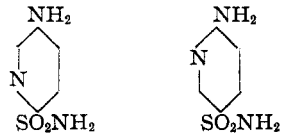
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF TEMPLE UNIVERSITY]

Substituted 2-Sulfonamido-5-aminopyridines

BY WILLIAM T. CALDWELL AND EDMUND C. KORNFELD[1a,1b]

Sulfanilamide and its numerous derivatives are all obtained from N-acetylsulfanilyl chloride or *p*-nitrobenzenesulfonyl chloride. In the hope of securing a group of compounds suited to comparative pharmacological studies and, of course, of obtaining products with superior therapeutic action, it seemed to us desirable to seek a new aromatic and isosteric sulfonyl chloride, *i. e.*, one which would serve as an intermediate for the preparation of a series of bactericides analogous to the many sulfanilamide derivatives already prepared.

The possible preparation of a *p*-aminopyridinesulfonamide, I or II, and its derivatives appeared



(I) (II)

intriguing in view of the presence of the pyridine nucleus in such physiologically active substances as nicotinamide, vitamin B_6, and sulfapyridine, and also because of the solubility in water of pyridine itself. 2-Amino-5-sulfonamidopyridine II and several derivatives have been prepared and studied by investigators abroad.[2,3,4] Our work therefore centered about the isomer I, which now has been synthesized in this Laboratory. Six derivatives of this product also have been prepared according to the scheme shown in Fig. 1.

In this connection, it may be noted that 3-aminopyridine resembles aniline more closely than does either 2- or 4-aminopyridine; indeed, compounds with substituents in position 3 of the pyridine nucleus usually differ considerably in chemical behavior from isomers with these substituents in position 2 or 4. It should, therefore, be a matter of interest to compare, both chemically and pharmacologically, 2-sulfonamido-5-aminopyridine I, in which the sulfonamido group occupies the position of somewhat anomalous reactivity and the amino group is in the position characterized by closer adherence to type, with 5-sulfonamido-2-aminopyridine II where the substituent groups are interchanged. Anticipation of certain differences and even difficulties of a chemical nature has already proved to be not without foundation, as will appear from what follows.

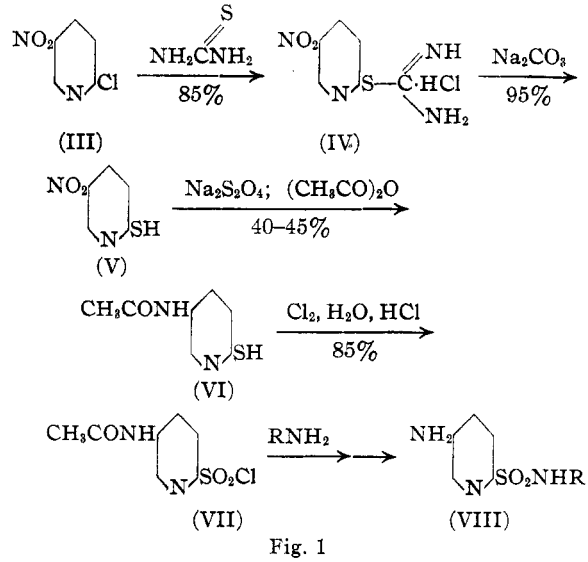
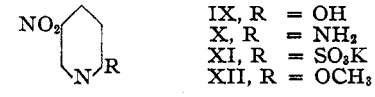


Fig. 1

The requisite intermediate for the preparation of the substituted sulfonamides VIII could be either 5-acetaminopyridine-2-sulfonyl chloride VII or a compound containing a nitro group in the 5 position. The latter possibility was abandoned when 2-thiol-5-nitropyridine V or 5,5′-dinitro-2,2′-dipyridyl disulfide could not be oxidized to the corresponding sulfonic acid in promising yield. Confirming and extending the work of Plazek,[5] we have found that oxidation of V with nitric acid, chromic acid, or potassium permanganate in acetone leads to the formation of 5-nitro-2-pyridone IX.



Treatment of (V) with ammoniacal potassium permanganate yields 2-amino-5-nitropyridine X

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(2) Naegeli, Kündig and Brandenburger, *Helv. Chim. Acta*, **21**, 1746 (1938).

(3) Tchitchibabine and Vialatout, *Bull. soc. chim.*, [5] **6**, 736 (1939).

(4) Ewins, Phillips and Newbery, British Patent 516,288 (1939).

