This concept of the mechanism of reaction is supported by the results in perchloric acid solution. Sherrill, *et al.*,[5] have shown that no complex is formed in cerium (IV) perchlorate. Under such conditions the observed reaction should be essentially the termolecular reaction (2). This would explain why the rate is greater in perchloric acid (Fig. 2), but reaction is still not instantaneous.

The catalytic effect of manganese (II) may be explained by the occurrence of bimolecular reactions, as suggested by Schaffer[1]

$$Ce^{IV} + Mn^{II} \longrightarrow Ce^{III} + Mn^{III}$$
$$Ce^{IV} + Mn^{III} \longrightarrow Ce^{III} + Mn^{IV}$$
$$Mn^{IV} + As^{III} \longrightarrow Mn^{II} + As^{V}$$

In the case of quinone, a similar series involving a semiquinone and hydroquinone is possible.

The pronounced effect of halogenides and of nitrate suggests that a series of bimolecular steps may be involved in these cases also, but further studies will be necessary to determine the nature of these effects.

The experimental results seem neither to require nor to support the bimolecular step postulated by Stefanovskii[7]

$$Ce^{++++} + AsO_2^- \longrightarrow Ce^{+++} + AsO_2$$

The values for the bimolecular rate constant calculated by Stefanovskii show a definite "drift" with time. This, coupled with the rather large uncertainty inherent in such measurements, renders the conclusion that the reaction is second order questionable and seems to offer no justification for postulating a tetravalent state for arsenic. Furthermore, a bimolecular mechanism suggests essentially instantaneous reaction in perchlorate solution and also leaves unexplained the catalytic effects observed.

It is evident, however, that no calculations based on total cerium (IV) values can give conclusive results for a system involving the cerium (IV) sulfate complex. Information is necessary concerning the nature and extent of dissociation of this complex. Spectrophotometric studies are now being carried out in these Laboratories in an attempt to obtain such information.

In conclusion, the authors wish to express their appreciation to the University of Texas Research Institute for a grant made to one of us (R. C. A.) for equipment and materials, and to Dr. A. R. Choppin, Louisiana State University, for his valuable suggestions made at the start of this investigation.

Summary

1. The rates of reaction of cerium (IV) and arsenic (III) ions in sulfuric acid solution and with added perchloric, nitric and hydrochloric acid, halogenides, quinone and manganese (II) sulfate have been observed.

2. The rate-determining step was found to be third-order. The rate of reaction in sulfuric acid is decreased greatly by the formation of a cerium (IV) and sulfate complex, but reaction is not instantaneous in the absence of such complex formation.

3. Substances such as manganese (II) sulfate may catalyze the reaction by making possible a bimolecular mechanism.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF TEMPLE UNIVERSITY]

Substituted 2-Sulfonamido-5-aminopyridines. II

BY WILLIAM T. CALDWELL, FLOYD T. TYSON AND LOTHAR LAUER[1]

In continuing our studies of substituted 2-sulfonamido-5-aminopyridines,[2] we have synthesized three series of compounds for pharmacological comparison. The compounds of each series contain, respectively, a single atom of halogen or two atoms of the same halogen, or a single cyano radical or its hydration products. We also prepared several compounds, not derivatives of 2-sulfonamido-5-aminopyridine but of sulfanilamide.

Most of the methods given for the preparation of 2-amino-5-iodopyridine[3] (I) were tried, but none gave satisfactory yields. We succeeded however in developing a new procedure by which excellent yields (90%) of the product (I) were obtained.

Iodination of 2-aminopyridine to form a diiodinated product has been tried previously,[3] but, although the corresponding chloro and bromo pyridines have been prepared, 2-amino-3,5-diiodopyridine (II) has not been synthesized before. In agreement with Magidson and Menshikov[3] we found that 2-amino-5-iodopyridine (I) could not be satisfactorily iodinated, although a small quantity of the required compound was isolated after the action of iodine monochloride on 2-amino-5-iodopyridine at 60° in tertiary butanol. Therefore we used an indirect method to obtain (II) as indicated by the following sequence of formulas.

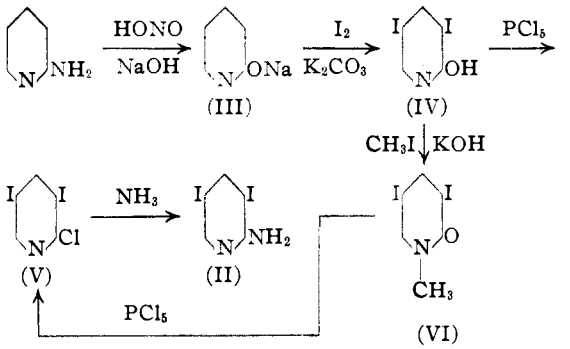
Sodium 2-pyridolate (III) was prepared by the method of Chichibabin and Rjazancev[4] in 95%

(1) Submitted in partial fulfillment of the requirements for the degree of Master of Arts.

