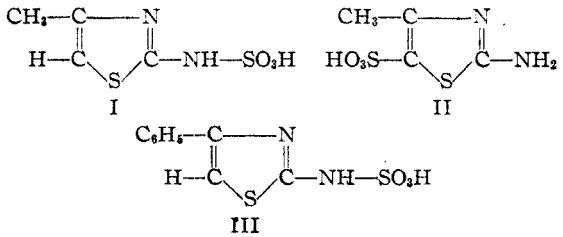
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Dipolar Ion Structures of the 2-Thiazolylsulfamic Acids[1]

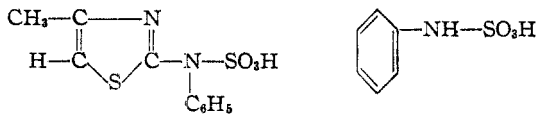
BY CHARLES D. HURD AND NORMAN KHARASCH

During a study of rearrangement reactions in the thiazole series, we had occasion to repeat the earlier work on the sulfonation of 4-methyl-2-thiazolylamine. In accord with the report of E. Otiai,[1a] we found that at low temperatures fuming sulfuric acid converted this amine to 4-methyl-2-thiazolylsulfamic acid (I, dec. 256°); and that at higher temperatures, the sulfamic acid was converted in high yield into an isomeric amino sulfonic acid (II, dec. 340–360°). Our interest in



I II III

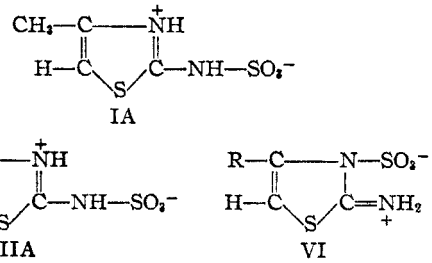
4-methyl-2-thiazolylsulfamic acid led us to obtain this compound by alternate procedures, and we also prepared a series of similar acids such as 4-phenyl-2-thiazolylsulfamic acid (III) and N-(4-methyl-2-thiazolyl)-phenylsulfamic acid (IV).



IV V

The 2-thiazolylsulfamic acids are crystalline, colorless substances which possess limited solubility in water and high stability toward hydrolytic and thermal cleavage. If these acids are indeed sulfamic acids, this stability is surprising because it is in sharp contrast with the known instability of simple arylsulfamic acids such as phenylsulfamic acid (V). Evidence for the instability of arylsulfamic acids will be considered in some detail in a following paper. For the present, it is sufficient to state that the decidedly unstable nature of such acids has been clearly established. In view of this, we questioned whether the acids in the thiazole series might be the isomeric amino sulfonic acids such as II, instead of sulfamic acids as I, III, IV. The following facts, however, convinced us that these acids are indeed sulfamic acids. In the first place, the 2-thiazolylsulfamic acids may be prepared by sulfonation of the corresponding amines at low temperatures and in the presence of inert solvents, whereas it would be expected that sulfonation of the thiazole nucleus would require more drastic conditions. Secondly, as mentioned above, when 4-methyl-2-thiazolylsulfamic acid is heated with concentrated sulfuric acid, it is converted into the isomeric 2-amino-4-methyl-5-thiazolesulfonic acid, II, which has distinctly different properties. Thirdly, 4-methyl-2-thiazolylsulfamic acid, although stable toward hydrolysis by dilute solutions of mineral acids, is hydrolyzed when refluxed with concentrated hydrochloric acid. The hydrolysate gives a heavy test for sulfate ions, pointing to cleavage at the N-S linkage, and 4-methyl-2-thiazolylamine may be isolated on neutralization with alkali. The isomeric amino sulfonic acid is not hydrolyzed under these conditions. Finally, we have found that the sodium salts of 4-methyl-2-thiazolylsulfamic acid and 2-thiazolylsulfamic acid are markedly sweet. This is in analogy with the reported sweetness of sodium cyclohexylsulfamate.[2] In contrast, we have found that sodium 2-amino-4-methyl-5-thiazolesulfonate (salt of II) possesses a bitter taste.

It became a problem of considerable interest, therefore, to explain why the 2-thiazolylsulfamic acids are so very stable, whereas acids such as phenylsulfamic acid and α-naphthylsulfamic acid are so unstable as to be incapable of isolation as such. It seemed reasonable to consider that the difference was associated with the presence of the basic nitrogen atom in the thiazole nucleus, and it was proposed that the 2-thiazolylsulfamic acids are better represented by dipolar ion formulas such as IA and IIIA. Structure VI is a possible alternative; but in the absence of additional evidence, we prefer formulas such as IA and IIIA.



IA IIIA VI

The stabilities displayed by the 2-thiazolylsulfamic acids, and those to be expected of them if the structures are such as IA and IIIA, are in accord with the known stabilities of the salts of arylsulfamic acids such as the barium,[3] sodium,[4] ammonium[5] and phenylammonium[6] salts of phenylsulfamic acid and similar acids. The dipolar ion structure of the 2-thiazolylsulfamic acids

(1) Presented before the Division of Organic Chemistry at the Cleveland Meeting of the American Chemical Society, April, 1944.

(1a) E. Otiai, *J. Pharm. Soc. Japan*, **58**, 1040 (1938).

