The Studies of 5-Aminosalicylaldehyde Derivatives. III.[1] The Preparation of 5-Aminosalicylaldehyde Hydrazones by Reduction of 5-(*p*-Sulfophenylazo)salicylaldehyde Hydrazone

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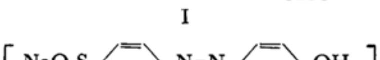
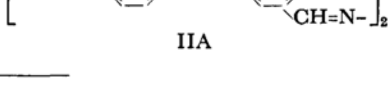
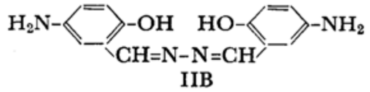
In a previous paper,[1] it was reported that the reduction of the sodium salt of 5-(*p*-sulfophenylazo)-salicylaldehyde (Formula I) with sodium hydrosulfite gave only a resinous product. This fact can be interpreted as follows. Even if the aminosalicylaldehyde is formed in the course of the reduction of I, the formyl and amino groups in aminosalicylaldehyde are so reactive that aminosalicylaldehyde may undergo spontaneous condensation polymerisation. Therefore, in order to obtain the monomeric compound, either the formyl or amino group must be protected from the polymerisation. The purpose of the present investigation is to prepare 5-aminosalicylaldehyde derivatives with the free amino group, which may be formed by the reductive cleavage of the azo linkage in the derivatives of I. According to Weil *et al.*,[2] Oddo *et al.*,[3] and Tanaka,[1] 5-aminosalicylaldehyde phenylhydrazone is one of only a few derivatives that are stable in spite of the presence of a free amino group. On the basis of this fact, I was converted to various kinds of hydrazones in order to block the formyl group.


I


IIA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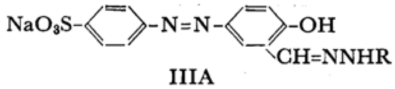
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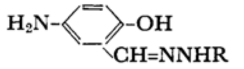
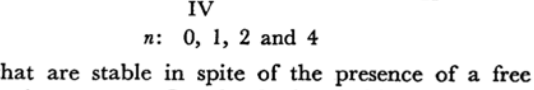

IIIB

R:
a $-CH_3$
b $-C_6H_5$
c $-C_6H_4CH_3(o)$
d $-C_6H_4CH_3(m)$
e $-C_6H_4CH_3(p)$
f $-C_6H_4Cl(p)$
g $-COCH_3$
h $-COC_2H_5$
i $-COC_6H_5$
j $-COC_6H_4OH(o)$
k $-COC_6H_4OH(m)$
l $-COC_6H_4OH(p)$
m $-COC_6H_4NH_2(o)$
n $-COC_6H_4NH_2(p)$
o $-COC_5H_4N(2)$
p $-COC_5H_4N(3)$
q $-COC_5H_4N(4)$
r $-CONH_2$
s $-CSNH_2$


IV

n: 0, 1, 2 and 4

The reaction of hydrazine with the sodium salt of I gave the sodium salt of 5-(*p*-sulfophenylazo)-salicylaldehyde azine (Formula IIA). In the similar way, methyl-, phenyl-, and tolyl-hydrazines

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[1] Part II: M. Tanaka, This Bulletin, **40**, 1724 (1967).

[2] H. Weil, M. Traun and Marcel, *Chem. Ber.*, **55**, 2664 (1958).

[3] G. Oddo and A. Giacalone, *Gazz. Chim. Ital.*, **58**, 290 (1928).

