[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF WALLACE & TIERNAN, INC.]

Sulfapyridine-1-oxides

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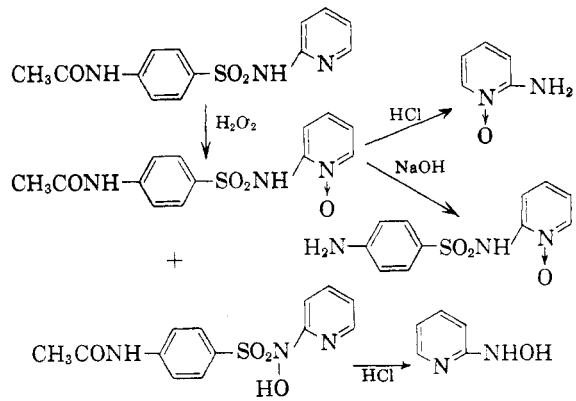
N^4-Acetylsulfapyridine has been oxidized with peroxide, giving N^4-acetylsulfapyridine-1-oxide and N^4-acetyl-N^1-hydroxysulfapyridine. The structures of the products have been established by hydrolysis. 2-*p*-Toluenesulfonamidopyridine and some of the homologs of N^4-acetylsulfapyridine were similarly oxidized.

In an attempt to prepare a more acidic sulfonamide than sulfapyridine we have synthesized sulfapyridine-1-oxide. N^4-Acetylsulfapyridine was oxidized with peroxide and the reaction mixture was found to contain two major products. The first of these was N^4-acetylsulfapyridine-1-oxide. Its structure was established after acid hydrolysis by isolation of the known 2-aminopyridine-1-oxide. Alkaline hydrolysis gave sulfapyridine-1-oxide which is indeed more acidic than the parent compound. Its pK_a is 5.2 in contrast to a pK_a of 8.4 for sulfapyridine. This increase in acid strength made possible the separation of the N^4-acetylsulfapyridine-1-oxide from the second major product of the peroxide oxidation. Upon treating the solid isolated from the reaction mixture with sodium bicarbonate solution, the N^4-acetylsulfapyridine-1-oxide dissolved leaving the second product as an insoluble residue. This product was identified as N^4-acetyl-N^1-hydroxysulfapyridine. Its structure was established by acid hydrolysis which freed the known 2-hydroxylaminopyridine. The reactions are indicated in the accompanying chart.

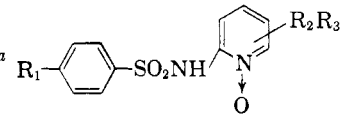


Similar oxidations were carried out with the four methyl homologs of N^4-acetylsulfapyridine, N^4-acetyl-4′,6′-dimethylsulfapyridine, N^4-acetyl-6′-ethylsulfapyridine and 2-*p*-toluenesulfonamidopyridine. Physical data are recorded in Tables I and II.

The sulfonhydroxamides caused methemoglobin formation *in vitro* and *in vivo* and were consequently eliminated from consideration as anti-bacterial agents. The sulfapyridine-1-oxides do not alter the blood pigment and are potent antimicrobial agents. Their antibacterial activity, like that of other sulfonamide drugs, is lost if the *p*-amino group is re-

TABLE I

SUBSTITUTED BENZENESULFONAMIDOPYRIDINE-1-OXIDES[a]