(2) Audrieth and Sveda, *J. Org. Chem.*, **9**, 89 (1944).

(3) Traube, *Ber.*, **23**, 1655 (1890).

(4) Hunter and Sprung, THIS JOURNAL, **53**, 1444 (1931).

(5) Paal and Kretschmer, *Ber.*, **27**, 1244 (1894).

(6) Michaelis and Petow, *ibid.*, **31**, 984 (1898); Wagner, *ibid.*, **19**, 1157 (1886).

is independently confirmed, however, by the following factors.

(1) **Conductivities and *p*H Values.**—If the 2-thiazolylsulfamic acids are correctly designated by structures as I, III, IV, they should display electrical conductivities of the same order as free sulfonic acids. If structures such as IA, IIIA are more correct, the conductivities would be predicted to be lower, and of the order of sulfanilic acid, which is well known to exist in a dipolar ion form. The facts favor the dipolar ion formulas. Aqueous solutions of the 2-thiazolylsulfamic acids display decidedly lower conductivities than would be expected from structures not involving internal salt formation. Similarly, if the 2-thiazolylsulfamic acids are correctly represented by formulas not involving internal salt formation, they should behave as strong acids. Instead, the *p*H values for aqueous solutions of 4-methyl-2-thiazolylsulfamic acid and 2-thiazolylsulfamic acid were found to be comparable to those of solutions of acetic acid of the same concentrations, and point unmistakably to internal neutralization of the sulfamic acid function.

(2) **Solubilities.**—If structures I, III, IV are correct, it would be predicted that the 2-thiazolylsulfamic acids would display high aqueous solubilities. The aqueous solubilities of these acids are, however, very limited. This observation aligns itself with the sparing aqueous solubilities of acids such as sulfanilic acid, 2-amino-4-methyl-5-thiazolesulfonic acid, aminopyridinesulfonic acids, and others which unquestionably exist as dipolar ions.

(3) **Crystalline Character, Thermal and Hydrolytic Stabilities.**—The 2-thiazolylsulfamic acids are salt-like in appearance and undergo thermal decomposition only at elevated temperatures. Also, they are not cleaved by water, or dilute aqueous solutions of mineral acids. In our opinion, this behavior further confirms the proposed internal salt structures; for it is well known that, with unstable acids, salt formation is generally accompanied by increased stability.

(4) **Prediction of the Stabilities of Other Sulfamic Acids.**—If the dipolar ion formulas are correct, other arylsulfamic acids, the structures of which would allow stabilization by internal salt formation, should be capable of isolation. Thus, whereas phenylsulfamic acid can be isolated only in the form of its salts, *p*-aminophenylsulfamic acid[7] and *p*-aminophenylphenylsulfamic acid[8] have been isolated as stable substances. In our work, we also predicted that 2-pyridylsulfamic acid should be sufficiently stabilized by its dipolar ion character to permit its isolation. This prediction has been verified by experiment. This accumulation of evidence, therefore, all points to the dipolar ion structures for the 2-thiazolylsulfamic acids.

(7) Weil and Wassermann, *Ber.*, **55**, 2533 (1922).

(8) Spiegel, *ibid.*, **18**, 1479 (1885).

Experimental[9]

4-Methyl-2-thiazolylsulfamic Acid

Procedure of Otiai.[9a]—One hundred grams of 25% fuming sulfuric acid was cooled in an ice–salt-bath. To the cold acid there was added slowly 25 g. of 4-methyl-2-thiazolylamine.[9a] The viscous, brown solution which was formed was kept at 0° for three days. When this was poured on 150 g. of crushed ice, a clear solution resulted. After a few minutes, there was a sudden evolution of heat and a solid product separated. The pale-yellow, granular crystals were collected, washed with three 15-ml. portions of cold water and, after drying at 50°, weighed 33 g. (77%). The product contained no sulfate ions by test, and its decomposition temperature (256°) corresponded exactly to that observed by Otiai who also reported its correct analysis.

Use of Chlorosulfonic Acid.—The following method is more rapid. Seventy grams (0.625 mole) of 4-methyl-2-thiazolylamine was dissolved in 300 ml. of carbon tetrachloride. The solution was placed in a dry, three-necked, one-liter flask which was fitted with a mechanical stirrer, an exit tube for the evolution of hydrogen chloride, and a dropping funnel. The flask was immersed in an ice-bath and stirring was begun. One and three-tenths moles (151.3 g.) of technical chlorosulfonic acid was added dropwise during one-half hour during which time a slow evolution of hydrogen chloride was noted. The ice-bath was removed and stirring was continued for an additional hour at room temperature. After this period the evolution of hydrogen chloride could no longer be noted, and a solid product had separated. The entire mixture was poured, with stirring, on 150 g. of crushed ice. A large quantity of solid soon deposited in the aqueous layer. The pale-tan precipitate was collected and washed with small portions of cold water. After drying at 50° it weighed 84 g. This product gave a negative test for chloride ions, and only a faint test for sulfate ions. It was suspended in a mixture of 50 ml. of acetone and 10 ml. of water, vigorously stirred, and recollected. It was now colorless, gave a negative test for sulfate ions, and the value determined for the neutralization equivalent was 195.0. Calcd. for $C_4H_6O_3N_2S_2$: 194.2. After recrystallization from 300 ml. of hot water, and drying at 110°, the weight of product was 74 g. (62%). The value for neutralization equivalent was now 193.5. When the mother liquor from the original precipitation of the acid, was partially evaporated, an additional 4 to 8 g. of the acid was recovered. The quantity thus obtained varied with the amount of solvent evaporated in the various runs.

