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

II. Derivatives of 2,6-Diaminopyridine[1]

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Of the pyridine derivatives reported in the previous paper[2] in this series, only 2,6-diaminopyridine showed any appreciable antiparasitic activity when tested against *P. lophurae* in ducklings. A number of derivatives of this compound have been prepared in order to determine if further substitution in the molecule would increase the antiparasitic activity of the parent compound.

Four general types of derivatives were made: acylated, alkylated, ring substituted and various fused ring derivatives of 2,6-diaminopyridine. Acylated derivatives were prepared (1) by the reaction of 2,6-diaminopyridine with acyl chlorides usually in an inert solvent at room temperature, (2) by the reaction of 2,6-diaminopyridine with acids or esters at elevated temperatures which allowed the water or alcohol formed to distill out of the reaction mixture; or (3) by the reaction of 2,6-diaminopyridine with isocyanates, by fusion of 2,6-diaminopyridine with urea, or by the action of alcoholic ammonia on the carbethoxy derivative which yielded ureido derivatives.

Alkylated derivatives of 2,6-diaminopyridine were prepared by the general method of Hertog and Wibaut[3]: the symmetrical derivatives by the reaction of primary or secondary amines with 2,6-dibromopyridine, and the unsymmetrical derivatives by reaction with 2-amino-6-bromopyridine.[3] The preparation of the unsymmetrical derivatives by the initial replacement of one of the bromines by reaction with a secondary amine, followed by the reaction with ammonia was a poor preparative method. Low yields were obtained in the replacement of the second bromine due to the apparently decreased activity of the bromine as compared to the bromine in 2,6-dibromopyridine or 2-amino-6-bromopyridine. Various acyl and alkyl derivatives are listed in Table I.

TABLE I

N-SUBSTITUTED DERIVATIVES OF 2,6-DIAMINOPYRIDINE

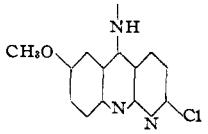
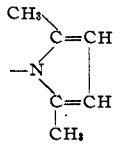
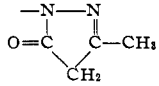
Substituted pyridine 2-	6-	Procedure[a]	Yield, %	Solvent for crystallization	M. p., °C.	Empirical formula	Analyses, % N Calcd.	Found	Activity[2]
—NH_2	—NH_2	..	..	Alcohol	81–83	$C_5H_8ClN_3$	[c]	[c]	0.2
—NH_2	—$NHCOCH_3$	A	40	Benzene–alcohol	156–157	$C_7H_9N_3O$	27.80	27.81	.2
—$NHCOCH_3$	—$NHCOCH_3$	[d]	95	Alcohol	202–203	$C_9H_{11}N_3O_2$	21.75	21.63	.2
—NH_2	—$NHCOCH_2CH_2CH_3$	A	25	Benzene–alcohol	152–153	$C_9H_{13}N_3O$	23.46	23.43	.1
—NH_2	—$NHCOCH_2CH_2COOH$	B	57	75% Methanol	174–175 (dec.)	$C_9H_{11}N_3O_3$	20.10	19.88	0
—NH_2	—NH—CO— (HO)	A[e]	44	Benzene–alcohol	178–179	$C_{12}H_{11}N_3O_2$	18.34	18.86[g]	0
—NH_2	—$NHCOCH_2COCH_3$[b]	C	10	Alcohol	146–147	$C_9H_{12}ClN_3O_2$	18.30	18.31[f]	0
—NH_2	—$NHCOCHC_6H_5$[h] ($OCOCH_3$)	A	23	Alcohol	151–153	$C_{16}H_{16}ClN_3O_4$	13.06	13.23[h]	0
—NH_2	—$NHCOCH_2CN$	D	85	Alcohol	152–153	$C_8H_8N_4O$	31.82	31.92	0
—$NHCOCH_2OH$	—$NHCOCH_2OH$	E	35	50% Alcohol	220–221	$C_9H_{11}N_3O_4$	18.66	18.71	0.1
—$NHCOCH_2COCH_3$	—$NHCOCH_2COCH_3$[b]	C	40	Alcohol	195–198	$C_{13}H_{16}ClN_3O_4$	13.39	13.00[i]	.1
—$NHCOCH_3$	—$NHCOCH_2COOC_2H_5$	D	41	Abs. alcohol	150–151.5	$C_{12}H_{18}N_3O_4$	15.85	15.83	0
—$NHCOCH_2N(C_2H_5)_2$	—$NHCOCH_2N(C_2H_5)_2$	F	55	*i*-Propanol	109.5–110.5	$C_{17}H_{29}N_5O_2$	20.89	21.05	0
—$NHCOCH_2NHCOCH_3$	—$NHCOCH_2NHCOCH_3$	G	19	70% Alcohol	260–261	$C_{13}H_{17}N_5O_4$	22.80	22.75	0
—NH_2	—$NHCO(CH_2)_4CONH$ (N) NH_2	A	72	1% HCl	228–229	$C_{16}H_{20}N_6O_2$	25.61	25.92	0–0.1
—NH_2	—$NHCO(CH_2)_8CONH$ (N) NH_2	A	55	Abs. alcohol	152–155	$C_{20}H_{28}N_6O_2$	21.87	21.46	0–0.1
—NH_2	—NH—C(=NH)—CH_2[b]	H	38	Abs. alcohol	246–247 (dec.)	$C_7H_{11}ClN_4$	30.03	30.05	0
—NH_2	—$NHCOOC_2H_5$	I	76	Benzene–hexane	111–112	$C_8H_{11}N_3O_2$	23.20	23.47	0
—$NHCOOC_2H_5$	—$NHCOOC_2H_5$	J	55	Benzene–hexane	132.5–133.5[j]	$C_{11}H_{15}N_3O_4$	16.60	16.90	0
—NH_2	—$NHCONH_2$	K	75	Abs. alcohol	175–176 (dec.)	$C_6H_8N_4O$	36.85	36.79	0
—$NHCONH_2$	—$NHCONH_2$	L	49	Water	Does not melt	$C_7H_9N_5O_2$	35.90	36.01	0
—NH_2	—NHCONH— (OC_2H_5)	M	86	2% HCl	168–169	$C_{14}H_{16}N_4O_2$	20.58	20.55	0
—NH_2	—NHCONH— (OCH_3, NH_2)	M[k]	50	Alcohol	182–184	$C_{13}H_{15}N_5O_2$	25.64	25.85	0