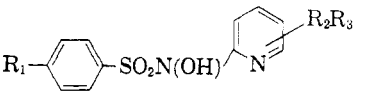


R_1	R_2	R_3	M.P., °C.[b]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3CONH	H	H	220–221	$C_{13}H_{13}O_4N_3S$					13.68	13.65
H_2N	H	H	188.5–189.5	$C_{11}H_{11}O_3N_3S$[c]	49.80	49.69	4.18	4.26	15.84	15.76
CH_3CONH	3-CH_3	H	234–236	$C_{14}H_{15}O_4N_3S$					13.08	12.89
H_2N	3-CH_3	H	196–198	$C_{12}H_{13}O_3N_3S$	51.60	51.80	4.69	4.91	15.05	14.86
CH_3CONH	4-CH_3	H	218–220	$C_{14}H_{15}O_4N_3S$					13.08	13.00
H_2N	4-CH_3	H	201.5–203	$C_{12}H_{13}O_3N_3S$	51.60	51.75	4.69	4.81	15.05	14.92
CH_3CONH	5-CH_3	H	248–250	$C_{14}H_{15}O_4N_3S$					13.08	13.04
H_2N	5-CH_3	H	209.5–211	$C_{12}H_{13}O_3N_3S$	51.60	51.75	4.69	4.76	15.05	15.02
CH_3CONH	6-CH_3	H	251–252	$C_{14}H_{15}O_4N_3S$					13.08	13.14
H_2N	6-CH_3	H	208–209.5	$C_{12}H_{13}O_3N_3S$[d]	51.60	51.70	4.69	4.74	15.05	14.93
CH_3CONH	6-C_2H_5	H	233–234	$C_{15}H_{17}O_4N_3S$					12.53	12.40
H_2N	6-C_2H_5	H	153–155	$C_{13}H_{15}O_3N_3S$	53.22	52.70	5.15	5.02	14.33	14.34
CH_3CONH	4-CH_3	6-CH_3	234–236	$C_{15}H_{17}O_4N_3S$					12.53	12.60
H_2N	4-CH_3	6-CH_3	221.5–222.5	$C_{13}H_{15}O_3N_3S$	53.22	53.56	5.15	5.20	14.33	14.37
CH_3	H	H	145.5–146.5	$C_{12}H_{12}O_3N_2S$	54.53	54.44	4.58	4.54	10.60	10.72

[a] These compounds gave deep orange-red colors with ferric chloride. [b] Corrected. [c] The pK_a was 5.2; the solubility at 26° (*p*H 4.1) was 0.12 g./100 ml. [d] The pK_a was 5.9; the solubility at 26° (*p*H 4.9) was 0.05 g./100 ml.

TABLE II

SUBSTITUTED BENZENESULFONHYDROXAMIDOPYRIDINES[a]



R_1	R_2	R_3	M.P., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3CONH	H	H	178 (dec.)	$C_{13}H_{13}O_4N_3S$	13.68	13.64
CH_3CONH	4-CH_3	H	176 (dec.)	$C_{14}H_{15}O_4N_3S$	13.08	13.20
CH_3CONH	5-CH_3	H	190 (dec.)	$C_{14}H_{15}O_4N_3S$	13.08	13.11
CH_3CONH	6-CH_3	H	172 (dec.)	$C_{14}H_{15}O_4N_3S$	13.08	13.14
CH_3CONH	6-C_2H_5	H	160 (dec.)	$C_{15}H_{17}O_4N_3S$	12.53	12.45
CH_3CONH	4-CH_3	6-CH_3	181 (dec.)	$C_{15}H_{17}O_4N_3S$	12.53	12.69
CH_3	H	H	159 (dec.)	$C_{12}H_{12}O_3N_2S$	10.60	10.68

[a] Purple colors were formed with ferric chloride except for the 4',6'-dimethyl compound which gave a brown color, and the 6'-ethyl compound which gave no color.

placed by a methyl group. The sulfapyridine-1-oxides do not form uroliths in experimental animals. A detailed account of their chemotherapeutic activity will be given elsewhere.

EXPERIMENTAL

Among the N^4-acetylsulfapyridines that were oxidized, N^4-acetyl-6'-ethylsulfapyridine and N^4-acetyl-4',6'-dimethylsulfapyridine have not been described previously.

N^4-Acetyl-4',6'-dimethylsulfapyridine was made in the usual way from 2-amino-4,6-dimethylpyridine and acetylsulfanilyl chloride in pyridine solution. Crystallized from aqueous alcohol it melted at 225–228°.

Anal. Calcd. for $C_{15}H_{17}O_3N_3S$: N, 13.16. Found: N, 13.15.

2-Amino-6-ethylpyridine. A mixture of 183 g. of sodium amide and 485 g. of 2-ethylpyridine in 485 g. of *p*-cymene was stirred and heated at 150° for 5 hr. Water was cautiously added to the cooled reaction mixture and the organic layer was separated, dried, and distilled. There was obtained 272 g. of 2-amino-6-ethylpyridine, b.p. 217–219°.

Anal. Calcd. for $C_7H_{10}N_2$: C, 68.82; H, 8.25. Found: C, 68.79; H, 8.36.

The *picrate* (from alcohol) melted at 198–200°.

Anal. Calcd. for $C_{13}H_{13}O_7N_5$: N, 19.94. Found: N, 19.76.

N^4-Acetyl-6'-ethylsulfapyridine. Prepared in the usual way from the amine and acetylsulfanilyl chloride, N^4-acetyl-6'-ethylsulfapyridine melted at 155–157°.

Anal. Calcd. for $C_{15}H_{17}O_3N_3S$: N, 13.16. Found: N, 12.98.