4-Methyl-2-thiazolylsulfamic acid was also prepared, without the use of an inert solvent and in about the same yield as above, by the slow addition of 4-methyl-2-thiazolylamine to approximately three molar proportions of cold chlorosulfonic acid, followed by decomposition of the reaction mixture with ice. This procedure is, however, more tedious to carry out and may be more hazardous.

Use of 4-Methyl-2-thiazolylammonium Chloride.—This salt was readily obtained, in yields of 70–80% and sufficiently pure for the preparation of the sulfamic acid, by refluxing a solution of 76 g. (1 mole) of thiourea in 300 ml. of water, with 92.5 g. (1 mole) of chloroacetone until the separate layers disappeared, evaporating the solution to small volume on the steam-bath, collecting the crystals which precipitated when the solution was cooled, and desiccating.

4-Methyl-2-thiazolylammonium chloride was obtained in pure condition by recrystallizing the product obtained above from hot water, slightly acidified with hydrochloric acid to prevent hydrolysis, and drying.

Anal. Calcd. for $C_4H_7N_2SCl$: neut. equiv., 150.5. Found: neut. equiv., 151.5.

(9) All melting and decomposition temperatures reported are uncorrected.

(9a) "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., Coll. Vol. II, p. 31, 1943.

2-Thiazolylammonium chloride was also prepared, in a similar manner as described above, from thiourea and ethyl chloroacetal.

Anal. Calcd. for $C_3H_5N_2SCl$: neut. equiv., 136.5. Found: neut. equiv., 136.5.

To obtain the sulfamic acid, 25 g. of dry, unrecrystallized 4-methyl-2-thiazolylammonium chloride was added to 100 g. of cold, 10% fuming sulfuric acid. When evolution of hydrogen chloride ceased, the solution was stoppered and set in the ice-chest for three days. It was then poured on 200 g. of crushed ice. After allowing complete crystallization to occur, there was isolated 9.8 g. (30.5%) of the desired acid: neut. equiv. 193; dec. 256°.

Sodium 4-Methyl-2-thiazolylsulfamate.—This salt was prepared by titrating the corresponding acid with dilute sodium hydroxide solution (phenolphthalein, external indicator) evaporating to dryness at 100°, and thrice crystallizing the crude salt from a 1:1 mixture of ethanol and water.

Anal. Calcd. for $C_4H_5O_3N_2S_2Na$: Na, 10.65. Found: Na, 10.55.

This salt, even in very dilute aqueous solution, possesses a remarkably sweet taste. It was found that if the 4-methyl-2-thiazolylsulfamic acid used in the preparation of this salt was obtained *via* chlorosulfonic acid, the sodium salt was sweet in two separate attempts; but when the sulfamic acid was prepared from oleum according to the method of Otiai, the salt obtained in two separate attempts was not sweet, but distinctly bitter. We suspect that in the preparation of the sulfamic acid according to the latter method there is formed some of the isomeric 2-amino-4-methyl-5-thiazolesulfonic acid. Since the sodium salt of this acid was found to be bitter, it may mask the sweet taste of the sodium 4-methyl-2-thiazolylsulfamate.

2-Thiazolylsulfamic Acid.—The second procedure described above for 4-methyl-2-thiazolylsulfamic acid was followed. Reaction of 41 g. (0.42 mole) of 2-aminothiazole[10] (m. p. 90°) with 99 g. (0.85 mole) of technical chlorosulfonic acid gave rise to 44 g. of the desired acid after recrystallization from water and drying in a vacuum desiccator. An additional 4.5 g. of acid was obtained from the original decomposition mixture by partial evaporation of the mother liquor. The yield was 66%. Like 4-methyl-2-thiazolylsulfamic acid, this acid is only slightly soluble in cold water, and it is insoluble in alcohol and non-polar solvents. It can be recrystallized readily from hot water. It forms very soluble salts with ammonium hydroxide and sodium hydroxide. When aqueous solutions of these salts are acidified with dilute hydrochloric acid, the sulfamic acid is reprecipitated in an analytically pure form. The acid decomposes at 256–258°.

Anal. (TSM).[10a] Calcd. for $C_4H_3O_3N_2S_2$: C, 19.98; H, 2.23, neut. equiv. 180.0. Found: C, 20.01; H, 2.17, neut. equiv. 179.5.

2-Thiazolylsulfamic acid was also prepared in 77% yield by the use of 25% fuming sulfuric acid, following the first directions listed for 4-methyl-2-thiazolylsulfamic acid. The amine used for this preparation was the technical product, supplied by Monsanto Chemical Company.

