[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Water-soluble Derivatives of *p*-Aminobenzenesulfonamide. I

BY H. G. KOLLOFF

The announcement by Domagk[1] that certain sulfonamide derivatives were specific remedies in the treatment of experimental infection by Beta streptococcus hemolyticus has been confirmed by several workers.[2-7]

Since *p*-aminobenzenesulfonamide (sulfanilamide) is only sparingly soluble in water, the preparation of derivatives which are water-soluble or whose salts are water-soluble is desirable.

This paper deals with the preparation of certain *p*-amino- and *p*-acetylaminobenzenesulfonanilides containing solubilizing groups in the anilide portion of the molecule as well as the preparation of modified alkyl amides of sulfanilic acid. In addition *p*-uraminobenzenesulfonamide is included here for the purpose of record.

The general method followed for the preparation of these compounds was the condensation of *p*-acetylaminobenzenesulfonyl chloride with the amine in the presence of excess amine, sodium carbonate or sodium hydroxide and the subsequent hydrolysis of the acetyl group by refluxing with approximately 5 *N* hydrochloric acid. The yields were good in all cases, averaging around 70%.

Experimental

***p*-Acetylaminobenzenesulfon-4-carboxyanilide.**—To 13.7 g. (0.1 mole) of *p*-aminobenzoic acid in 50 cc. of water was added 8.0 g. (0.2 mole) of sodium hydroxide and then portionwise with shaking and cooling 23.4 g. (0.1 mole) of *p*-acetylaminobenzenesulfonyl chloride. After three hours the resultant solution was acidified and the precipitated material collected. The product was washed with very dilute hydrochloric acid and water and finally recrystallized from 70% alcohol.

***p*-Aminobenzenesulfon-4-carboxyanilide.**—To 50 cc. of 4.9 *N* hydrochloric acid and 25 cc. of alcohol was added 20 g. of *p*-acetylaminobenzenesulfon-4-carboxyanilide and the suspension refluxed until all the material was in solution and then for one-half hour longer. The crystalline material which separated on cooling was dissolved in 10% sodium carbonate and the free acid liberated by cautious acidification with dilute hydrochloric acid. The free acid was recrystallized from 25% alcohol.

About 6 g. of material which separated on cooling the hydrolysis mixture was insoluble in 10% sodium carbonate but soluble in 10% sodium hydroxide. This material on acid hydrolysis without the addition of alcohol gave a product identical with the original carbonate soluble material. Evidently hydrolysis in dilute alcohol leads to partial esterification of the carboxyl group.

***p*-Acetylaminobenzenesulfon-4-sulfonic Acid Anilide.**—Sodium sulfanilate (39.0 g., 0.2 mole) was dissolved in 200 cc. of water, 46.8 g. of *p*-acetylaminobenzenesulfonyl chloride and 10.6 g. of anhydrous sodium carbonate were added portionwise with stirring. The clear solution which resulted deposited a heavy precipitate of soapy crystals on chilling. These were collected, washed with acetone, and finally recrystallized from small volumes of water.

***p*-Aminobenzenesulfon-4-sulfonic Acid Anilide.**—Ten grams of the sodium salt of *p*-acetylaminobenzenesulfon-4-sulfonic acid anilide was dissolved in water and acidified with concentrated hydrochloric acid. The precipitated sulfonic acid was collected and refluxed for one hour with 30 cc. of water. The insoluble deacetylated compound which separated was dissolved in the calculated amount of 10% sodium carbonate and the product obtained by pouring into cold acetone. Purification was accomplished by repeating this acetone precipitation.

***p*-Acetylaminobenzenesulfon-di-(β-hydroxyethyl)-amide.**—To 23.4 g. (0.1 mole) of *p*-acetylaminobenzenesulfonyl chloride suspended in 200 cc. of water was added 22 g. (0.2 mole) of diethanolamine. After shaking for one-half hour the reaction was complete. The solid material which separated on chilling was washed with a small amount of dilute hydrochloric acid and water and recrystallized from water.