Oxidation of N^4-acetylsulfapyridine (Method A). A solution of 520 g. of N^4-acetylsulfapyridine in 2.9 l. of 90% formic acid was treated with 175 ml. of 30% hydrogen peroxide. The temperature slowly rose to 55°. Three hours later an additional 175 ml. of peroxide was added. After 12 hr. the iodide test for peroxide became negative. The solvent was removed under reduced pressure on a water bath. The residue was dissolved in 1 l. of hot 10% acetic acid and allowed to crystallize. The crystals were filtered off, washed with water, suspended in 1.5 l. of water containing 70 g. of sodium bicarbonate and stirred for 1 hr. Undissolved material (largely N^4-acetyl-N^1-hydroxysulfapyridine) was separated. The alkaline filtrate on acidification afforded 170 g. of crude N^4-acetylsulfapyridine-1-oxide (m.p. 216–218°). Recrystallized from aqueous alcohol, the product melted at 220–221° (See Table I). A second treatment of the insoluble portion with bicarbonate gave an additional 10 g. of N^4-acetylsulfapyridine-1-oxide. The remaining 285 g. of crude N^4-acetyl-N^1-hydroxysulfapyridine (m.p. 172° dec.) on recrystallization from aqueous alcohol melted at 178° dec.

2-*p*-Toluenesulfonamidopyridine was also oxidized by Method A.

Oxidation of N^4-acetyl-6'-methylsulfapyridine (Method B). Thirty grams of N^4-acetyl-6'-methylsulfapyridine was suspended in 90 g. of acetic acid and 30 g. of 40% peracetic acid. The suspension was maintained at room temperature for 24 hr. with occasional agitation. The compound slowly dissolved as the reaction took place. The solvent was then removed under reduced pressure. To the residue was added 400 ml. of water with sufficient sodium bicarbonate to give an alkaline solution. After standing overnight the insoluble material was separated and the alkaline filtrate was acidified. Both products were then worked up as before to give 14 g. of crude N^4-acetyl-6'-methylsulfapyridine-1-oxide (m.p. 244°) and 9.5 g. of crude N^4-acetyl-N^1-hydroxy-6'-methylsulfapyridine (m.p. 168° dec.). Other data are in the tables.

The oxidation of N^4-acetyl-5'-methylsulfapyridine and N^4-acetyl-6'-ethylsulfapyridine proceeded similarly. It was necessary to heat the reaction mixtures containing N^4-acetyl-3'-methylsulfapyridine and N^4-acetyl-4'-methylsulfapyridine at 60° for 16 hr. and the yield was poorer. In the case of N^4-acetyl-3'-methylsulfapyridine, the bicarbonate-insoluble matter was largely unreacted starting material. Although this portion gave a positive Tollens test, indicating the presence of N^4-acetyl-N^1-hydroxy-3'-methyl-sulfapyridine, the compound was not isolated. During the oxidation of N^4-acetyl-4',6'-dimethylsulfapyridine, N^4-acetyl-N^1-hydroxy-4',6'-dimethylsulfapyridine crystallized out of the reaction mixture.

Alkaline hydrolysis. Hydrolysis of the acetyl group in the N^4-acetylsulfapyridine-1-oxides was accomplished by heating for 1 hr. in refluxing 2*N* sodium hydroxide (9 ml. for 1 g.). The products are described in Table I.

Similar treatment of the N^4-acetyl-N^1-hydroxysulfapyridines resulted in decomposition.

Structure of the oxidation products of N^4-acetylsulfapyridine. In order to assign the correct structures to the two products resulting from the oxidation of N^4-acetylsulfapyridine, each compound was hydrolyzed in refluxing 6*N* hydrochloric acid for 1 hr. N^4-Acetylsulfapyridine-1-oxide, the bicarbonate-soluble fraction, gave acetic acid, sulfanilic acid and 2-aminopyridine-1-oxide. The latter was isolated by means of a chloroform extraction of the hydrolysis mixture after the addition of sodium hydroxide. The white powder recovered from this extract melted at 162–164°, and the melting point was unchanged when the product was mixed with an authentic sample.[1] It gave a blue color with ferric chloride which was discharged by hydrochloric acid. A Tollens test was negative.

The hydrolysis of N^4-acetyl-N^1-hydroxysulfapyridine, the bicarbonate-insoluble portion, gave 2-hydroxylaminopyridine as well as acetic acid and sulfanilic acid. The hydroxyl-

(1) R. Adams and S. Miyano, *J. Am. Chem. Soc.*, 76, 2785 (1954).

aminopyridine was isolated as the hydrochloride and crystallized from ethanol. It slowly decomposed above 200°.