(5) Plazek, *Roczniçki Chem.*, **17**, 97 (1937); *Chem. Zentr.*, **108**, II, 73 (1937).

together with a little potassium-5-nitropyridine-2-sulfonate XI, while oxidation with chlorine results in 2-chloro-5-nitropyridine III. Oxidation of 5-nitro-2-pyridylpseudothiourea hydrochloride IV with chlorine also failed to produce the desired result. Obviously the 5-nitro group activates the 2-position to a remarkable extent. Most interesting of all, perhaps, is the fact that on treating 2-chloro-5-nitropyridine with sodium sulfite[6] in dilute methanol, 2-methoxy-5-nitropyridine XII is formed and not the desired sulfonic acid.

Therefore, to obviate the labilizing influence of the nitro group, 2-thiol-5-nitropyridine V was reductively acetylated in order to obtain 2-thiol-5-acetaminopyridine VI. This step was effected without difficulty by use of sodium hydrosulfite and acetic anhydride, and it was of particular moment to us to discover that this compound could be oxidized in excellent yield to the desired 5-acetamino-2-pyridinesulfonic acid with hydrogen peroxide (30%) in acetic acid. Nevertheless, all attempts to convert this acid to the sulfonyl chloride VII have been unsuccessful. In this connection, it is perhaps of interest to point out that King and Ware[7] were unable to obtain 4-pyridinesulfonyl chloride from 4-pyridinesulfonic acid.

Fortunately, however, 2-thiol-5-acetaminopyridine VI was found to be easily and directly convertible by the action of chlorine into the requisite intermediate, 5-acetamino-2-pyridinesulfonyl chloride VII, by the excellent method of Johnson, Sprague and Douglass.[8]

Condensations of this sulfonyl chloride with various amines have been found to be entirely analogous to those using N-acetylsulfanilyl chloride. We are reporting at this time the preparation of seven analogs of sulfanilamide and its derivatives, and the work will be continued if these show promise as therapeutic agents.

Pharmacological tests on these compounds are being made by Dr. A. E. Livingston and Dr. E. J. Fellows of the Department of Pharmacology, Temple University Medical School; the results will be published in detail elsewhere.

We wish to thank Mr. Furness Thompson of Smith, Kline and French, Inc., and Dr. James M. Sprague of Sharp and Dohme, Inc., for generous samples of some of the heterocyclic amines used in this work, and also to express our gratitude to the Temple University Committee on Research and Publication for a grant-in-aid.

Experimental[9]

2-Chloro-5-nitropyridine, III.—This compound was prepared by a method similar to that of Phillips,[10] but the synthesis had been worked out independently in this Laboratory. It is based on the original work of Tchitchibabine.[11] 2-Aminopyridine (200 g., 2.13 moles) was added with efficient mechanical agitation to 800 ml. of concd. sulfuric acid while keeping the temperature below 50° by cooling in ice. Then 120 ml. (2.53 moles) of fuming nitric acid (d. 1.49) was run in below 40°. The solution was kept at 45° with occasional cooling in ice until the temperature no longer rose spontaneously above 45°, thus indicating that the rearrangement of 2-nitraminopyridine to 2-amino-3 or 5-nitropyridine was complete (three-quarters of an hour). The reaction mixture was kept at 45° for about one hour, allowed to stand at room temperature for several hours and was then neutralized by pouring cautiously into a mixture of concd. ammonia and ice. If it is desired to isolate 2-amino-3-nitropyridine, the mixture is steam distilled until about 18 liters are collected. This distillate on cooling deposits about 20–21 g. of 2-amino-3-nitropyridine; yield, 7%. The neutralized mixture, with or without steam distillation, was cooled, filtered, and the product washed with ice water. The crude 2-amino-5-nitropyridine was then dissolved in 1500 ml. of water containing 200 ml. of concd. sulfuric acid, decolorizing carbon was added, and the mixture filtered. A concentrated solution of 140 g. of sodium nitrite was then run in drop by drop at 10–15°. Very efficient mechanical stirring was essential. The thick mixture was then heated to boiling, cooled to 0°, and the product, 5-nitro-2-pyridone, filtered, washed with water, and dried; yield, 59% based on 2-aminopyridine. This may be used without further purification to prepare 2-chloro-5-nitropyridine using phosphorus pentachloride and phosphorus oxychloride[10]; yield, 90–95%. Recrystallization from methanol, using carbon, gave a product melting at 107–108°.

