hydrogen bond than H(42). The H(41) · · · O(1) distance is 2.28(3) while the H(42) · · · O(1) distance is 2.78(3) and is actually slightly longer than the sum of the van der Waals radii (*ca.* 2.76 Å).[16] O(1) is associated with both N–H hydrogen atoms.

*Solid-state Reactions of Salicylic Acids, Aminosalicylic Acids, and Their Hydrochlorides.*—Solid *p*-aminosalicylic acid decomposed at 70 °C and *p*-aminosalicylic acid hydrochloride at 100 °C. For purposes of comparison the decarboxylation of several solid salicylic acids were studied at 100 °C. *p*-Aminosalicylic acid completely decomposed to *m*-aminophenol in 10 h. Mixed m.p.s indicated that the eutectic m.p. of *p*-aminosalicylic acid and *m*-aminophenol was *ca.* 110 °C, suggesting that at 100 °C the reaction is proceeding in the solid state. The salicylic acids (V)—(IX) did not measurably decompose even when heated for 1 week.




The rate constants $k_H^A$ for decarboxylation of *p*-$NH_2$, *p*-OH, *p*-$OCH_3$, and *p*-$CH_3$, *p*-amino-, -hydroxy-, -methoxy-, and -methylsalicylic acids in solution gave a Hammett $\rho^+$ plot with a $\rho$ 4.38.[17] The predicted decomposition rates of salicylic acids (VIII), (VI), (VII), (IX), and (V) relative to *p*-aminosalicylic acid were $10^{-4}$, $10^{-5}$, $10^{-5}$, $10^{-6}$, and $10^{-7}$. The $\sigma$ rather than the $\sigma^+$ was used for the *meta*-substituents in estimating these rates.[18] The fact that solids (V)—(IX) did not decompose is consistent with these predicted rates. Sodium *p*-salicylate was also stable under these conditions. This would rule out the possibility of a carbanion mechanism of the type which is operative in the decarboxylation of trinitrobenzoic acid.[19]

TABLE 5

Intermolecular distances <3.70 Å involving non-hydrogen atoms, and for hydrogen atoms involved in hydrogen bonds

| | | | |
|---|---|---|---|
| N(1) · · · O(1$^{I}$) | 3.420(3) | C(5) · · · O(3$^{III}$) | 3.486(3) |
| C(5) · · · O(1$^{I}$) | 3 536(2) | O(3) · · · C(6$^{III}$) | 3.417(3) |
| C(5) · · · O(2$^{I}$) | 3.586(3) | C(6) · · · O(3$^{IV}$) | 5.582(3) |
| O(1) · · · H(42$^{I}$) | 2.78(3) | H(41) · · · O(1$^{IV}$) | 2.28(3) |
| H(71) · · · O(2$^{I}$) | 1.71(3) | O(2) · · · O(3$^{V}$) | 2.650(2) |
| C(3) · · · C(2$^{II}$) | 3.496(3) | O(2) · · · C(7$^{V}$) | 3.393(2) |
| C(1) · · · C(7$^{II}$) | 3.494(3) | O(3) · · · O(3$^{V}$) | 3.607(2) |
| N(1) · · · C(4$^{II}$) | 3.540(3) | O(3) · · · C(7$^{V}$) | 3.519(2) |
| C(5) · · · C(6$^{II}$) | 3.490(3) | N(1) · · · O(1$^{VI}$) | 3.189(3) |

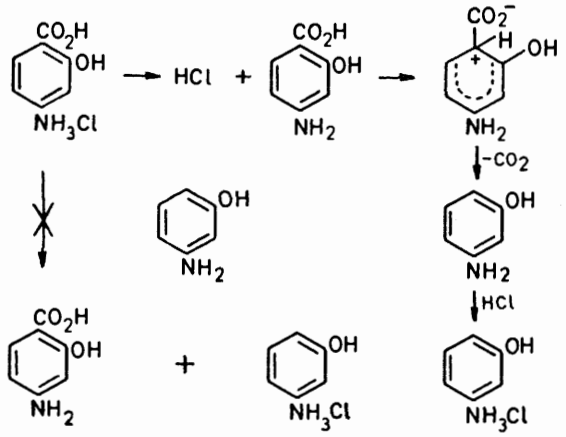
Roman numeral superscripts refer to molecules related to the one at the origin by the following symmetry operations:

| | | | |
|---|---|---|---|
| I | $1 + x, y, z$ | IV | $2 - x, -y, -z$ |
| II | $x, 1 + y, z$ | V | $1 - x, -y, -z$ |
| III | $2 - x, 1 - y, -z$ | VI | $2 - x, 1/2 + y, 1/2 - z$ |