***p*-Aminobenzenesulfon-di-(β-hydroxyethyl)-amide.**—*p*-Acetylaminobenzenesulfon-di-(β-hydroxyethyl)-amide (15 g.) was refluxed for one-half hour with 40 cc. of 4.9 *N* hydrochloric acid. The reaction mixture was neutralized with dry sodium carbonate, the precipitated base extracted from the salt with acetone and finally recrystallized from 10% alcohol.

***p*-Acetylaminobenzenesulfon-glycine.**—To a solution of 7.5 g. (0.1 mole) of glycine in 50 cc. of water containing 8.0 g. (0.2 mole) of sodium hydroxide was added 23.4 g. (0.1 mole) of *p*-acetylaminobenzenesulfonyl chloride. After shaking for two hours the solution was filtered, acidified, and the precipitated material recrystallized from 60% alcohol.

***p*-Aminobenzenesulfon-glycine.**—The acetyl compound (12.5 g.) was refluxed for thirty-five minutes with 4.9 *N* hydrochloric acid. The crystalline hydrochloride which separated on cooling was dissolved in a small quantity of water and the free base precipitated by the addition of the calculated quantity of sodium hydroxide. The product was recrystallized from water.

(1) Domagk, *Deut. med. Wochschr.*, **61**, 250 (1935).

(2) Trefouel, Trefouel, Nitti and Bovet, *Compt. rend. soc. biol.*, **120**, 756 (1935).

(3) Fuller, *Lancet*, **1**, 194 (1937).

(4) Buttle, Gray and Stephenson, *ibid.*, **1**, 1286 (1936).

(5) Long and Bliss, *J. Am. Med. Assoc.*, **108**, 32 (1937).

(6) Rosenthal, Bauer and Branham, *Public Health Reports*, **52**, 662 (1937).

(7) The voluminous literature in this field makes it impractical to include a complete bibliography at this point.

TABLE I

Compound	M. p., °C.	Solvent	Formula	Analyses, % Calcd. C	H	N	S	Found C	H	N	S
p-Acetylaminobenzenesulfon-											
-4-sulfonic acid anilide[a]	.....	Water	$C_{14}H_{13}O_4N_2S_2Na$	42.86	3.31	7.14	16.35	43.04	3.59	7.06	16.03
-4-sulfamido-anilide[b]	279–280	50% EtOH	$C_{14}H_{14}O_3N_3S_2$	45.53	4.1	11.4	17.37	45.29	4.28	11.55	17.54
-4-carboxy-anilide	253–254	50% EtOH	$C_{15}H_{14}O_3N_2S$	53.89	4.19	8.38	9.60	54.04	3.97	8.50	9.41
-3-carboxy-anilide	274–275	Ethylene glycol	$C_{15}H_{14}O_3N_2S$	53.89	4.19	8.38	9.60	53.71	4.04	8.43	9.83
-2-carboxy-anilide	240	30% EtOH	$C_{15}H_{14}O_3N_2S$	53.89	4.19	8.38	9.60	54.20	4.04	8.46	9.73
-di-(β-hydroxyethyl)-amide	161–162	Water	$C_{12}H_{18}O_5N_2S$	47.68	5.96	9.27	10.61	47.56	6.00	8.96	10.39
-glycine[c]	237.5–238.5	60% EtOH	$C_{10}H_{12}O_5N_2S$	44.12	4.41	10.29	11.78	44.26	4.62	10.46	11.56
p-Aminobenzenesulfon											
-4-sulfonic acid anilide[a,f]	.....	[e]	$C_{12}H_{11}O_3N_2S_2Na$	41.14	3.14	8.00	18.31	40.82	3.23	7.76	18.47
-4-sulfamido anilide·HCl[b]	224–225	10% EtOH[d]	$C_{12}H_{13}O_4N_3S_2\cdot HCl$	39.62	3.85	11.56	17.63	39.50	3.68	11.54	17.64
-4-carboxy-anilide[g]	202	25% EtOH	$C_{13}H_{12}O_4N_2S$	53.42	4.11	9.59	10.97	53.17	4.38	9.71	10.77
-3-carboxy-anilide	196–197	25% EtOH	$C_{13}H_{12}O_4N_2S$	53.42	4.11	9.59	10.97	53.57	4.27	9.29	10.81
-2-carboxy-anilide[a]	315 (dec.)	Water	$C_{13}H_{11}O_4N_2SNa$	49.68	3.50	8.92	10.20	49.76	3.67	8.65	10.28
-di-(β-hydroxyethyl)-amide	110–111	10% EtOH	$C_{16}H_{16}O_4N_2S$	46.16	6.15	10.77	12.32	46.22	6.15	10.58	12.40
-glycine[c]	150–151	Water	$C_8H_{10}O_4N_2S$	41.74	4.35	12.17	13.93	41.82	4.23	11.89	13.98
p-Uraminobenzene-sulfonamide	208–209	Water	$C_7H_9O_3N_3S$	39.07	4.19	19.54	14.90	39.22	3.94	19.65	15.08

