heated at 140° for two hours. After fifteen minutes the oil had solidified. The product which weighed 20 g. (84%) melted at 260–262° after recrystallization from benzene.

Summary

The methods of preparation of various type derivatives of 2,6-diaminopyridine are described and a number of such derivatives have been made and characterized.

The relative antiparasitic activity of these derivatives has been indicated.

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[CONTRIBUTION FROM THE DIVISION OF MEDICINAL CHEMISTRY, THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

III. Some Substituted Sulfanilamidopyridines

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The observation that 2-amino-5-iodopyridine and 2,6-diaminopyridine[1] exhibited activity against *P. lophurae*, coupled with the knowledge that various N^1-substituted sulfanilamides also showed such activity, made it seem of interest to prepare various substituted sulfanilamidopyridines as possible antimalarial agents. Several such compounds had been prepared previously as general chemotherapeutic agents. Fosbinder and Walter[2] have described the preparation of 6-amino-2-sulfanilamidopyridine, while Raiziss,[3] Roblin and Winnek[4] and Winterbottom[5] have reported a number of sulfanilamidopyridines. In addition a number of patents have been granted on the preparation of this type of compound. Several new sulfanilamidopyridines, described in Table I, have been prepared during the course of this research. These compounds are mainly 5- or 6-substituted-2-sulfanilamidopyridines. For purposes of completeness and comparison, several of the previously reported compounds, which we had also prepared, are included.

TABLE I

SUBSTITUTED SULFAPYRIDINES

Pyridine derivative	Procedure[b]	Yield, %[c]	% Aq. C_2H_5OH	M. p., °C.	Empirical formula	% Nitrogen Calcd.	% Nitrogen Found
2-S[a]-3-CH_3	F	40	50	212–214	$C_{12}H_{13}N_3O_2S$	15.97	15.57
2-S-4-CH_3	F	56	95	233.5–234.5[d]	$C_{12}H_{13}N_3O_2S$	15.97	15.92
2-S-5-CH_3	F	67	95	188–189	$C_{12}H_{13}N_3O_2S$	15.97	15.79
2-S-6-CH_3	F	58	95	217–218[e]	$C_{12}H_{13}N_3O_2S$	15.97	15.76
2-S-5-$COOC_2H_5$	G	82	95	201–202	$C_{14}H_{15}N_3O_4S$	13.08	13.00
2-S-5-COOH	H	83	95	252–253	$C_{12}H_{11}N_3O_4S$	14.33	14.47
2-S-5-$CONH_2$	G[f]	55	[g]	202.5–203.5	$C_{12}H_{12}N_4O_3S$	19.18	18.92
2-S-5-I	E	95	95	219–221[h]	$C_{11}H_{10}IN_3O_2S$	11.20	11.42
2-S-6-NH_2	[i]	54	95	204–205	$C_{11}H_{12}N_4O_2S$	21.21	21.34
2-S-6-$NHCOCH_3$	G	25	100	111.5–113	$C_{13}H_{14}N_4O_3S$	18.30	18.49
2-S-6-$NHCOOC_2H_5$	E	83	75	176–177	$C_{14}H_{16}N_4O_4S$	16.67	16.50
2-S-6-$NHCONH_2$	I	42	100	214–216 (dec.)	$C_{12}H_{13}N_5O_3S$	22.80	22.35
2-S-6-$N(C_2H_5)_2$	F	53	100	155–156.5	$C_{15}H_{20}N_4O_2S$	17.50	17.36
2-S-6-OCH_3	F	39	[k]	145–148	$C_{12}H_{13}N_3O_3S$	15.05	15.00
5-S-2-OCH_3	E	94	50	176–177[j]	$C_{12}H_{13}N_3O_3S$	15.05	14.94
2-S-6-$NHCH(CH_2)_3N(C_2H_5)_2$ | CH_3	F	95	100	169–170	$C_{20}H_{31}N_5O_2S$	17.28	17.16

[a] Sulfanilamido. [b] Refers to general preparation described in experimental part. [c] Yield of purified material. [d] M. p. 255° reported in Belgian Patent 447,660. [e] M. p. 218–219° reported in French Patent 846,191. [f] U. S. Patent 2,381,-873. [g] Purified by solution in dilute alkali and precipitation with acetic acid. [h] M. p. 220–221°, reported by Roblin and Winnek, ref. 4. [i] Fosbinder and Walter, ref. 2. [j] M. p. 178°, reported by Raiziss, Clemence and Freifelder, ref. 3. [k] Isopropanol.

The general method of preparation was the condensation of *p*-acetamidobenzenesulfonyl chloride with the appropriately substituted aminopyridine,[6] followed by the hydrolysis of the acetylsulfanilamidopyridine (Table II).