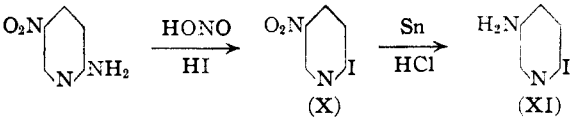
(2) Caldwell and Kornfeld, THIS JOURNAL, **64**, 1695 (1942).

(3) (a) Magidson and Menshikov, *Ber.*, **58**, 113 (1925); (b) Austrian Patent 121,246; (c) German Patents 513,293, 503,920, 473,213, 526,803, 491,681; (d) Swiss Patent 129,173; (e) Chichibabin and Kirsanov, *Ber.*, **60**, 766 (1927).

(4) Chichibabin and Rjazancev, *J. Russ. Phys.-Chem. Soc.*, **47**, 1571 (1915).



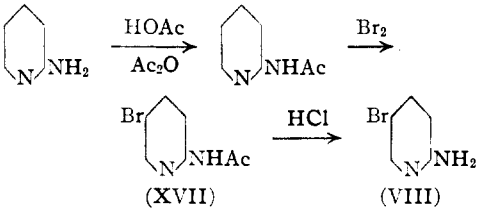
yield. It was iodinated by a procedure similar to that used in a German patent[5] to give (IV). This compound was identical with that obtained

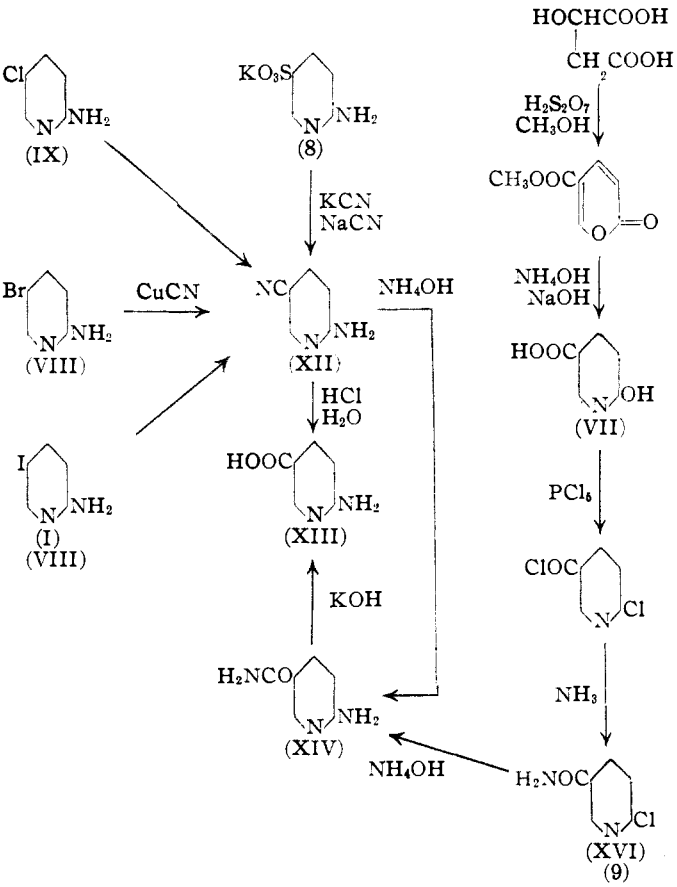


by Räth[6] from 2-hydroxy-5-pyridinecarboxylic acid (VII). Subsequent treatment with phosphorus pentachloride yielded 2-chloro-3,5-diiodopyridine (V). Reaction of phosphorus pentachloride with 1-methyl-3,5-diiodo-2-pyridone (VI) also gave this compound in approximately the same yield. Heating 2-chloro-3,5-diiodopyridine (V) in a sealed tube with alcoholic ammonia in the presence of sodium iodide gave (II). Conversion by diazotization into 3,5-diiodo-2-pyridone (IV) established its structure.

Roblin and Winnek[7] have found that the sulfanilyl derivatives of 5-amino-2-bromopyridine and of 5-amino-2-chloropyridine are physiologically active whereas those of 2-amino-5-bromopyridine (VIII) and 2-amino-5-chloropyridine (IX) have no known chemotherapeutic value. We therefore synthesized 5-amino-2-iodopyridine (XI) to see if its substitution into a sulfanilamide or 5-amino-2-pyridinesulfonamide would effect a desirable change in chemotherapeutic index. It was prepared as indicated. Compounds (XII), (XIII), and (XIV) were prepared as shown.

To synthesize (XII) we replaced the bromine in (VIII) by the cyanogen radical. Replacement of iodine in (I) by this group took place with better yield; however, we preferred the former method since the bromo derivative was more available. We also developed a new procedure for making (VIII).