2-Methoxy-5-nitropyridine, XII.—To a solution of 7.9 g. (0.05 mole) of 2-chloro-5-nitropyridine in 200 ml. of hot methanol was added a solution of 10 g. (0.079 mole) of anhydrous sodium sulfite in 150 ml. of hot water.[6] The mixture was then refluxed for three hours, filtered hot, and the filtrate cooled. White needles separated which were recrystallized from dilute methanol, m. p. 108–108.5°. A mixed melting point with a sample of 2-methoxy-5-nitropyridine prepared from the silver salt of 5-nitro-2-pyridone and methyl iodide[12] was also 108–108.5°.

5-Nitro-2-pyridylpseudothiourea Hydrochloride, IV.—This was prepared by the method of Lindwall and Surrey[13]; yield, 85%.

2-Thiol-5-nitropyridine,[13] V.—The crude 5-nitro-2-pyridylpseudothiourea hydrochloride IV from 188 g. of 2-

(6) Erdman and Erdman, German Patent 65,240, prepared 2,4-dinitrobenzenesulfonic acid from 2,4-dinitrochlorobenzene by this method.

(7) King and Ware, *J. Chem. Soc.*, 873 (1939).

(8) Johnson, Sprague and Douglass, THIS JOURNAL, **58**, 1348 (1936); **59**, 1837, 2439 (1937); **60**, 1486 (1938); **61**, 176, 2548 (1939).

(9) All melting points are corrected.

(10) Phillips, *J. Chem. Soc.*, 9 (1941).

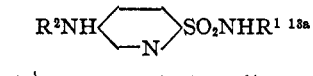
(11) Tchitchibabine, *J. Russ. Phys.-Chem. Soc.*, **46**, 1240 (1914); **47**, 1286 (1915); **50**, 471 (1918).

(12) Rath, *Ann.*, **484**, 52 (1930).

(13) Surrey and Lindwall, THIS JOURNAL, **62**, 1697 (1940).

TABLE I

PROPERTIES OF SUBSTITUTED 5-AMINOPYRIDINE-2-SULFONAMIDES



R^1	Solvent	M. p., °C., cor.	Formula	Analyses, % Calcd.	Found	Nitrogen Calcd.	Found
			R^2 = H-				
H-	Water	184–185	$C_5H_7N_3O_2S$			24.26	23.75
C_5H_5N-	Dil. EtOH	205–206[a]	$C_{10}H_{10}N_4O_2S$			22.39	23.00[b]
C_6H_5-	Dil. EtOH	164–165	$C_{11}H_{11}N_3O_2S$			16.86	16.91[b]
CH_4N_3-	Water	220–221[a]	$C_6H_9N_5O_2S$			32.54	32.36[b]
C_3H_2NS-	Dil. EtOH	226–227[a]	$C_8H_8N_4O_2S_2$			21.86	21.64[b]
$C_4H_3N_2$-	Diox. H_2O[c]	283–285[a]	$C_9H_9N_5O_2S$			27.88	27.69[b]
C_5H_3NI	Dil. EtOH	219–220[a]	$C_{10}H_9N_4O_2IS$			I, 33.74	33.62
			R^2 = CH_3CO-	Carbon		Hydrogen	
H-	Water	232–233	$C_7H_9N_3O_3S$			N, 19.53	19.17
C_5H_5N-	*d*	231–232[a]	$C_{12}H_{12}N_4O_3S$	49.30	49.08[b]	4.14	4.34[b]
C_6H_5-	Dil. MeOH	213–214	$C_{13}H_{13}N_3O_3S$	53.59	53.64[b]	4.50	4.34[b]
CH_4N_3-	Water	228–229[a,e]	$C_8H_{11}N_5O_3S$	37.35	37.58[b]	4.31	4.55[b]
C_3H_2NS-	Dil. EtOH	234–235[a]	$C_{10}H_{10}N_4O_3S_2$	40.26	40.16[b]	3.38	3.57[b]
$C_4H_3N_2$-	Dil. MeOH	231–232[a]	$C_{11}H_{11}N_5O_3S$			S, 10.93	10.70
C_5H_3NI-	Dil. EtOH	225–226[a]	$C_{12}H_{11}N_4O_3IS$			I, 30.35	30.19

[a] Melts with decomposition. [b] Analyses by Carl Tiedcke. [c] Best purified by evaporating a solution of the compound in dilute ammonia. [d] Best purified by precipitation from alkaline solution by acid. [e] Dried at 150°.

chloro-5-nitropyridine III was suspended in 2 liters of water and 68 g. of sodium carbonate added with stirring. Agitation was continued for fifteen minutes, and then a solution containing 102 g. of sodium hydroxide was added to dissolve the product. The red-orange solution was then filtered to remove a small amount of 5,5′-dinitro-2,2′-dipyridyl sulfide and the filtrate acidified with concd. hydrochloric acid. The product was cooled, filtered, washed with water, and dried. The yield, based on 2-chloro-5-nitropyridine III, was 80–83%; m. p. 188–191° (d.).