The attempted hydrolysis of ethyl 6-acetylsulfanilamidonicotinate to ethyl 6-sulfanilamidonicotinate was unsuccessful, so for this series of derivatives the *p*-nitrobenzenesulfonylamidopyridines were prepared and reduced to the corresponding

(1) Bernstein, Stearns, Shaw and Lott, THIS JOURNAL, **69**, 1151 (1947).

(2) Fosbinder and Walter, *ibid.*, **61**, 2032 (1939).

(3) Raiziss, Clemence and Freifelder, *ibid.*, **63**, 2739 (1941).

(4) Roblin and Winnek, *ibid.*, **62**, 1999 (1940).

(5) Winterbottom, *ibid.*, **62**, 160 (1940).

(6) The preparation of most of the starting amines is described in ref. 1. The aminopicolines can be obtained from Reilly Coal Tar Company.

TABLE II

INTERMEDIATE ACETYL COMPOUNDS

Pyridine derivative	Method of prepn.[b]	Yield, %[c]	% Aq. C_2H_5OH	M. p., °C.	Empirical formula	% Nitrogen Calcd.	% Nitrogen Found
2-R[a]-3-CH_3	A	53	95	232–234	$C_{14}H_{15}N_3O_3S$	13.77	13.74
2-R-4-CH_3	A	87	50	268–270	$C_{14}H_{15}N_3O_3S$	13.77	13.86
2-R-5-CH_3	A	52	70	230–232	$C_{14}H_{15}N_3O_3S$	13.77	13.87
2-R-6-CH_3	A	56	97	214–215[d]	$C_{14}H_{15}N_3O_3S$	13.77	13.72
2-R-5-$COOC_2H_5$	A	88	95	219–220	$C_{16}H_{17}N_3O_5S$	[e]	[e]
2-R-5-I	B	58	95	228–230[f]	$C_{13}H_{12}IN_3O_3S$	10.07	10.18
2-R-6-NH_2	[g]	76	95	239–240	$C_{13}H_{14}N_4O_3S$	[g]	[g]
2-R-6-$NHCOCH_3$	C	53	50	225–226	$C_{15}H_{16}N_4O_4S$	16.09	16.17
2-R-6-$NHCOOC_2H_5$	B	76	100	195–197	$C_{16}H_{18}N_4O_5S$	14.81	14.55
2-R-6-$N(C_2H_5)_2$	B	73	50	178–179	$C_{17}H_{22}N_4O_3S$	15.47	15.21
2-R-6-$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$	A	45	50	189–190	$C_{22}H_{33}N_5O_3S$	15.66	14.77
2-R-6-OCH_3	A	83	95	170–171	$C_{14}H_{15}N_3O_4S$	13.08	13.26
5-R-2-OCH_3	B	77	25	194–195	$C_{14}H_{15}N_3O_4S$	13.08	12.93

[a] R is acetylsulfanilamido. [b] Refers to general preparation described in experimental part. [c] Yield of product before crystallization. [d] M. p. 215–217°, reported in Swiss Patent 213,151. [e] *Anal.* Calcd. S, 8.81. Found: S, 9.37. [f] M. p. 234° reported in French Patent 846,191. [g] Fosbinder and Walter, ref. 2.

TABLE III

INTERMEDIATE NITRO COMPOUNDS

Pyridine derivative	Method of prepn.[b]	Yield, %[c]	Solvent for crystn.	M. p., °C.	Empirical formula	% Nitrogen Calcd.	% Nitrogen Found
2-R[a]-5-CN	A	75	Acetone–water	217–219	$C_{12}H_8N_4O_4S$	[d]	[d]
2-R-5-$COOC_2H_5$	A	73	95% Alcohol	182–183	$C_{14}H_{13}N_3O_6S$	11.97	12.29
2-R-5-$CONH_2$	D	70	[e]	183–184	$C_{12}H_{10}N_4O_5S$	17.39	17.18
2-R-6-$NHCOCH_3$	B	64	Abs. alcohol	172–173	$C_{13}H_{12}N_4O_5S$	16.67	17.40

[a] R is *p*-nitrobenzenesulfonylamido. [b] Refers to general method described in experimental part. [c] Yield of crude product. [d] *Anal.* Calcd.: S, 10.53. Found: S, 10.48. [e] Purified by solution in dilute alkali and precipitation with acetic acid.

amino bodies. The preparation of 2-sulfanilamido-6-ureidopyridine was carried out by ammonolysis of the corresponding carbethoxy derivative similar to the procedure used to convert 2-amino-6-carbethoxyamidopyridine to 2-amino-6-ureidopyridine.[1]

None of the compounds prepared showed any marked activity against *P. lophurae* in ducklings. However, it is of interest to note that several of the derivatives of 2-sulfanilamido-6-aminopyridine show slight activity against *P. cathemerium* in ducklings, a type of activity which is not exhibited by other sulfanilamides such as sulfapyridine and sulfamerazine.