Sodium 2-Thiazolylsulfamate.—This sodium salt was prepared in the same manner as was sodium 4-methyl-2-thiazolylsulfamate. In this instance, the sodium salt was sweet irrespective of the manner in which the corresponding acid was prepared. The Abbott Laboratories tested this substance for sweetness and reported that, in aqueous solution, three grains of it has the sweetening power of one-fourth ounce of sugar or one-fourth grain of saccharin soluble. Sodium 2-thiazolylsulfamate was found to be only one-third as sweet as is sodium cyclohexylsulfamate, but the sweetness is of the same kind, and it leaves no bitter aftertaste which is noticeable in strong solutions of saccharin.

Anal. Calcd. for $C_3H_3O_3N_2S_2Na$: Na, 11.36. Found: Na, 11.28.

4-Phenyl-2-thiazolylsulfamic Acid.—Seventeen grams (0.1 mole) of 4-phenyl-2-thiazolylamine[11] (m. p. 146–148°) was dissolved in 200 ml. of carbon tetrachloride. Thirty grams (0.26 mole) of technical chlorosulfonic acid was added during half an hour from a dropping funnel. The reaction mixture was kept cold by means of an ice-bath and was stirred mechanically. Evolution of hydrogen chloride was noted during the addition of the acid, the reaction mixture turned brown, and a solid product collected on the walls of the reaction flask. After complete addition of the acid, the cold reaction mixture was stirred for one hour. It was then allowed to attain room temperature, and stirred for another half hour. When the reaction mixture was poured on approximately 100 g. of crushed ice, an excellent amount of pale-yellow granular crystals was obtained. The product adhering to the walls of the reaction flask was easily removed by shaking with a few milliliters of acetone. The solid was collected, washed with several portions of cold water, and then with acetone and ether to remove any adhering carbon tetrachloride. Washing with the latter solvents resulted in a product which was nearly colorless. After drying on the filter plate, the crude product weighed 21 g. It was very insoluble in cold water, but dissolved with difficulty when heated on the steam-bath with about fifty parts of water. A better method of preliminary purification was to suspend the crude acid in fifty parts of cold water and add dilute ammonium hydroxide until the mixture was just basic. Nearly complete solution of the solid occurred, but even after heating on the steam-bath, there was a solid residue of 0.5 g. of the original amine. This was separated (m. p. 146–148°) and to the clear filtrate, dilute hydrochloric acid solution was added until it was just acid. Almost immediately, beautiful clusters of soft, needlelike crystals appeared. The mixture was cooled, and the crystals were collected. These were washed with small portions of water, alcohol, and ether. The product obtained in this way was analytically pure, but it may also be recrystallized from hot water if desired. After recrystallization from hot water, and drying in the vacuum desiccator, it weighed 13.5 g. (54%), dec. 215–218°.

Anal. (TSM) Calcd. for $C_9H_8O_3N_2S_2$: C, 42.12; H, 3.15; neut. equiv., 256. Found: C, 42.25; H, 3.20; neut. equiv., 255.

N-(2-Thiazolyl)-phenylsulfamic Acid.—The same general procedure was used for the preparation of this acid as for 4-phenyl-2-thiazolylsulfamic acid. N-(2-Thiazolyl)-aniline, m. p. 124–126°, was prepared in high yield by reaction of equimolar quantities of phenylthiourea (m. p. 153–154°) and ethyl chloroacetal (b. p. 62–64° at 20 mm.) following the directions of Nef[12] for the preparation of this amine, except that Nef used α,β-dichloroethyl ethyl ether. Fourteen grams (0.08 mole) of this amine was dissolved in 200 ml. of technical carbon tetrachloride. To the cold, vigorously stirred solution of the amine there was added dropwise, during ten minutes, 18 g. (0.15 mole) of technical chlorosulfonic acid. The cold reaction mixture was then stirred for one hour and, after being allowed to attain room temperature, was stirred for an additional two-hour period. The reaction mixture was cooled in an ice-bath, and there was added dropwise, 5 ml. of cold water to decompose the excess of chlorosulfonic acid. When the reaction mixture was poured on about 100 g. of crushed ice, there was immediately formed a heavy, white, crystalline precipitate. The product was collected, and after drying at 50° weighed 18 g. It was dispersed in 150 ml. of water, and concentrated ammonium hydroxide solution was added to definite basicity. Nearly complete solution occurred, but there was a small quantity of finely-divided

(10) This amine was prepared following the procedure of Traumann, *Ann.*, **249**, 36 (1888), using ethyl chloroacetal in place of α,β-dichloroethyl ethyl ether; yield 79%.

(10a) Analyses other than neut. equiv. marked (TSM) were performed by Dr. T. S. Ma of the University of Chicago. All other microanalyses for carbon, hydrogen and nitrogen were made by Margaret M. Ledyard of Northwestern University.

(11) Traumann, *Ann.*, **249**, 36 (1888).

(12) Nef, *ibid.*, **265**, 126 (1891).

solid which was proved to be the unreacted amine. The filtrate obtained was slightly cloudy. It was boiled for five minutes with 5 g. of activated carbon. The clarified filtrate was diluted with 100 ml. of water and, upon acidification with dilute hydrochloric acid solution, there was formed a quantity of white, lustrous crystals which, after drying at 50°, weighed 10.1 g. (49.5%). The product was very insoluble in cold water, but dissolved readily in hot water. After crystallization from water the acid was a monohydrate (dec. 283–285°) which lost its molecule of water only after long heating at 111° in an evacuated Abderhalden pistol charged with phosphorus pentoxide.