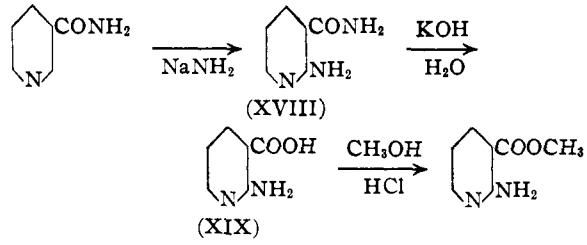




2-Amino-5-cyanopyridine (XII) could be converted into the corresponding amide by hydrolysis in aqueous ammonia, but it proved more convenient to prepare the amide by an independent synthesis starting with malic acid. The acid (XIII) was obtained either from the nitrile by acid hydrolysis according to Räth and Schiffmann[10] or from the amide by hydrolysis in presence of potassium hydroxide.

Direct amination of nicotinamide and nicotinonitrile appeared to be a feasible method for obtaining amino derivatives. Accordingly, sodium amide and nicotinamide were brought together under various conditions. That the product was (XVIII) was proved by the fact that the acid formed from it by alkaline hydrolysis gave a methyl ester having the same melting point as that reported by Kirpal[11] for methyl 2-amino-3-pyridinecarboxylate. Attempts to aminate nicotinonitrile by the same method were without success.

(5) German Patent 513,293 (1930).
(6) Räth and Prange, *Ann.*, **467**, 1 (1928).
(7) Roblin and Winnek, THIS JOURNAL, **62**, 1999 (1940).
(8) Chichibabin and Vialatout, *Bull. soc. chim.*, **6**, 736 (1939).
(9) Mills and Widdows, *J. Chem. Soc.*, **93**, 1372 (1908).
(10) Räth and Schiffmann, *Ann.*, **487**, 127 (1931).
(11) Kirpal, *Monatsh.*, **21**, 957 (1900).



The amines were coupled with the sulfonyl chlorides in pyridine or where the amines were not very soluble in pyridine, mixtures of pyridine and acetone. Usually the acetyl groups were hydrolyzed in presence of aqueous alkali, but in a few cases the hydrolysis had to be carried out in dilute alcoholic solution because of low solubility of the intermediate.

Because of difficulty experienced in hydrolyzing the acetyl group without affecting other groups in the same molecule, 2-amino-3- or 2-amino-5-pyridinecarboxylic acid amide and 2-amino-5-cyanopyridine were coupled not with 5-acetamino-2-pyridinesulfonyl chloride but with 5-nitro-2-pyridinesulfonyl chloride (XX). This compound was prepared from 5-nitro-2-pyridinethiol by the action of chlorine in dilute aqueous hydrochloric acid solution, a procedure analogous to that used by Caldwell and Kornfeld[2] for the preparation of 5-acetamino-2-pyridinesulfonyl chloride. The products obtained were then reduced to the amines by sodium hydrosulfite.

Pharmacological tests on the derivatives obtained are being made by Dr. A. E. Livingston and Dr. E. J. Fellows of the Department of Pharmacology, Temple University Medical School.

We wish to express our gratitude to Smith, Kline and French, Inc., for contribution of reagents and to the Temple University Committee on Research and Publications for a Grant-in-aid.

Experimental

Melting points are uncorrected.

2-Amino-5-iodopyridine (I).—In a 5-liter flask 100 g. of 2-aminopyridine was dissolved in 150 ml. of water and 180 g. of powdered iodine was added in small portions, with vigorous stirring, care being taken that all of the iodine previously added had dissolved before introducing the next portion. After three hours, 100 ml. of 60% aqueous potassium hydroxide was added, and stirring continued for half an hour. The material was then acidified with concentrated hydrochloric acid. The above procedure was repeated twice, first with 80 g. of iodine and 60 ml. of 60% aqueous potassium hydroxide and then with 40 g. of iodine and just enough 60% aqueous potassium hydroxide to make the mixture alkaline. Agitation of the solution was continued for three to four hours, and its alkalinity ascertained from time to time. The solution was saturated with sodium chloride and subjected to steam distillation using an apparatus like that recommended by Fieser ("Experiments in Organic Chemistry," p. 160). After collecting about 15 liters of distillate, no more oil was left in the flask. The distillate was cooled and any precipitated product was filtered off. The filtrate was acidified with hydrochloric acid and concentrated *in vacuo* to 200 ml. This solution was decolorized with charcoal, made alkaline with dilute potassium hydroxide, and cooled. The precipitate was combined with the product obtained above and dried. Upon recrystallization from benzene, the product formed white needles, m. p. 129–130°; yield 80–90%.