2-Thiol-5-acetaminopyridine, VI.—2-Thiol-5-nitropyridine V (31.2 g., 0.2 mole) was suspended in 300 ml. of water, and 120 g. (0.69 mole) of sodium hydrosulfite was added with stirring, keeping the temperature below 50°. The mixture turned from orange to yellow, and all solids went into solution. Acetic anhydride (26 ml., 0.275 mole) was then added below 50°. The product, 2-thiol-5-acetaminopyridine, gradually separated from the warm solution. The mixture was stirred for one hour, cooled in ice, and the product filtered, washed with water, and dried; yield, 40–45% based on 2-thiol-5-nitropyridine. On recrystallization from water the bright yellow compound melted at 244–246°.

Anal. Calcd. for $C_7H_8N_2OS$: N, 16.66. Found: N, 16.78.

5,5′-Diacetamino-2,2′-dipyridyldisulfide.—2-Thiol-5-acetaminopyridine VI (0.84 g.) was dissolved in 20 ml. of warm water and a few drops of 30% hydrogen peroxide added. The white solid which separated immediately from the warm solution was cooled, filtered, washed with water, and dried; yield, 90%. Repeated crystallization from dilute ethanol gave a product melting at 240–241°.

Anal. Calcd. for $C_{14}H_{14}N_4O_2S_2$: N, 16.76. Found: N, 16.70.

5-Acetaminopyridine-2-sulfonic Acid.—To 37.5 g. (0.22 mole) of 2-thiol-5-acetaminopyridine VI suspended in 250 ml. of glacial acetic acid was added 78 ml. (0.76 mole) of 30% hydrogen peroxide keeping the temperature below 70° by cooling in ice. The solids dissolved, and the mixture became brown. When the temperature no longer rose spontaneously (one hour), the reaction mixture was allowed to stand overnight. Crystals of the sulfonic acid had deposited in 24 hours or less. These were cooled well in ice, filtered, washed with ethanol, and dried; yield, 82%. On recrystallization from water the acid melted at 302–303° (d.).

Anal. Calcd. for $C_7H_8N_2O_4S$: N, 12.96; S, 14.83; neut. equiv., 216.2. Found: N, 13.22; S, 14.75; neut. equiv., 215.3.

S-Benzylthiuronium Salt of 5-Acetaminopyridine-2-sulfonic Acid.—This compound was prepared by the method of Chambers and Watt[14]; m. p. after recrystallization from water, 93–95°.

Anal. Calcd. for $C_{15}H_{18}N_4O_4S_2 \cdot 2H_2O$: N, 14.35. Found: N, 14.37.

5-Acetamino-2-pyridone.—This was prepared to compare with 5-acetaminopyridine-2-sulfonic acid. To 1.4 g. of 5-nitro-2-pyridone in 20 ml. of water was added 6 g. of sodium hydrosulfite and then 1.3 ml. of acetic anhydride. Needles deposited on standing overnight; m. p. 232–233° after recrystallization from water.

Anal. Calcd. for $C_7H_8N_2O_2$: N, 18.41. Found: N, 18.14.

5-Acetamino-2-pyridinesulfonyl Chloride VII.—Attempts to prepare this compound from the corresponding sulfonic acid using chlorosulfonic acid, phosphorus pentachloride, thionyl chloride, sulfuryl chloride, sulfur chloride, or benzotrichloride[15] resulted only in unchanged sulfonic acid or dark, non-crystalline masses, which showed no properties of a sulfonyl chloride. The following procedure, however, gave the acid chloride in 85% yield. 2-Thiol-5-acetaminopyridine VI (60 g.) was dissolved in 450 ml. of

(13a) System based on that of Northey, *Chem. Rev.*, **27**, 85 (1940).

(14) Chambers and Watt, *J. Org. Chem.*, **6**, 376 (1941).

(15) Kranzlein and Hopff, German Patent 574,836.

cold, concd. hydrochloric acid, and then 100 ml. of ice water was added. Chlorine was bubbled into the solution, keeping the temperature below 10° throughout by external cooling. The solution became dark brown at first, and the chlorination was complete when the temperature no longer rose and when the color of the solution lightened (two and one-half hours). The solution was then diluted with 1200 g. of ice and water, keeping the temperature still below 10°. The product which separated was filtered, washed with ice water, dried *in vacuo* over phosphorus pentoxide, and recrystallized the same day from ethylene dichloride. The sulfonyl chloride should be dried and recrystallized rapidly to prevent decomposition to the sulfonic acid. An analytical sample melted at 165–166° (d.).