Anal. of anhydrous substance. Calcd. for $C_3H_8O_3N_2S_2$: neut. equiv., 256.3. Found: neut. equiv., 257.3.

Anal. of hydrate. Calcd. for $C_3H_8O_3N_2S_2 \cdot H_2O$: C, 39.76; H, 3.67; N, 10.20; neut. equiv., 274.3. Found: C, 39.53; H, 3.77; N, 10.26; neut. equiv., 274.9.

N-(4-Methyl-2-thiazolyl)-aniline.—This amine was prepared in 84% yield by reaction of equimolar quantities of phenylthiourea and chloroacetone following the usual procedure for the preparation of 2-thiazolylamines. From 25 g. of phenylthiourea and 16 g. of chloroacetone there was obtained 26 g. of the amine, m. p. 115–117°. It was insoluble in water but dissolved readily in dilute hydrochloric acid solution and was reprecipitated by addition of alkali.

Anal. Calcd. for $C_{10}H_{10}N_2S$: C, 63.10; H, 5.30. Found: C, 63.28; H, 5.22.

N-(4-Methyl-2-thiazolyl)-acetanilide.—N-(4-Methyl-2-thiazolyl)-aniline failed to acetylate when refluxed with an excess of acetic anhydride. The addition of a small amount of concentrated sulfuric acid, however, effected acetylation. Five grams of the amine was refluxed for three and one-half hours with a mixture of 25 ml. of acetic anhydride and 1 ml. of concentrated sulfuric acid. The mixture was cooled and poured on 50 g. of ice, and the precipitated solid was collected and dried at 50° (5.6 g., 91%). The crude acetyl derivative was best recrystallized from hot acetic anhydride (m. p. 173–174°).

Anal. Calcd. for $C_{12}H_{12}ON_2S$: N, 12.07. Found: N, 12.03.

N-(4-Methyl-2-thiazolyl)-phenylsulfamic Acid.—Into a cold, stirred solution of 9.5 g. (0.05 mole) of N-(4-methyl-2-thiazolyl)-aniline (m. p. 115–117°) in 200 ml. of carbon tetrachloride, there was added during ten minutes 14.5 g. (0.125 mole) of chlorosulfonic acid. Lumps of product immediately began to form. The mixture was stirred in the cold for one hour, then at room temperature for another hour. It was then poured on about 75 g. of crushed ice, and the solid adhering to the walls of the reaction flask was removed by shaking with a few milliliters of acetone. The solid was collected, suspended in 100 ml. of water, converted to the soluble ammonium salt by use of dilute ammonium hydroxide solution, and filtered from a small residue of unreacted amine. The filtrate was boiled with 2 g. of Norit, and the clarified filtrate was acidified with dilute hydrochloric acid. There was immediate precipitation of a crystalline solid. This was collected and recrystallized from hot water. After drying at 50° it weighed 4.9 g. (36%). It melted at 233–235° with slight discoloration starting at 225°.

Anal. Calcd. for $C_{10}H_{10}O_3N_2S_2$: C, 44.41; H, 3.73; neut. equiv., 270.2. Found: C, 44.15; H, 3.97; neut. equiv., 270.2.

4-*m*-Nitrophenyl-2-thiazolylamine.—This amine was prepared by reaction of thiourea with *m*-nitrophenacyl bromide. The latter (m. p. 93–95°) was prepared by bromination of *m*-nitroacetophenone (m. p. 79–81°) following the general procedure given for the bromination of *p*-nitroacetophenone.[13] Into a solution of 5.5 g. (0.72 mole) of thiourea, 30 ml. of water and 50 ml. of 95% ethanol was added 18 g. of *m*-nitrophenacyl bromide. After twenty minutes of refluxing a clear yellow solution was formed from which a yellow crystalline product separated in considerable quantity on cooling. This was presumably the amine hydrobromide but it was not isolated. The solid was dissolved by gentle heating and 20% sodium hydroxide solution was added until the reaction mixture was strongly basic. The heavy, yellow precipitate was collected and dried at 50° for one hour (20.0 g.). The crude amine was recrystallized from about 300 ml. of hot alcohol and yielded 14 g. (91%) of bright yellow crystals, m. p. 189–191°.

Anal. Calcd. for $C_9H_7O_2N_3S$: C, 48.84; H, 3.19. Found (TSM): C, 49.54; H, 3.19; (MML, sample from different prepn.) C, 49.44; H, 3.51.

N-(4-*m*-Nitrophenyl-2-thiazolyl)-acetamide.—The above amine was converted to the acetyl derivative (92%) by reaction with excess hot acetic anhydride. The product which precipitated from the reaction mixture was not sufficiently pure for analysis. Because of its marked insolubility in water, alcohol and other solvents it could not be suitably recrystallized in the usual manner. It was best purified by dissolving in 0.1 *M* sodium hydroxide solution, filtering, and reprecipitating by addition of dilute hydrochloric acid. The pale-yellow crystals were collected, washed with water, and dried at 111° in an Abderhalden pistol, dec. 310–314°. The ready solubility of this compound in alkali is undoubtedly a result of the acidic nature of the remaining hydrogen atom of the amino group. N-(4-Methyl-2-thiazolyl)-acetamide was also found to be soluble in dilute alkali.