Sodium 2-Pyridolate (III).—This compound was made by a method similar to that of Chichibabin and Rjazancev[4] as follows: 15 g. of 2-aminopyridine was dissolved in a mixture of 32 g. of concentrated sulfuric acid and 50 g. of water. The solution was cooled to −5°, 100 g. of finely chopped ice was added and then 15 g. of sodium nitrite was introduced slowly with stirring, while keeping the temperature of the solution below 5°. Stirring was continued for three hours during which the temperature of the solution rose to that of the room. It was allowed to stand overnight and then heated on the steam-bath until no more nitrogen came off (ten to fifteen minutes). The solution was cooled to room temperature and, with external cooling, sodium hydroxide solution (1:3) was added until no more precipitate formed. The precipitate was filtered off, suspended in 100 ml. of 1:3 sodium hydroxide solution and refiltered. Recrystallization from 95% alcohol gave lustrous plates of the salt in 90 to 95% yield.

3,5-Diiodo-2-pyridone (IV).—Thirty-one grams of sodium 2-pyridolate and 46 g. of anhydrous potassium carbonate were dissolved in 600 ml. of water and 162 g. of powdered iodine was gradually added while the mixture was stirred. After all of the iodine had been added (two hours) the mixture was stirred for several hours longer, first at 60° until no more carbon dioxide was evolved, then at the temperature of the steam-bath. After cooling, the mixture was acidified with concentrated hydrochloric acid and a 40% solution of sodium bisulfite was cautiously added until the iodine color just disappeared. The product was filtered off and recrystallized from 600 to 700 ml. of glacial acetic acid; 58 g. of white crystals was obtained, m. p. 268–270°; yield 60%.

Anal. Calcd. for $C_5H_3ONI_2$: N, 4.04; I, 73.18. Found: N, 4.17; I, 72.43.

2-Chloro-3,5-diiodopyridine (V): (a) **From 3,5-Diiodo-2-pyridone** (IV).—Forty-five grams (0.13 mole) of 3,5-diiodo-2-pyridone was intimately mixed with 30 g. (0.14 mole) of phosphorus pentachloride (analytical reagent grade) and 2 ml. of freshly distilled phosphorus oxychloride was added. The mixture was heated under reflux for five to six hours at 130–135° in an oil-bath. The temperature should be brought up slowly to keep decomposition at a minimum. The volatile compounds of phosphorus were then removed by distillation under reduced pressure and, after cooling, 300 ml. of ice water was added to the gummy residue in the flask. The mixture was stirred in an ice-bath for about fifteen minutes until the oil had turned into a dark brown powder. This was filtered and washed with ice water, then suspended in 100 ml. of ice-cold 20% sodium bisulfite solution and stirred to remove the free iodine that had been formed. The precipitate was filtered off again, washed with water and recrystallized from 95% alcohol; yield 40–50%, m. p. 72–73°.

Anal. Calcd. for $C_5H_2NClI_2$: N, 3.83; I, 69.47. Found: N, 4.15; I, 68.72.

(b) **From 3,5-Diiodo-1-methyl-2-pyridone** (VI).—Ten grams of 3,5-diiodo-1-methyl-2-pyridone was intimately mixed with 6 g. of phosphorus pentachloride (analytical reagent grade) and two drops of freshly distilled phosphorus oxychloride was added. The mixture was heated at 150–155° under reflux in an oil-bath for eight hours. The volatile compounds of phosphorus were then removed under reduced pressure and the residue was worked up in exactly the same way as under (a); yield 40–50%.

2-Amino-3,5-diiodopyridine (II).—Five grams of 2-chloro-3,5-diiodopyridine (V) and 2 g. of sodium iodide were suspended in 30 ml. of 95% ethanol and the mixture saturated with ammonia at 0°. It was then heated in a sealed tube at 150–160° for six hours. The mixture was heated to boiling and filtered from inorganic salts. The alcohol was then removed under reduced pressure and the residue was recrystallized from dilute alcohol; white needles, m. p. 135–137°; yield 40%. The compound had a faint odor like that of 2-aminopyridine and was found to be

easily soluble in all common organic solvents and but slightly soluble in water.

Anal. Calcd. for $C_5H_4N_2I_2$: N, 8.10; I, 73.38. Found: N, 8.33; I, 72.85.

This compound was converted into 3,5-diiodo-2-pyridone as follows: 5.5 g. of the amine was dissolved in a solution of 3.2 g. of concentrated sulfuric acid and 5 g. of water. The solution was cooled to 0° and after adding 10 g. of finely chopped ice, 1.5 g. of sodium nitrite was introduced, keeping the solution below 5°. The solution was diluted with 50 ml. of water, heated to boiling, and cooled. The precipitate was filtered off, washed with water, and recrystallized from glacial acetic acid, m. p. 268–270°. This melting point and the fact that a sample of this compound, mixed with 3,5-diiodo-2-pyridone prepared previously, showed no depression of melting point proved that these substances were identical.