The authors are indebted to Mr. J. F. Alicino of this Institute for the microanalyses reported.

Experimental[7]

A. 2-(N⁴-acetylsulfanilamido)-4-methylpyridine.—To a well-stirred solution of 19.9 g. (0.176 mole) of 2-amino-4-methylpyridine in 60 cc. of pyridine, there was added 41.1 g. (0.176 mole) of *p*-acetylaminobenzenesulfonyl chloride in small portions. The temperature of the reaction mixture during the addition was maintained at 10–15° by cooling in an ice-bath. After all the chloride had been added, the solution[8] was warmed on a steam-bath for two hours. The reaction mixture was then poured into ice and water, containing approximately 0.4 mole of hydrochloric acid. After the *p*H of the solution had been adjusted to about 5, the solid was filtered off and washed several times with water. The crude product which weighed 40 g. (87%) melted at 261–264°. After crystallization from 50% alcohol the product melted at 268–270°.

B. 2-(N⁴-acetylsulfanilamido)-6-carbethoxyamidopyridine.—A mixture of 335 g. (1.434 mole) of *p*-acetylamidobenzenesulfonyl chloride and 247 g. (1.364 mole) of 2-amino-6-carbethoxyamidopyridine was ground in a mortar and 225 g. (2.8 mole) of anhydrous pyridine added slowly with vigorous stirring. The reaction mixture was then warmed for one hour on a steam-bath, cooled and poured into four liters of water. The mixture, after standing overnight, was filtered; and the solid washed several times with water and air-dried. The crude product which weighed 395 g. (76% yield) and melted at 186–188° was crystallized from two and one-half liters of absolute alcohol. The 2-(N⁴-acetylsulfanilamido)-6-carbethoxyamidopyridine which weighed 275 g. (53%) melted at 195–197°.

C. 2-Acetylamido-6-N⁴-acetylsulfanilamidopyridine.—A mixture of 50 g. (0.18 mole) of 2-amino-6-N⁴-acetylsulfanilamidopyridine, 30 g. (0.29 mole) of acetic anhydride and 100 cc. of acetic acid was refluxed for two hours. The reaction mixture was then poured into water and the solid filtered off and washed several times with water. After crystallization from 1500 cc. of absolute alcohol, the product which weighed 33.0 g. (53%) melted at 225–226°.

D. 6-*p*-Nitrobenzenesulfonamidonicotinamide.—To a solution of 20 g. (0.066 mole) of 2-*p*-nitrobenzenesulfonamido-5-cyanopyridine in 200 cc. of water, containing 5.0 g. of sodium hydroxide there was added 35 cc. of a 30% hydrogen peroxide solution. The reaction mixture was warmed for one hour at 70°; cooled and acidified with

(7) All melting points are uncorrected.

(8) In several cases, precipitation of the product occurred during the addition of the chloride. The mixture was then warmed in order to obtain complete solution and the remainder of the chloride added in portions to the warm solution.

acetic acid. The precipitated solid was filtered off, washed with water and suspended in a sodium bicarbonate solution to remove any free acid. The solid was filtered off, washed several times with water and air-dried. The product which weighed 15.0 g. (70%) melted at 183–184°.

E. Acid Hydrolysis of 2-(N^4-Acetylsulfanilamido)-5-iodopyridine.—A solution of 10 g. (0.024 mole) of 2-(N^4-acetylsulfanilamido)-5-iodopyridine in 100 cc. of 10% hydrochloric acid and 100 cc. of alcohol was refluxed for ninety minutes.[9] The solution was treated with decolorizing carbon, filtered and the *p*H adjusted to about 5. The alcohol was then removed under reduced pressure and the precipitated solid filtered off, washed with water and air-dried. After crystallization from alcohol the product, which weighed 8.5 g. (94%), melted at 219–221°.

F. Alkaline Hydrolysis of 2-(N^4-acetylsulfanilamido)-5-methylpyridine.—A solution of 74.5 g. (0.244 mole) of 2-(N^4-acetylsulfanilamido)-5-methylpyridine in 750 cc. of a 5% aqueous sodium hydroxide solution and 25 cc. of alcohol was refluxed for thirty-five minutes.[9] Five grams of decolorizing carbon was added, the solution refluxed for an additional ten minutes and then filtered. The *p*H of the filtrate was adjusted to about 5 and the precipitated solid filtered off, washed several times with water and air-dried. The crude product, weighing 61 g. (95%), melted at 184–186°. After crystallization from 95% alcohol the 2-sulfanilamido-5-methylpyridine which weighed 43 g. (67%) melted at 188–189°.