Anal. Calcd. for $C_{11}H_9O_3N_3S$: C, 50.20; H, 3.42. Found: C, 50.66; H, 3.66.

4-*m*-Nitrophenyl-2-thiazolylsulfamic Acid.—Two grams (0.009 mole) of 4-*m*-nitrophenyl-2-thiazolylamine (m. p. 189–191°) was added slowly, with stirring, to 18 g. (0.15 mole) of technical chlorosulfonic acid at room temperature. The amine dissolved readily with evolution of some heat. The reaction mixture was allowed to stand at room temperature for ten minutes and was then poured on 50 g. of crushed ice. A white, crystalline solid formed immediately. This was collected, washed with small quantities of cold water, alcohol, and ether. When dry it weighed 2.3 g. (85%). The product dissolved freely in 10% sodium hydroxide solution to produce a yellow solution. Acidification of the latter (hydrochloric acid) caused it to become colorless with separation of the original white crystals. The product was not soluble in water, alcohol or ether. It decomposed at 268–270° with some preliminary discoloration at 260°. It gave negative tests for the presence of chloride and sulfate ions.

Anal. Calcd. for $C_9H_7O_5N_3S_2$: C, 35.85; H, 2.34; neut. equiv., 301.2. Found: C, 35.87; H, 2.57; neut. equiv., 301.2.

2-Pyridylsulfamic Acid.—The various methods described above for the preparation of the 2-thiazolylsulfamic acids did not lend themselves conveniently to the preparation of 2-pyridylsulfamic acid. In only one experiment did we obtain, by the reaction of chlorosulfonic acid (47 g.) on 2-pyridylamine (25 g.), in 300 ml. of carbon tetrachloride, the same product (4 g.; dec. 216–218°: neutralization equivalent, 174.0) which we later obtained by the method described below.

Sulfonation of 2-Pyridylamine with Sulfur Trioxide.—A solution of 9.4 g. (0.1 mole) of 2-pyridylamine (m. p. 57.5–60°) in 130 ml. of distilled ethylene chloride (b. p. 83°) was placed in a dry, three-necked, one-liter flask, fitted with a mercury-sealed stirrer and an outlet tube connected to a gas bottle containing sulfuric acid. Sulfur trioxide (8 g., 0.1 mole) was passed into the cooled and stirred solution of the amine during thirty minutes, from an all-glass generator containing 60% oleum. A white, solid product formed as the sulfur trioxide was passed in. The reaction mixture was poured on 60 g. of crushed ice, and the product adhering to the walls of the reaction flask was scraped into an additional 50 g. of crushed ice. The crystalline product was collected. Its weight when dry was 4.8 g. It was found that this could be recrystallized from hot water, but the following method entailed less loss.

(13) Engler and Zielke, *Ber.*, **22**, 203 (1889).

The crude product was suspended in 25 ml. of cold water and concentrated ammonium hydroxide was added to definite basicity. The resulting solution was filtered to remove traces of impurities. On acidifying the filtrate with dilute hydrochloric acid, beautiful white needles were formed when the solution was cooled. The solid was collected, washed with small quantities of cold water, alcohol and ether, and after drying at 50°, weighed 3.1 g. (18%). The product contained no sulfate ions and decomposed at 216–218°.

Anal. Calcd. for $C_5H_6O_3N_2S$: C, 34.46; H, 3.47; neut. equiv., 174.1. Found: C, 34.31; H, 3.58; neut. equiv., 173.5.

Several attempts to repeat the preparation of 2-pyridylsulfamic acid by reaction of chlorosulfonic acid with 2-pyridylamine were not successful in permitting isolation of 2-pyridylsulfamic acid in reasonable yield. It seems that in the preparation using chlorosulfonic acid there is simultaneously formed another low-melting and very water-soluble product, whose nature we have as yet only tentatively established. Its presence makes the isolation of the desired sulfamic acid from the reaction mixture a difficult task.

Conversion of 4-Methyl-2-thiazolylsulfamic Acid to 2-Amino-4-methyl-5-thiazolesulfonic Acid.—Fifteen grams of 4-methyl-2-thiazolylsulfamic acid (dec. 256°) was heated at 100–110° for three hours with 37.5 ml. of 96% sulfuric acid. The sulfamic acid dissolved and the mixture turned somewhat dark. It was cooled and poured slowly on about 100 g. of crushed ice. A fine, white crystalline precipitate formed after a few minutes. The product was collected and washed with a few small portions of cold water. It was free of sulfate ions. After drying at 50°, it weighed 12.5 g. (83%). It was very insoluble in cold water, alcohol, acetone or ether, but dissolved readily in dilute solutions of sodium hydroxide or ammonium hydroxide. The value determined for neutralization equivalent was 193.0. Calcd. for 2-amino-4-methyl-5-thiazolesulfonic acid: 194.1. This acid decomposed at 340–360° and is identical with the product which Otiai[13a] obtained by action of fuming sulfuric acid on 4-methyl-2-thiazolylsulfamic acid. Otiai has reported a correct analysis for carbon and hydrogen for the amino sulfonic acid. In contrast to 4-methyl-2-thiazolylsulfamic acid, this 2-amino-4-methyl-5-thiazolesulfonic acid does not hydrolyze when heated for long periods with concentrated hydrochloric acid solution. Sodium 2-amino-4-methyl-5-thiazolesulfonate was prepared from its corresponding acid in exactly the same manner as was described for the sodium salts of 4-methyl-2-thiazolylsulfamic acid and 2-thiazolylsulfamic acid. This sodium salt has a bitter taste, in contrast to the sweetness of the other sodium salts.