Surprisingly, the hydrochloride salt of *p*-aminosalicylic acid [20] showed a slight amount of decomposition (<10%) after 10 h at 100 °C, even though its predicted relative rate in solution should be *ca.* $10^{-10}$. After longer reaction times sublimed *m*-aminophenol hydrochloride could be isolated near the top of a closed vial. Analysis of the material remaining on the bottom of the vial showed it was *p*-aminosalicylic acid hydrochloride and a trace of *p*-aminosalicylic acid. In contrast the hydrochloride salts of (VII), (VIII), and (IX) did not decarboxylate after 1 week at 150 °C. However, analysis showed that these compounds had lost hydrogen chloride gas. Resonance considerations indicate that *p*-aminosalicylic acid should be a weaker base than other aromatic amines lacking *p*-carboxy-groups and this was evident since we always obtained some *p*-aminosalicylic acid upon recrystallization of its hydrochloride. Thus *p*-aminosalicylic acid hydrochloride can undergo relatively facile dehydrochlorination reactions. Based on this evidence we suggest that the decarboxylation of *p*-aminosalicylic acid hydrochloride involves initial loss of HCl, followed by decarboxylation, sublimation of *m*-aminophenol, and finally hydrochlorination of the *m*-aminophenol product. This sequence (Scheme) is consistent with the fact that no solid–solid reaction between *m*-aminophenol and *p*-aminosalicylic acid hydrochloride was observed, when crystals of the two were placed in contact. In addition no detectable amount of *m*-aminophenol hydrochloride has been found on the bottom of the vial. Control experiments suggested that *m*-aminophenol hydrochloride would not

[16] A. I. Kitaigorodskii, 'Organic Chemical Crystallography,' Consultants Bureau, New York, p. 7.
[17] A. V. Willi and J. F. Stocker, *Helv. Chim. Acta*, 1954, **37**, 1113; A. V. Willi, *Trans. Faraday Soc.*, 1959, **55**, 433; A. V. Willi and P. Vilk, *Z. phys. Chem.*, 1963, **59**, 189.
[18] J. Hine, 'Physical Organic Chemistry,' McGraw-Hill, New York, 1962, p. 87.
[19] See *e.g.*, W. M. Schubert and J. D. Gardner, *J. Amer. Chem. Soc.*, 1953 75, 1481 (1953); D. Trivich and F. H. Verhoek, *J. Amer. Chem. Soc.*, 1943, **65**, 1919; (*c*) F. H. Verhoek, *ibid.*, 1939, **61**, 186.
[20] See *e.g.* M. D. Cohen and B. S. Green, *Chem. in Britain*, 1973, p. 490, and references therein.

readily sublime under these conditions. This evidence appears to rule out a reaction involving solid–solid



SCHEME

transfer of HCl to *m*-aminophenol and direct decarboxylation.

react.[20] Based on this photochemical evidence we have determined all contacts of <5 Å between the acid proton H(71) and the C(1) carbon atom. (The H · · · C contact in the acid dimers was excluded). These contacts (and symmetry positions) are: C(1) · · · H($71^{II}$) 3.98(3), C(1) · · · H($71^{III}$) 4.99(3), C(1) · · · H($71^{IV}$), 4.60(3), and C(1) · · · H(71) (at $1-x, 1-y, -z$), 4.42(3). The protons and carbon atom designated with a dot in Figure 4 are those involved in these contacts. These close contacts suggest that the reaction can proceed through the crystal in several directions.

A crystal of *p*-aminosalicylic acid heated at 72 °C on a microscope hot-stage decomposed with nucleation on the (102) crystal face, as indicated by pitting (see Figure 6 of ref. 6*d*). Observation of other crystals viewed from directions other than that described in ref. 6*d* showed that the reaction consistently began on the (10$\bar{2}$) crystal face.

The nucleation of the reaction on the (10$\bar{2}$) crystal face is consistent with crystal packing which showed that there were layers of polar carboxy-groups and nonpolar

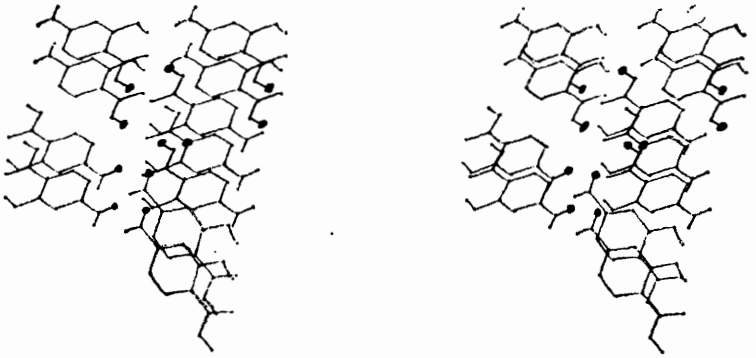


FIGURE 4 Stereoscopic view of *p*-aminosalicylic acid showing the acid protons within 5 Å of the nucleophilic ring carbon atom. The acid protons and the ring carbon atom of interest are denoted with heavy dots. The *a* crystal axis is horizontal in this view

All the foregoing suggest that the solid-state decarboxylation of *p*-aminosalicylic acid proceeds by the same mechanism as does the solution reaction. One explanation of the solid-state reaction is that it proceeds through the crystal by addition of a carboxylate proton to either $ArCO_2H$ or $ArCO_2^-$, as does the reaction in aqueous solution. This postulate is consistent with the crystal packing.

Studies of solid-state photochemical reactions indicated that double bonds within *ca.* 5 Å of each other could aromatic groups approximately perpendicular to the (10$\bar{2}$) face and parallel to the (100) face (see Figure 7, ref. 6*d*). Thus, carbon dioxide, once formed, would be expected to exit from the (10$\bar{2}$) face in preference to the (100) face as observed.

This research was supported by a grant from the National Institute of Health. We thank Professor D. Y. Curtin, Department of Chemistry, University of Illinois, Urbana, for helpful discussions.

[7/935 *Received*, 30*th May*, 1977]