2-Iodo-5-nitropyridine (X).—A solution of 14 g. of 2-amino-5-nitropyridine dissolved in 170 ml. of glacial acetic acid was added to one of 8 g. of sodium nitrite in 56 ml. of concentrated sulfuric acid (prepared according to Hodgson and Walker,[12] keeping the temperature below 20°. After stirring at 25° for two hours the solution was poured into one of 25 g. of potassium iodide in 20 ml. of water. The mixture was allowed to stand overnight, then almost all the acid was neutralized by careful addition of sodium hydroxide solution (1:3) below 20°. The precipitate was filtered off and recrystallized from methanol as yellow needles, m. p. 155–156°; yield 35–45%.

Anal. Calcd. for $C_5H_3O_2N_2I$: N, 13.86; I, 62.80. Found: N, 13.30; I, 61.97.

5-Amino-2-iodopyridine (XI).—16.5 g. of 2-iodo-5-nitropyridine was suspended in 200 ml. of 1:1 hydrochloric acid; then 38 g. of granulated tin was introduced and constantly shaken with the mixture. When the temperature started to fall, the solution was warmed on the water-bath for one hour; finally it was boiled under reflux until all the tin had dissolved. The solution was then evaporated to dryness *in vacuo* and the residue was taken up in 400 ml. of water. Hydrogen sulfide then was passed through this solution to saturation, and the precipitated stannous sulfide filtered off and washed with water. The filtrate and the washings were concentrated *in vacuo* to 100 ml. and the amine precipitated by making alkaline with potassium carbonate. After recrystallization from alcohol, white needles were obtained; m. p. 132°; yield 60–70%.

Anal. Calcd. for $C_5H_5N_2I$: N, 12.7; I, 57.7. Found: N, 13.0; I, 57.2.

2-Amino-5-chloropyridine (IX) and 2-Amino-3,5-dichloropyridine (XXI).—These compounds were prepared according to the direction of Chichibabin and Egorov.[13] 2-Amino-5-bromopyridine (VIII) may be synthesized by a method given by Chichibabin and Tyazhelova[14] but since almost two-thirds of the product obtained consisted of 2-amino-3,5-dibromopyridine, we employed their procedure primarily for the preparation of the dibromoaminopyridine; for the synthesis of the monobromoaminopyridine, however, we used a different procedure:

A mixture of 47 g. of 2-aminopyridine, 160 g. (152 ml.) of glacial acetic acid, and 56 g. (52 ml.) of acetic anhydride was refluxed for three hours. Eighty-two g. (27 ml.) of bromine was then added drop by drop between 45 and 55°. After the addition of every drop of bromine the flask was shaken until the color of bromine disappeared. The greater part of the solvent was then removed under reduced pressure and the residue diluted with water to which some sodium bisulfite had been added. The solution was then rendered almost alkaline with sodium carbonate, the precipitate filtered off and recrystallized from alcohol. The fact that the product melted sharply at 175° and that it gave no depression when mixed with the compound prepared according to Ptazek and Sucharda[15] proved that it was 2-acetylamino-5-bromopyridine.

The crude product from the above bromination was dissolved in 150 ml. of boiling 95% alcohol, 125 ml. of concentrated hydrochloric acid added, and the mixture refluxed on the steam-bath for three hours (if the solution is thoroughly cooled at this point, needle-like, colorless crystals of the hydrochloride will precipitate). Most of the solvent was then removed under reduced pressure; the residue, while still hot, was stirred with charcoal, filtered and rendered alkaline with a saturated solution of potassium carbonate. The solution was cooled to 0°, the precipitate filtered off, and the product recrystallized from benzene; m. p. 137°. It was identical with the compound prepared according to Chichibabin and Tyazhelova.[14] The yield was 50–60% based on 2-aminopyridine.

2-Amino-5-cyanopyridine (XII).—A mixture of 11 g. of 2-amino-5-bromopyridine (VIII) and of 5 g. of anhydrous cuprous cyanide was heated cautiously with vigorous shaking in a 200-ml. retort until the entire mass had just fused. The retort was then set for distillation under reduced pressure and heated further until reaction started. During the reaction it was cooled only so much by occasional immersion in water as just to prevent distillation of the bromopyridine from the flask. As soon as the reaction subsided, the pressure was reduced to 2 mm. and as much volatile material distilled as would come over using a free smoky flame. If not quickly distilled the whole mass went to a tar. The distillate, which solidified immediately, was purified by vacuum distillation, keeping only the fraction that came over between 240 and 250° under 15 mm. pressure; m. p. 164°; yield 35–40%. The identity of this product with that prepared according to Räth and Prange[6] from 2,5-diaminopyridine was established by a mixed melting point and by conversion into 2-aminonicotinic acid according to the directions given by these authors.

The same compound was also prepared from 2-amino-5-iodopyridine by the same procedure and in 50–60% yield.