Anal. Calcd. for $C_5H_2ON_2 \cdot HCl$: C, 40.97; H, 4.81; N, 19.11; Found: C, 41.26; H, 4.43; N, 19.05.

Conversion to the base gave 2-hydroxylaminopyridine which melted at 83–84°. It gave a positive Tollens test and with ferric chloride a blue color which became green, then yellow with additional reagent. This color test is given by 2-hydroxylaminopyridine according to Newbold and Spring[2] who observed a m.p. of 83–85°.

NEWARK, N. J.

(2) G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, S 133 (1949).

[CONTRIBUTION FROM THE UNIVERSITY OF NEW MEXICO, LABORATORY OF PHARMACEUTICAL CHEMISTRY]

Pyridylimidazolidines and Pyridyloxazolidines

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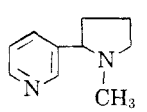
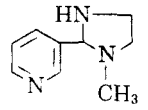
Nine pyridylimidazolidines and three pyridyloxazolidines have been prepared as structural and position analogs of nicotine. These compounds were screened for pharmacological activity and found inactive. The ultraviolet absorption spectra of some of these compounds have been determined. The ultraviolet absorption spectrum of 3-methyl-2-(2-pyridyl)oxazolidine indicates that this compound is unstable in aqueous solution, regenerating the original aldehyde and aminoalcohol.

This work continues a search for analogs of physiologically active compounds which retain the desirable physiological properties of the parent compound but have lesser undesirable activities and toxicity.

The recent availability of pyridine aldehydes, especially pyridine-3-aldehyde, prompted the synthesis of structural and position analogs of nicotine. The pyrrolidine ring of nicotine has been replaced by imidazolidine and oxazolidine rings, respectively, and the position of attachment of the five-membered rings to the pyridine rings has been 2-, 3-, and 4-, respectively. Structures I, II, and III show nicotine, 1-methyl-2-(3-pyridyl)imidazolidine, and 3-methyl-2-(3-pyridyl)oxazolidine, respectively. Compounds II and III were designed as complete structural analogs of nicotine. Besides II, eight other pyridylimidazolidines have been prepared, as shown in Table I.



I



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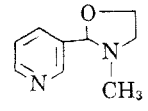

III

TABLE I

PYRIDYLIMIDAZOLIDINES

Compound	B.P., °C	Yield, %	Refractive Index	Formula	Analyses Calcd. C	Calcd. H	Calcd. N	Found, % C	Found, % H	Found, % N
1-Methyl-2-(2-pyridyl)-imidazolidine	97°–0.1 mm.	56	n_D^{26} 1.5410	$C_9H_{13}N_3$	66.23	8.03		65.95	7.85	
1-Methyl-2-(3-pyridyl)-imidazolidine	97°–0.1 mm.	62	n_D^{25} 1.5450	$C_9H_{13}N_3$	66.23	8.03		66.50	8.07	
1-Methyl-2-(4-pyridyl)-imidazolidine	100°–0.05 mm.	55	$n_D^{25.5}$ 1.5440	$C_9H_{13}N_3$	66.23	8.03	25.75	65.83	8.07	26.00
1-Methyl-2(6-methyl-2-pyridyl)imidazolidine	94°–0.05 mm.	53	n_D^{23} 1.5390	$C_{10}H_{15}N_3$	67.76	8.53	23.71	67.56	8.33	23.90
4,4-Dimethyl-1-isopropyl-2-(2-pyridyl)imidazolidine	101°–0.08 mm.	77	n_D^{20} 1.5121	$C_{13}H_{21}N_3$	71.19	9.65		71.55	9.93	
4,4-Dimethyl-1-isopropyl-2-(3-pyridyl)imidazolidine	106°–0.07 mm.	85	n_D^{20} 1.5180	$C_{13}H_{21}N_3$	71.19	9.65		70.52	9.24	
4,4-Dimethyl-1-isopropyl-2-(4-pyridyl)imidazolidine	105.5°–0.1 mm.	82	n_D^{20} 1.5131	$C_{13}H_{21}N_3$	71.19	9.65		70.60	9.60	
4,4-Dimethyl-1-isopropyl-2-(6-methyl-2-pyridyl)-imidazolidine	114°–0.1 mm.	78	n_D^{20} 1.5104	$C_{14}H_{23}N_3$	72.06	9.93		71.49	9.98	
2,6-Bis(4,4-dimethyl-1-isopropyl-2-imidazolidinyl)-pyridine	168°–0.1 mm. M.p. 52–53°	68		$C_{21}H_{37}N_5$	70.14	10.37		69.40	10.13	