TABLE 1. HYDRONE DERIVATIVE OF SODIUM SALT OF

Hydrazone	Appearance	Formula
IIA	Yellowish powder	$C_{26}H_{18}O_8N_6S_2Na_2\cdot 1.5H_2O$
IIIA, a	Yellowish plates	$C_{14}H_{13}O_4N_4SNa$
IIIA, b	Yellowish powder	$C_{19}H_{15}O_4N_4SNa$
IIIA, c	Reddish orange plates	$C_{20}H_{17}O_4N_4SNa\cdot 2H_2O$
IIIA, d	Orange plates	$C_{20}H_{17}O_4N_4SNa\cdot 2.5H_2O$
IIIA, e	Orange yellow plates	$C_{20}H_{17}O_4N_4SNa\cdot 4H_2O$
IIIA, f	Brown red needles	$C_{19}H_{14}O_4N_4SClNa$
IIIA, g	Orange yellow needles	$C_{15}H_{13}O_5N_4SNa\cdot 3H_2O$
IIIA, h	Yellowish needles	$C_{16}H_{15}O_5N_4SNa\cdot 3H_2O$
IIIA, i	Orange yellow needles	$C_{20}H_{15}O_5N_4SNa\cdot 6H_2O$
IIIA, j	Orange yellow needles	$C_{20}H_{15}O_6N_4SNa\cdot 3H_2O$
IIIA, k	Orange yellow needles	$C_{20}H_{15}O_6N_4SNa\cdot 5.5H_2O$
IIIA, l	Orange needles	$C_{20}H_{15}O_6N_4SNa\cdot 2H_2O$
IIIA, m	Orange needles	$C_{20}H_{16}O_5N_5SNa\cdot 3.5H_2O$
IIIA, n	Orange needles	$C_{20}H_{16}O_5N_5SNa\cdot 2.5H_2O$
IIIA, o	Orange plates	$C_{19}H_{14}O_5N_5SNa\cdot 3H_2O$
IIIA, p	Orange yellow plates	$C_{19}H_{14}O_5N_5SNa\cdot 3H_2O$
IIIA, q	Yellowish plates	$C_{19}H_{14}O_5N_5SNa\cdot 3H_2O$
IIIA, r	Yellowish plates	$C_{14}H_{12}O_5N_5SNa\cdot H_2O$
IIIA, s	Yellowish needles	$C_{14}H_{12}O_4N_5S_2Na\cdot H_2O$
IV, 0	Yellowish plates	$C_{28}H_{20}O_{10}N_8S_2Na_2\cdot 2H_2O$
IV, 1	Yellowish plates	$C_{29}H_{22}O_{10}N_8S_2Na_2\cdot 2H_2O$
IV, 2	Yellowish plates	$C_{30}H_{24}O_{10}N_8S_2Na_2\cdot 2H_2O$
IV, 4	Yellowish plates	$C_{32}H_{28}O_{10}N_8S_2Na_2\cdot 2.5H_2O$

TABLE 2. HYDRAZONE DERIVATIVE OF

Hydrazone	Appearance	Recryst. solvent	Mp, °C	Formula
IIB	Yellowish powder	Dimethyl formamide	over 300	$C_{14}H_{14}O_2N_4$
IIIB, b	Yellowish powder	Benzene	165	$C_{13}H_{13}ON_3$
IIIB, i	Yellowish powder	Benzene	167	$C_{14}H_{13}O_2N_3\cdot H_2O$
IIIB, j	Yellowish powder	Methyl cellosolve	226	$C_{14}H_{13}O_3N_3$
IIIB, k	Yellowish powder	Methyl cellosolve	206	$C_{14}H_{13}O_3N_3$
IIIB, l	Yellowish powder	Methyl cellosolve	244—246	$C_{14}H_{13}O_3N_3\cdot H_2O$
IIIB, o	Yellowish powder	Benzene	186	$C_{13}H_{12}O_2N_4$
IIIB, p	Yellowish powder	Benzene	220	$C_{13}H_{12}O_2N_4\cdot H_2O$
IIIB, q	Yellowish powder	Benzene	over 300	$C_{13}H_{12}O_2N_4\cdot H_2O$
IIIB. r	Pale yellow powder	Water-ethanol	over 300	$C_8H_{10}O_2N_4$
IIIB, s	White yellow powder	Water-ethanol	over 300	$C_8H_{10}ON_4S$

invariably yielded the corresponding hydrazones (Formula IIIA, a—f). The reaction product of I with acid hydrazide differed depending on the solvent used and on the chemical nature of the acid hydrazide. Acetyl-, propionyl-, oxalyl-, malonyl-, succinyl-, or adipoyl-hydrazine and I gave the expected hydrazone (Formula IIIA, g and h. Formula IV, *n*: 0, 1, 2 and 4) in alcohol or in a pyridine-water mixed solvent. However, in an aqueous solution these hydrazine derivatives all gave the same compound, IIA. This fact was confirmed by the elementary analysis and by a study of the infrared spectrum. Oxalyl-, benzoyl-, hydroxybenzoyl-, aminobenzoyl-, or pyridylcarbonyl-hydrazine, -semicarbazide, or -thiosemicarbazide and I yielded the expected hydrazones (Formula IV. *n* : 0. Formula IIIA. i—s) in any solvent (water, alcohol, or a pyridine-water