Anal. Calcd. for $C_7H_7ClN_2O_3S$: N, 11.94; Cl, 15.11. Found: N, 11.75; Cl, 14.97.

Substituted Acetaminopyridinesulfonamides.—2-Sulfonamido-5-acetaminopyridine was prepared by adding one part of the sulfonyl chloride to four parts of concd. ammonia (25%), and evaporating the excess ammonia on the steam-bath. The product crystallized out on cooling; yield, 86%. The guanidine derivative was made by the method of Marshall, Bratton, White and Litchfield[16]; yield, 51%. The derivatives of the cyclic amines were prepared in 62–98% yields by adding an equivalent of 5-acetaminopyridine-2-sulfonyl chloride to the cyclic amine dissolved in dry pyridine, the weight of the latter being equal to that of the total solids. Solution took place with evolution of heat and the reactions were completed by warming at 60° for one-half to one hour. The crude derivatives obtained by pouring the dark solutions into ice water were dissolved in one equivalent of aqueous sodium hydroxide, decolorized, and reprecipitated by addition of hydrochloric acid.

Hydrolysis of the N^4-Acetyl Group.—Six of the acetyl compounds were hydrolyzed by refluxing 0.5 to 1.0 molar solutions containing 2.5 equivalents of sodium hydroxide for two and one-half to three hours. The acetyl derivative of the guanidine condensation product was hydrolyzed with 6-molar hydrochloric acid by the method of Marshall, *et al.*[16]

(16) Marshall, Bratton, White and Litchfield, *Bull. Johns Hopkins Hosp.*, **67**, 163 (1940).

Summary

1. 5-Acetaminopyridine-2-sulfonyl chloride has been prepared and is available as an intermediate for the preparation of a new series of chemotherapeutic agents.

2. The preparation of seven new substituted 5-aminopyridine-2-sulfonamides and their acetyl derivatives is reported.

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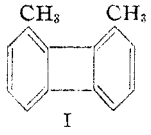
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF TRINITY COLLEGE]

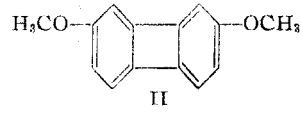
1,8-Dimethyl and 2,7-Dimethoxybiphenylene

BY WARREN C. LOTHROP

Continuing a line of investigation recently reported,[1] the present paper describes the preparation of two substituted biphenylenes. These new substances were obtained by following the procedure previously worked out for the parent substance, biphenylene, and have been assigned the structures



I



II

1,8-dimethylbiphenylene (I) and 2,7-dimethoxybiphenylene (II).

The hydrocarbon (I) was prepared with considerable difficulty and in very poor yield by the pyrolysis of 4,5-dimethylbiphenylene iodonium iodide with cuprous oxide. The over-all yield for the whole series of reactions starting with 100 g. of 2-amino-3-nitrotoluene was only 100 mg. of a pale yellow hydrocarbon crystallizing in plates from methanol. It melted at 79–80° and formed a picrate crystallizing in long crimson needles from ethanol and melting at 126°. It was lower melting and less highly colored than its isomer, 2,7-dimethylbiphenylene,[2] but otherwise similar.

For the preparation of II, a series of reactions previously reported[3] was followed but with variations in procedure materially improving the yields of all steps. Acetylation of *p*-anisidine (97%) followed by nitration with dilute nitric acid at room temperature (78%), and hydrolysis with alcoholic hydrochloric acid (95%) gave 3-nitro-*p*-anisidine[4] III. This when coupled by the procedure of Atkinson, *et al.*,[5] gave 2,2′-dinitro-*p*,*p*′-bianisole IV contaminated by a con-

(1) Lothrop, THIS JOURNAL, **63**, 1187 (1941).

(2) Recrystallization and careful drying of the picrate of this compound gave needles (m. p. 110–111°) which were evidently free of the alcohol of crystallization previously reported.[1] *Anal.* Calcd. for $C_{14}H_{12}\cdot C_6H_3O_7N_3$: N, 10.27. Found: N, 9.90, 10.43.

(3) Hata, Tatematsu and Kubota, *Bull. Chem. Soc. Japan*, **10**, 425 (1935).

(4) *Cf.* Reverdin, *Ber.*, **29**, 2595 (1896).

(5) Atkinson, Lawler, Heath, Kimball and Read, THIS JOURNAL, **63**, 730 (1941).