[a] Analyzed as sodium salt. [b] Previously described by Buttle, Gray, and Stephenson[4] and Rosenthal, Bauer, and Branham.[5] [c] Mentioned but not described by Kamlet at American Chemical Society Meeting, Rochester, N. Y., September, 1937. [d] From 10% alcohol a product melting at 132° was obtained. This is a mixture of the salt and free base as was shown by analysis. In order to obtain the pure salt it is necessary to add a trace of hydrochloric acid to the dilute alcohol used for crystallizing. [e] Sodium salt purified by precipitation with acetone. [f] Reported but not described by Dochez and Slanetz [*Science*, **87**, 142 (1938)]. [g] Reported but not described by Bauer and Rosenthal [*Public Health Reports*, **53**, 40 (1938)].

p-Uraminobenzenesulfonamide.—The procedure used in this preparation is that of Buck and Ferry.[8]

A mixture of 34.4 g. of *p*-aminobenzenesulfonamide and 24 g. of nitrourea in 50 cc. of alcohol was warmed gently until evolution of gas ceased. The alcohol was then boiled off and the resulting solid recrystallized from water.

The author wishes to thank Mr. Harold Emerson for the micro-analyses reported.

(8) Buck and Ferry, THIS JOURNAL, **58**, 854 (1936).

The pharmacology of these compounds will be reported later.

Summary

New water-soluble derivatives of *p*-aminobenzenesulfonamide (sulfanilamide) have been prepared and described.

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Sodium Naphthalene. II. Preparation and Properties of Dihydronaphthalene Dicarboxylic Acids

BY J. F. WALKER AND N. D. SCOTT

The ease with which sodium naphthalene is prepared from sodium and naphthalene in such solvents as dimethyl ether and the glycol diethers[1] makes it an excellent starting material for the preparation of dihydronaphthalene dicarboxylic acids and related compounds. Schlenk and Bergmann[2] previously have reported the isolation of a dihydronaphthalene dicarboxylic acid from the products obtained by the carbonation of lithium naphthalene in ethyl ether, but the extreme slowness with which lithium naphthalene is formed in this solvent makes this method unsatisfactory as a preparative procedure. The formation of sodium naphthalene in dimethyl ether or dimethyl glycol ether, however, is extremely rapid and good yields of crystalline isomeric dihydronaphthalene dicarboxylic acids can be obtained by following the proper carbonation technique.

When carbon dioxide is passed into a solution of sodium naphthalene at room temperature, the main reaction product is a mixture of resin-like acids and considerable carbon dioxide is liberated when the crude sodium salts are acidified. However, when the carbonation is carried out at low temperatures such as −70 to −80°, more than 80% of the theoretical yield of isomeric crystalline dihydronaphthalene dicarboxylic acids is produced and very little carbon dioxide is set free on work-

(1) Scott, Walker and Hansley, THIS JOURNAL, **58**, 2442 (1936).
(2) Schlenk and Bergmann, *Ann.*, **463**, 91 (1928).