Methyl Coumalinate (XV).—50 g. of dry malic acid was gradually introduced into 75 g. of 20% fuming sulfuric acid (specific gravity 1.91 at 20°) and the mixture heated on the steam-bath with stirring until no more carbon monoxide was evolved (one hour). The solution was then cooled in a freezing mixture and 50 ml. of absolute methanol was added slowly. The mixture was shaken and heated under reflux on the steam-bath for one hour. After cooling it was cautiously mixed with 400 ml. of water. The tarry material that separated was filtered off, and the filtrate almost neutralized with hydrated soda. The mixture was allowed to stand for a few hours; then the crude ester was filtered off. By extracting the filtrate with four 70-ml. portions of ether and removing the solvent about 20% more ester was obtained. The dried product was purified by mixing it with activated charcoal and extracting with petroleum ether (b. p. 50–60°) in a Soxhlet extractor, m. p. 74°; yield 50–55%. The product was identical with that prepared according to the method of von Pechmann.[16]

2-Hydroxy-5-pyridinecarboxylic Acid (VII).—**a. From methyl coumalinate** by a method similar to that of H. v. Pechmann[17] the acid was prepared as follows: 14 g. of pulverized methyl coumalinate (XV) was gradually introduced into 25 ml. of concentrated aqueous ammonia, keeping the temperature of the mixture below 25°. The clear solution was allowed to stand overnight, and then refluxed with 10 g. of sodium hydroxide in 40 ml. of water for five minutes. On acidifying the cooled solution with concentrated hydrochloric acid a yellow powder separated. After recrystallization from 50% acetic acid, the acid was obtained in 70% yield in the form of a white, microcrystalline precipitate, m. p. 303° (d.).

b. From Sodium 2-Pyridolate (III).—In an autoclave, 6 g. of dry sodium 2-pyridolate was mixed with 18 g. of anhydrous potassium carbonate. The autoclave was filled with carbon dioxide at about 50 atmospheres pressure and

(12) Hodgson and Walker, *J. Chem. Soc.*, 1620 (1933).

(13) Chichibabin and Egorov, *J. Russ. Phys.-Chem. Soc.*, **60**, 683 (1928).

(14) Chichibabin and Tyazhelova, *ibid.*, **50**, 483 (1920).

(15) Ptazek and Sucharda, *Ber.*, **61B**, 1813 (1928).

(16) H. v. Pechmann, *Ann.*, **264**, 279 (1880).

(17) H. v. Pechmann, *Ber.*, **17**, 2384 (1884).

TABLE I

PROPERTIES OF SUBSTITUTED 5-AMINOPYRIDINE-2-SULFONAMIDES, $R^2C_5H_3NSO_2NHR^1$

R^2	R^1	Solvent (The range is about 1°)	M. p., °C.[a]	Formula	Water soly., g./liter at 25°	Analyses, % Calcd. N	Calcd. X	Found N	Found X
							(X = Cl, Br or I)		
—NHCOCH$_3$		dil. CH$_3$OH	247	$C_{12}H_{10}O_3N_4SI_2$	..	...	46.65	...	46.11
—NH$_2$	3-I, 5-I	70% CH$_3$COOH	229	$C_{10}H_8O_2N_4SI_2$	4.2	...	50.56	...	50.09
—NHCOCH$_3$		dil. C$_2$H$_5$OH	240	$C_{12}H_{11}O_3N_4SBr$	..	...	21.53	...	21.32
—NH$_2$	5-Br	60% CH$_3$COOH	234	$C_{10}H_9O_2N_4SBr$	6.0	...	24.28	...	23.97
—NHCOCH$_3$		dil. CH$_3$OH	232	$C_{12}H_{10}O_3N_4SBr_2$	..	...	35.51	...	35.17
—NH$_2$	3-Br, 5-Br	75% CH$_3$COOH	212	$C_{10}H_8O_2N_4SBr_2$	4.3	...	39.17	...	39.10
—NHCOCH$_3$		dil. C$_2$H$_5$OH	237	$C_{12}H_{11}O_3N_4SCl$	..	...	10.85	...	10.58
—NH$_2$	5-Cl	60% CH$_3$COOH	221	$C_{10}H_9O_2N_4SCl$	5.1	19.68	12.45	19.24	11.88
—NHCOCH$_3$		dil. CH$_3$OH	215	$C_{12}H_{10}O_3N_4SCl_2$	..	...	19.63	...	19.42
—NH$_2$	3-Cl, 5-Cl	80% CH$_3$COOH	201	$C_{10}H_8O_2N_4SCl_2$	5.6	...	22.22	...	21.85
—NHCOCH$_3$		dil. C$_2$H$_5$OH	221	$C_{12}H_{11}O_3N_4SI$	..	...	30.35	...	29.79
—NH$_2$	6-I	65% CH$_3$COOH	217	$C_{10}H_9O_2N_4SI$	5.8	14.90	33.74	14.81	33.15
—NHCOCH$_3$		60% CH$_3$COOH	287	$C_{13}H_{12}O_5N_4S$	..	16.66	...	16.21	...
—NH$_2$	6-COOH	60% CH$_3$COOH	281	$C_{11}H_{10}O_4N_4S$	11.2	19.04	...	18.71	...
—NO$_2$		dil. C$_2$H$_5$OH	251	$C_{11}H_7O_4N_5S$	..	22.95	...	22.36	...
—NH$_2$	6-CN	dil. C$_2$H$_5$OH	249	$C_{11}H_9O_2N_5S$	6.2	25.45	...	24.98	...
—NO$_2$		dil. C$_2$H$_5$OH	260	$C_{11}H_9O_5N_5S$	..	21.67	...	21.32	...
—NH$_2$	6-CONH$_2$	dil. C$_2$H$_5$OH	248	$C_{11}H_{11}O_3N_6S$	8.9	23.88	...	23.71	...
—NO$_2$		dil. C$_2$H$_5$OH	253	$C_{11}H_9O_5N_5S$	..	21.67	...	21.20	...
—NH$_2$	6-H$_2$NCO	dil. C$_2$H$_5$OH	239	$C_{11}H_{11}O_3N_5S$	8.7	23.88	...	23.53	...
Properties of substituted 4-aminobenzenesulfonamides, $R^2NHC_6H_4SO_2NHR^1$									
—COCH$_3$		dil. C$_2$H$_5$OH	242	$C_{13}H_{11}O_3N_3SI_2$	..	...	46.73	...	46.31
—H	3-I, 5-I	80% CH$_3$COOH	217	$C_{11}H_9O_2N_3SI_2$	4.5	...	50.66	...	50.26
—COCH$_3$		dil. C$_2$H$_5$OH	217	$C_{13}H_{12}O_3N_3SI$	..	...	30.42	...	30.09
—H	6-I	70% CH$_3$COOH	205	$C_{11}H_{10}O_2N_3SI$	5.8	11.20	...	10.81	...