5-(*p*-SULFOPHENYLAZO)SALICYLALDEHYDE (Formula IIA and IIIA)

Analysis, %							
Found				Calcd			
C	H	N	Na	C	H	N	Na
46.02	3.28	12.51	6.36	45.95	3.11	12.37	6.77
47.74	3.60	15.70	6.31	47.19	3.68	15.72	6.45
54.58	3.72	13.47	5.63	54.51	3.61	13.39	5.49
51.11	4.30	12.08	6.56	51.28	4.52	11.96	6.84
50.38	4.77	11.74	4.45	50.31	4.64	11.73	4.82
47.94	5.10	11.20	4.64	47.61	4.99	11.11	4.56
50.67	3.22	12.28	5.01	50.39	3.12	12.37	5.08
41.84	4.28	13.24	5.30	41.86	4.45	13.02	5.34
42.53	4.73	12.52	5.14	42.48	4.68	12.38	5.08
43.37	4.79	10.17	4.13	43.32	4.91	10.10	4.15
46.47	4.24	10.92	4.50	46.51	4.10	10.85	4.45
42.62	4.79	9.78	4.01	42.78	4.67	9.98	4.06
47.78	4.09	11.12	4.46	48.19	3.84	11.24	4.61
45.48	4.35	13.10	4.05	45.80	4.42	13.35	4.38
47.64	4.36	13.98	4.82	47.43	4.18	13.83	4.54
45.34	4.18	13.76	4.65	45.51	4.02	13.97	4.58
45.25	4.03	13.87	4.21	45.51	4.02	13.97	4.58
45.68	4.24	14.17	4.34	45.51	4.02	13.97	4.58
41.89	3.31	17.07	5.37	41.66	3.50	17.36	5.26
38.50	3.73	15.89	5.10	38.44	3.69	16.01	5.26
43.53	3.38	14.69	5.36	43.47	3.13	14.48	5.94
44.06	3.52	14.01	5.48	44.16	3.32	14.21	5.83
44.89	3.50	13.92	5.62	44.89	3.52	13.96	5.73
45.86	4.09	13.24	5.35	45.77	3.96	13.34	5.48

5-AMINOSALICYLALDEHYDE (Formula IIB and IIIB)

Analysis, %							
Found				Calcd			
C	H	N	H_2O	C	H	N	H_2O
62.44	5.36	20.73		62.21	5.22	20.73	
68.04	5.86	18.65		68.70	5.77	18.49	
61.90	5.66	15.35	6.32	61.53	5.53	15.38	6.59
61.56	4.85	15.03		61.98	4.83	15.49	
61.69	5.03	15.42		61.98	4.83	15.49	
58.17	5.24	14.37	6.58	58.12	5.23	14.53	6.23
60.84	5.14	21.57		60.93	4.72	21.87	
57.03	5.12	20.13	6.23	56.93	5.15	20.43	6.57
57.13	5.15	20.24	6.88	56.93	5.15	20.43	6.57
49.30	5.28	28.96		49.48	5.19	28.85	
45.78	4.63	26.88		45.70	4.79	26.66	

mixture). The experimental results are listed in Table 1.

The marked difference in the hydrazone formation in an aqueous solution between acylated hydrazine and oxalyl- or aroyl-hydrazine or semicarbazides, appears to be due to the difference between stabilities in the face of the hydrolysis of the acid hydrazides.