G. Reduction of Ethyl 6-*p*-Nitrobenzenesulfonylamidonicotinate.—A mixture of 72 g. (0.206 mole) of ethyl 6-*p*-nitrobenzenesulfonylamidonicotinate, 200 g. of iron powder and 650 cc. of 95% alcohol was placed in a 2-liter, 3-necked flask fitted with a mercury-sealed stirrer, reflux condenser and dropping funnel. The reaction mixture was heated to reflux and 14 cc. of 18% hydrochloric acid added dropwise with vigorous stirring. The mixture was heated for five and one-half hours after the addition of the acid was complete, and then allowed to stand overnight at room temperature. The solid was filtered off, suspended in 1400 cc. of water and 5% sodium hydroxide solution added until the solution was alkaline. The mixture was filtered and the filtrate acidified with acetic acid to obtain the crude product. The extraction of the iron residue was repeated until the filtrate gave no precipitate upon acidification. The product was purified by solution in aqueous ammonia, treatment with decolorizing carbon and acidification. After crystallization from 95% alcohol the material weighing 54.9 g. (82%) melted at 201–202°.

H. Hydrolysis of Ethyl 6-Sulfanilamidonicotinate.—A mixture of 19 g. (0.06 mole) of ethyl 6-sulfanilamidonicotinate, 19 g. of barium oxide, 800 cc. of 95% alcohol and 8 cc. of water was refluxed for five and one-half hours, then cooled and the solid filtered off. The precipitate was dissolved in water, treated with decolorizing carbon, filtered and the solution acidified to *p*H 6 with concentrated hydrochloric acid. The solid was filtered off, washed with water and air-dried. The acid, which weighed 15.0 g. (85%), melted at 251°; crystallization from alcohol raised the melting point to 252–253°.

I. 2-Sulfanilamido-6-ureidopyridine.—A solution of 80 g. (0.238 mole) of 2-sulfanilamido-6-carbethoxyamidopyridine in 360 cc. of absolute alcohol, containing 20 g. of ammonia, was heated at 105–110° for twelve hours. The solution was then concentrated to 120 cc. and cooled. The solid which crystallized out was filtered off and washed with a small amount of cold absolute alcohol. The crude product, which weighed 50 g. (68%) and melted at 200–205° dec., was purified by solution in dilute sodium hydroxide, treatment with decolorizing carbon and precipitation with dilute hydrochloric acid. After crystallization from absolute alcohol the product, weighing 31 g. (42%), melted at 214–216° dec.

(9) In the hydrolysis of each compound, refluxing was continued until the potassium nitrite titer of an aliquot had reached a maximum. The potassium nitrite titration could not be used with derivatives of 2,6-diaminopyridine so the hydrolyses of these compounds were carried out for sixty to ninety minutes unless otherwise noted.

Summary

A number of substituted sulfanilamidopyridines have been synthesized. None of the compounds synthesized showed any promise as antimalarial agents.

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[CONTRIBUTION FROM CALCO CHEMICAL DIVISION, AMERICAN CYANAMID CO.]

Chemical Constitution and Reactivity. II. The Decomposition of *o*-Methoxybenzenediazonium Chloride

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Introduction

The assignment of chemical structures to the molecular forms which diazo compounds may assume under various conditions of *p*H, dilution, etc., has occupied the attention of many chemists since the time of Peter Griess. The earlier investigators based their conclusions largely on organochemical investigations. The work of Hantzsch[1a] on the structure of diazotates marked one of the first uses of physico-chemical methods in the accumulation of evidence in support of an organic chemical structure. More recently such workers as Waters,[2] Waring,[3] and ourselves[4] have demonstrated the usefulness of *chemical kinetics* in pointing to the probable truth of one or another concept of the structure of certain diazo compounds. Among the diazo compounds whose decomposition rates we have studied is an extraordinary family of which a simple member is *o*-methoxybenzenediazonium chloride. In the present paper the behavior of this compound is discussed. Other members of the family are to be reported later.

Experimental

Unless otherwise specifically stated, the diazo solutions were studied at 0.1 molar strength and were prepared from

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(1a) N. V. Sidgwick, "Organic Chemistry of Nitrogen," Oxford Press, New York, N. Y., 1937, p. 414.

(2) Waters, *J. Chem. Soc.*, 113 (1937).

(3) Waring and Abrams, THIS JOURNAL, **63**, 2757 (1941).

(4) Crossley, Kienle and Benbrook, *ibid.*, **62**, 1400 (1940).