[a] All with decomposition.

heated at 200° for twenty-four hours. After cooling, the contents were dissolved in 200 ml. of water and the acid was precipitated in almost pure form by acidifying with concentrated hydrochloric acid; yield, 60%. (This method was given by Chichibabin[18] and in the German Patent 436,443, but neither exact conditions nor yields were stated in the two references.)

2-Amino-5-pyridinecarboxylic Acid Amide (XIV).—a. From 2-Chloro-5-pyridinecarboxylic Acid Amide (XVI).—Five grams of XVI was suspended in 50 ml. of concentrated aqueous ammonia to which 0.5 g. of sodium iodide had been added. The mixture was heated in a sealed tube at 150–160° for four to five hours. It was then evaporated to dryness *in vacuo* and the residue recrystallized from 50% aqueous alcohol; white powder, m. p. 200°; yield 50%.

b. From 2-Amino-5-cyanopyridine (XII).—Twelve grams of the nitrile was suspended in 60 ml. of concentrated aqueous ammonia and the mixture was heated in a sealed tube at 110 to 120° for twelve hours. The solution was worked up in exactly the same way as above and an identical product was obtained in approximately the same yield.

(18) Chichibabin, *Ber.*, **57**, 1161 (1924).

Anal. Calcd. for $C_6H_7ON_3$: N, 30.6. Found: N, 30.1.

2-Amino-5-pyridinecarboxylic Acid (XIII).—Five grams of 2-amino-5-pyridinecarboxylic acid amide was suspended in 50 ml. of 10% sodium hydroxide solution and the mixture was refluxed until all the solid had gone into solution. After cooling, the solution was acidified with hydrochloric acid. The acid that precipitated in quantitative yield was almost pure and identical with that prepared according to Räth and Schiffmann[10] as shown by determination of a mixed melting point, m. p. 312°.

2-Amino-3-pyridinecarboxylic Acid Amide (XVIII).—To 12.5 g. of nicotinamide suspended in 50 ml. of pure dimethylaniline, was added 25 g. of finely pulverized sodium amide. The mixture was carefully heated in a metal bath to 140° (bath temp.) with vigorous mechanical stirring and in an atmosphere of nitrogen. Evolution of ammonia was quite vigorous when the temperature of the bath reached 100°, but it rapidly subsided and hydrogen was given off instead. Heating at 140–145° was continued for twelve hours. After cooling, the reaction mixture was cautiously diluted with 200 ml. of ice-water and the dimethylaniline was removed with several portions of petroleum ether (b. p. 35–60°). The aqueous layer was exactly neutralized with concentrated hydrochloric acid and allowed to stand in a refrigerator for 24 hours. The amide then was filtered off and recrystallized from aqueous alcohol, m. p. 195°; yield 20–25%.

The amide was hydrolyzed to the acid by a procedure analogous to that given above for its isomer and the acid was converted into the methyl ester according to Kirpal.[11] The m. p. of this ester (85°) was the same as that reported for methyl α-aminonicotinate by that author.