Anal. Calcd. for $C_4H_5O_3N_2S_2Na$: Na, 10.65. Found: Na, 10.64.

Hydrolysis of 4-Methyl-2-thiazolylsulfamic Acid by Concentrated Hydrochloric Acid.—We have found that 4-methyl-2-thiazolylsulfamic acid remains unchanged by action of water, or cold hydrochloric, sulfuric or phosphoric acids. With concentrated hydrochloric acid, at elevated temperatures, hydrolysis is effected. Five grams of 4-methyl-2-thiazolylsulfamic acid (dec. 256°, and free of sulfate ions) was added to 30 ml. of concentrated hydrochloric acid. The mixture was heated near reflux temperature for eight hours. A clear, yellow solution was formed. A small portion of this solution gave a heavy positive test for sulfate ions. The remainder of the solution was cooled and poured on 15 g. of crushed ice. No precipitate was obtained. Ten per cent. sodium hydroxide solution was added until the mixture was strongly basic. The odor of the liberated amine was pronounced and the solution became opalescent. The mixture was extracted with ether. After evaporation of the ether there remained an oily residue which was proved to be 4-methyl-2-thiazolylamine by converting it to slightly over 1 g. of the pure acetyl derivative, m. p. 133–134°.

Qualitative Studies of Conductance.—For these observations, there was used a simple student-type ionization apparatus. This consisted of a pair of acid resistant, metal electrodes in series with a clear-glass 60-watt filament lamp, and was connected to a source of 110-volt alternating current. The lower conductances of the solutions of the 2-thiazolylsulfamic acids were clearly indicated by the observed differences in lamp glow when these solutions were used to complete the circuit. The solutions were prepared with ordinary distilled water and were studied at room temperature (26–28°).

TABLE I

Conducting medium	Observed lamp glow
Distilled water	Zero
Tap water	Zero
0.01 *M* Sodium hydroxide	Bright
0.01 *M* *p*-Toluenesulfonic acid monohydrate[a]	Bright
0.01 *M* Sulfanilic acid[b]	Poor, but definite glow
0.01 *M* 4-Methyl-2-thiazolylsulfamic acid	Decidedly poorer than sulfanilic acid
0.01 *M* 2-Thiazolylsulfamic acid	Decidedly poorer than sulfanilic acid

[a] The Eastman product (EK 984), m. p. 106–107° was purified by passing steam through a concentrated solution of it till the distillate was neutral: Shriner, "Organic Analysis," Edwards Bros. Inc., Ann Arbor, Michigan, 1938, p. 38. The residual solution was concentrated until crystals appeared. [b] Eastman product (EK 238) once recrystallized from hot water; neut. equiv. found, 174.

Conductance of 4-Methyl-2-thiazolylsulfamic Acid.—An aqueous solution of exactly 100 ml. volume, containing 1.931 g. of pure 4-methyl-2-thiazolylsulfamic acid (0.0995 *M*), was prepared. The apparatus used for the conductivity determinations was a Dike modification of a Jones Conductance bridge manufactured by Leeds and Northrup.[14] The bridge was used in conjunction with a cathode-ray oscillograph as a null point instrument. The conductance cell, equipped with platinum electrodes, had a cell constant of 0.055. The temperature was thermostatically controlled. In each determination, the bridge was balanced several times. The original solution of 4-methyl-2-thiazolylsulfamic acid was successively diluted by means of a calibrated pipet to the concentrations shown in Table II. The well known formulas used for the calculations of L, Λ, α, and K_i are listed below.

$$L = k/R;\ \Lambda = 1000\,L/C;\ \alpha = \Lambda/\Lambda_0;\ K_i = C\alpha^2/(1-\alpha)$$

where k = cell constant (0.055); L = specific conductance; Λ = equivalent conductance; Λ_0 = equivalent conductance at infinite dilution; α = apparent degree of ionization or conductance ratio; K_i = dissociation constant; C = molar concentration.

TABLE II

CONDUCTANCE OF AQUEOUS SOLUTIONS OF 4-METHYL-2-THIAZOLYLSULFAMIC ACID

Soln.	C	t, °C.	R, ohms	L	α	K_i
A	0.0995	23.70	44	1.25×10^{-3}	0.033	10.0×10^{-5}
B	.0497	23.85	68	8.09×10^{-4}	.043	9.6×10^{-5}
C	.0248	24.00	101	5.45×10^{-4}	.058	8.8×10^{-5}
D	.0124	24.10	152	3.61×10^{-4}	.076	7.7×10^{-5}

In the calculation of α and K_i there was made the assumption that the equivalent conductance at infinite dilution for 4-methyl-2-thiazolylsulfamic acid would be 382, which is the same as the values listed in "International Critical Tables"[15] for acids such as the *o*, *m* and *p*-aminobenzenesulfonic acids, 2,4-dimethyl-5-thiazolecarboxylic acid, etc.