These hydrazones and azine were used for the preparation of 5-aminosalicylaldehyde derivatives with a free amino group. In the case of the stable 5-(*p*-sulfophenylazo)salicylaldehyde hydrazones, the reductive cleavage of the azo linkage was accomplished in an aqueous solution without any change in the hydrazone group, and the corresponding 5-aminosalicylaldehyde hydrazones (Formula IIIB, b, i—l and o—s) were obtained. The less stable 5-(*p*-sulfophenylazo)salicylaldehyde hydrazones derived from acylated hydrazines underwent drastic change in the hydrazone moiety during the reduction; they gave 5-aminosalicylaldehyde azine, which was also obtained by reducing bis [5-(*p*-sulfophenylazo)salicylaldehyde] azine (Formula IIB). These results, confirmed by the results of the elementary analyses and by the infrared spectra, are tabulated in Table 2.

Thus, the above-mentioned experimental results show that the less stable hydrazones are reduced at the hydrazone moiety, whereas the stable hydrazones are reduced to 5-aminosalicylaldehyde hydrazone without any change in the hydrazone moiety.

Experimental

Sodium Salt of 5-(*p*-Sulfophenylazo)salicylaldehyde (I). This salt was prepared by Tummely's method.[4] (Found: C, 42.65; H, 3.52; N, 7.83; Na, 5.98%.)

Sodium Salt of Bis[5-(*p*-sulfophenylazo)salicylaldehyde]azine (IIA). To a hot stirred, solution of 3.64 g of I in 150 m*l* of water, there was added, drop by drop 0.628 g of hydrazine hydrate (80%) in 50 m*l* of water. The precipitate was collected by filtration, washed with water, and recrystallized from a pyridine-water mixture. The yield was almost quantitative.

Sodium Salt of 5-(*p*-Sulfophenylazo)salicylaldehyde methylhydrazone (IIIA, a). To a hot stirred, solution of 3.64 g of I in 150 m*l* of water, there was added 0.46 g of methylhydrazine in 150 ml of methanol. The precipitate was treated in a manner similar to that described above.

Sodium Salt of 5-(*p*-Sulfophenylazo)salicylaldehyde Arylhydrazone (IIIA, b, c, d, e and f). A mixture of 0.01 mol arylhydrazine hydrochloride and 0.01 mol of sodium acetate monohydrate (or 0.005 mol of sodium carbonate) in 50 m*l* of ethanol was added to a hot solution of 0.01 mol of the I in 150 m*l* of water. The precipitate was then collected and recrystallized from a pyridine-water mixture.

Sodium Salt of Aliphatic Monocarboxylic Acid Hydrazone and Aliphatic Dicarboxylic Acid Dihydrazone of 5-(*p*-Sulfophenylazo)salicylaldehyde (IIIA, g and h. IV. *n*: 0, 1, 2 and 4). To a hot solution of 0.01 mol of the I in 100 m*l* of a pyridine-water mixture, there was added a solution monohydrazide (0.01 mol) or dihydrazide (0.005 mol) in water or ethyl alcohol. The precipitate was collected and recrystallized from a pyridine-water mixture.

Sodium Salt of Aroylhydrazone, Semicarbazone and Thiosemicarbazone of 5-(*p*-Sulfophenylazo)-salicylaldehyde (IIIA, i—s). To a hot solution of 0.01 mol of the I in 150 m*l* of water, there was added a solution of aroylhydrazine, semicarbazide, or thiosemicarbazide in ethyl alcohol. The precipitate was then treated in a manner similar to that described above.

Bis(5-aminosalicylaldehyde)azine (IIB). To a solution of 4.40 g of IIA and 1.60 g of sodium hydroxide in 300 m*l* of water, 8.40 g of sodium hydrosulfite were added at 60—70°C. The precipitate was then collected by filtration and washed with water. The products were recrystallized from dimethylformamide and washed with ethyl alcohol.

Aryl-, Aroyl-, Pyridylcarbonyl-, Carbamoyl- and Thiocarbamoyl-hydrazones of 5-Aminosalicylaldehyde (IIIB. b and i—s). To a solution of 0.01 mol of IIIA (b and i—s) and 1.60 g of sodium hydroxide in 200 m*l* of water, 4.20 g of sodium hydrosulfite were added at 60—70°C. The precipitate was treated in a manner similar to that described above. The hydrazones, together with the solvents for crystallization, are listed in Table 2.

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[4] E. Tummely, *Ann.*, **251**, 180 (1889).