5-Nitro-2-pyridinesulfonyl Chloride (XX).—This compound was prepared from 5-nitro-2-pyridinethiol by a method analogous to that employed by Caldwell and Kornfeld[2] for the preparation of 5-acetylamino-2-pyridinesulfonyl chloride. After recrystallization from chloroform the compound melted at 212–213° (dec.).

Anal. Calcd. for $C_5H_3O_4N_2Cl$: Cl, 17.16; S, 15.51. Found: Cl, 16.93; S, 14.97.

Substituted Nitropyridine Sulfonamides, Acetaminopyridine Sulfonamides, and Acetylsulfanilamides.—One equivalent of 5-nitro-2-pyridinesulfonyl chloride or of 5-acetamino-2-pyridinesulfonyl chloride was added to one equivalent of the amine dissolved in four equivalents of pyridine, keeping the temperature of the solution below 50°. In those cases where the amine was not completely soluble in this quantity of solvent, enough dry acetone was added to get it completely into solution. The solutions were heated on the steam-bath for one hour and the derivatives were then precipitated by diluting with five volumes of water. The derivatives of acetylsulfanilyl chloride were prepared in the same way.

Substituted 2-Sulfonamido-5-aminopyridines.—Most of the acetyl compounds were hydrolyzed by refluxing 0.5 to 1.0 molar aqueous solutions containing 2.5 equivalents of sodium hydroxide for two hours. The derivatives of the dihalogenated aminopyridines were hydrolyzed in 50% aqueous alcohol solutions containing 2.5 equivalents of potassium hydroxide by boiling under reflux for fifteen to thirty minutes. In all cases the products were isolated by exactly neutralizing with concentrated hydrochloric acid and recrystallizing the precipitates formed from 60–80% acetic acid; yield 50–70%.

The nitro derivatives were reduced with sodium hydrosulfite in a way illustrated by the following example: 6 g. of 5-nitro-2-(N-5′-cyano-2′-pyridyl)-pyridinesulfonamide was suspended in 30 ml. of water containing 1.5 g. of sodium hydroxide, and 12 g. of sodium hydrosulfite was added with stirring while keeping the temperature below 50°. The amine was then obtained by neutralizing exactly with hydrochloric acid and recrystallizing the precipitate formed from aqueous alcohol; yield 30–40%.

Summary

1. A series of new substituted 2-sulfonamido-5-aminopyridines and two new derivatives of sulfanilamide have been prepared as indicated in the foregoing table.

2. Syntheses of new compounds, 5-nitro-2-pyridinesulfonyl chloride, 2-amino-3,5-diiodopyridine, 2-iodo-5-aminopyridine, and 2-amino-5-pyridinecarboxylic acid amide are described.

3. New procedures for preparing 2-amino-5-bromopyridine, 2-amino-5-cyanopyridine, 2-amino-3-pyridinecarboxylic acid amide, and 2-iodo-5-nitropyridine are given.

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The Behavior of Sulfur Dioxide as an Acid in Methanol

BY L. S. GUSS* AND I. M. KOLTHOFF

The acidity of aqueous solutions of sulfur dioxide is ordinarily attributed to the acids derived from sulfurous acid, H_2SO_3, HSO_3^- and H_3O^+. That H_2SO_3 is actually present in water solutions is evident from the work of Morgan and Maass,[1] Johnstone and Leppla,[2] Wright[3] and others. The first dissociation constant of the acid, 1.7×10^{-2}, refers to the total concentration of un-ionized sulfur dioxide. It is an apparent constant and the true constant of H_2SO_3 must be greater than this value, but is still unknown.

In the extended definition of Lewis,[4] sulfur dioxide exhibits an acidity itself without its having to react with a protolytic solvent like water. In other words, water solutions contain the proto-acid,[5] SO_2, which should have acidic properties. Whether it can act as a "catalyst acid," for example in the inversion of sugar in aqueous medium, has apparently never been investigated. Lewis[4] states that sulfur dioxide in acetone as a solvent gives a bright red color with thymol blue and a more or less red color with butter yellow.

It is of interest to consider the solution of sulfur dioxide in anhydrous solvents, such as methanol. In the absence of water, sulfurous acid cannot be

* Dr. L. S. Guss passed away on May 17, 1944.

(1) O. M. Morgan and O. Maass, *Can. J. Res.*, **5**, 162 (1931); see also W. B. Campbell and O. Maass, *ibid.*, **2**, 42 (1930).

(2) H. F. Johnstone and P. W. Leppla, THIS JOURNAL, **56**, 2233 (1934).

(3) R. Wright, *J. Chem. Soc.*, **105**, 2907 (1914).

(4) G. N. Lewis, *J. Franklin Inst.*, **226**, 293 (1938).

(5) I. M. Kolthoff, *J. Phys. Chem.*, **48**, 51 (1944).