(14) Dike, *Rev. Sci. Instruments*, **2**, 379–395 (1931).

(15) "International Critical Tables," Vol. VI, McGraw-Hill Book Co., Inc., 1929, Table C, p. 261 ff.

Thus, while the above values for the dissociation constant of the acid are not to be considered as strictly accurate, the measurements nevertheless indicate a lower order of conductance for 4-methyl-2-thiazolylsulfamic acid than would be expected if this acid was not internally neutralized.

pH Values.—The values for pH of solutions of 4-methyl-2-thiazolylsulfamic acid, solutions (A) and (D) above, were found, respectively, to be 2.72 and 3.20. The pH of aqueous, 0.0960 M, solution of 2-thiazolylsulfamic acid at 23° was found to be 2.80, and on dilution of this solution at the same temperature to 0.0480 M, the pH found was 2.92. These values are in agreement with what would be expected of solutions of these concentrations if the 2-thiazolylsulfamic acids dissociate to approximately the same extent as does acetic acid.

Acknowledgment.—This investigation was supported by a grant from the Abbott Fund of Northwestern University. We are also grateful to Dr. E. H. Volwiler of Abbott Laboratories for determination of the sweetness of sodium 2-thiazolylsulfamate.

Summary

A series of 2-thiazolylsulfamic acids has been prepared. Evidence is presented that these acids are derivatives of sulfamic acid and not isomeric aminosulfonic acids.

The thermal and hydrolytic stabilities displayed by the 2-thiazolylsulfamic acids contrast sharply with the great instabilities of simple arylsulfamic acids such as phenylsulfamic acid and α-naphthylsulfamic acid. It is proposed that the greater stabilities of the 2-thiazolylsulfamic acids result from their existence as internal salts. Studies of the properties of these acids confirm their dipolar ion character. It was predicted that 2-pyridylsulfamic acid should also be capable of existing in a dipolar ion form and should therefore be capable of isolation. This prediction has been verified by experiment.

EVANSTON, ILLINOIS RECEIVED NOVEMBER 21, 1945

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Application of the Principle of the Concentration Cell to Kinetic Studies. I. Hydrolysis of *t*-Butyl Chloride in 95% Water–5% Acetone Solution

BY C. GARDNER SWAIN AND SIDNEY D. ROSS

The hydrolysis of *t*-butyl chloride in solvents containing more than 50% water is too fast to be measured by the usual kinetic methods.[1] In the current investigation a kinetic technique was developed which utilizes the principle of the concentration cell. This new technique makes it possible to follow accurately reactions with half-lives as short as ten seconds, in concentrations as low as 0.001 M, and with solution volumes as small as 5 cc. It can be used to follow the consumption or production of H^+, Cl^-, CN^-, I_2, $KMnO_4$, Zn^{++}, etc., or, in general, of any ion or substance for which an electrode sensitive to changes in concentration is known. In the present paper it is applied to a study of the hydrolysis of *t*-butyl chloride in 95% water–5% acetone solution. Here it is used to follow the production of both chloride and hydrogen ion, independently. In a future paper it will be applied to a study of the mechanism of oxidation of oxalic acid by ceric sulfate, by following the consumption of ceric ion.

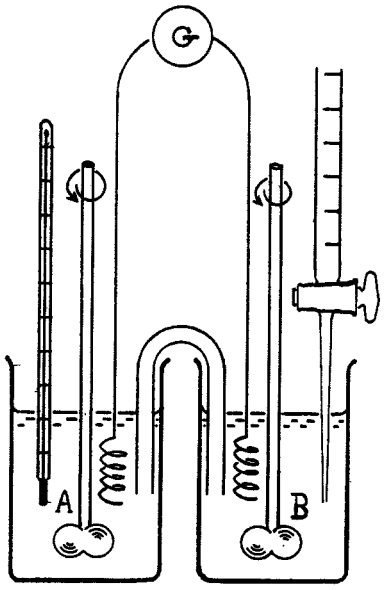


Fig. 1.—Diagram of apparatus employed in concentration cell method.

Description of the Method.—The apparatus is represented diagrammatically in Fig. 1. The "reaction cell," A, is connected to the "titration cell," B, by a salt bridge. To follow production of chloride ion from *t*-butyl chloride, electrodes of silver wire are used in each cell. These electrodes are connected through galvanometer, G. At zero time both cells contain a 95% water–5% acetone solution, which is 0.144 M in sodium perchlorate, but, in addition, cell A contains 0.001 M *t*-butyl chloride. As soon as hydrolysis occurs the galvanometer is thrown out of balance by chloride ion accumulating in cell A. Small measured additions of a solution of chloride are run rapidly into cell B every few seconds, and the time is recorded at each moment when hydrolysis in cell A again throws the galvanometer back across the null point. The concentration of the

(1) Hughes, *J. Chem. Soc.*, 255 (1935); Bateman, Hughes and Ingold, *ibid.*, 963 (1940).