(1) Presented in part before the Division of Medicinal Chemistry of the American Chemical Society, Atlantic City, April 8–12, 1946.

(2) Bernstein, Stearns, Dexter and Lott, THIS JOURNAL, **69** 1142 (1947).

(3) Hertog and Wibaut, *Rec. trav. chim.*, **55**, 126 (1936).

TABLE I (*Concluded*)

2-	Substituted pyridine 6-	Procedure[a]	Yield, %	Solvent for crystallization	M. p., °C.	Empirical formula	Analyses, % N Calcd.	Found	Activity[s]
—NH_2	—NHCONH(2-pyridyl)NH_2	A	71	[v]	Does not melt	$C_{11}H_{12}N_6O$	34.43	33.49	0
—NH_2	—NH(2-pyridyl)NH_2[b]	N	60	Alcohol	Does not melt	$C_{10}H_{12}ClN_5$	29.47	29.77[i]	0–0.1
—$NHCH_3$	—$NHCH_3$	O	59	Hexane	70–71	$C_7H_{11}N_3$	30.66	30.61[k]	0.1
—NH_2	—$N(C_2H_5)_2$[b]	P	81	Alcohol–ether	143–144	$C_9H_{16}ClN_3$	20.84	20.77[l]	0–0.1
—$N(C_2H_5)_2$	—$N(C_2H_5)_2$[b]	Q	76	[w]	120–122	$C_{13}H_{24}ClN_3$	16.31	16.32[m]	0–0.1
—NH_2	—$NH(CH_2)_3N(C_2H_5)_2$[n]	P	53	[v]	65–75	$C_{12}H_{24}Cl_2N_4$	[o]	[o]	0
—$NHCOCH_3$	—$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$	P	51	Hexane	106–108	$C_{16}H_{28}N_4O$	19.18	19.10	0.1
—NH_2		R	61	50% Alcohol	232–233	$C_{19}H_{15}ClN_4O$	15.98	16.04	0
—$NHCOCH_3$	—$N{=}C(CH_3)CH_2COCH_3$	D	40	Abs. alcohol	146–147.5	$C_{12}H_{15}N_3O_2$	18.02	18.22[q]	0
—$NHCOCH_3$		D	54	Hexane–benzene	147.5–148.5	$C_{13}H_{16}N_2O$	18.34	18.54[r]	0
—$NHCOCH_3$	—$NHNO_2$	S	65	Water	193 (dec.)	$C_7H_8N_4O_3$	28.57	28.57	0
—NH_2		S	44	Abs. alcohol	188–189.5	$C_9H_{10}N_4O$	29.47	29.69	0

[a] Refers to general method of preparation in experimental part. [b] Product described is monohydrochloride. [c] Tschitschibabin and Seide reported m. p. 81–83°, *C. A.*, **18**, 1496 (1924). [d] Tschitschibabin and Seide reported m. p. 203°, *C. A.*, **18**, 1496 (1924). Additional analysis: Calcd.: C, 55.95; H, 5.69. Found: C, 56.02; H, 5.62. [e] *Anal.* Calcd.: C, 62.88; H, 4.80. Found: C, 62.50; H, 4.77. [f] *Anal.* Calcd.: Cl, 15.47. Found: Cl, 15.27. [g] Product isolated as the hydrochloride monohydrate. [h] Nitrogen analysis was on the anhydrous hydrochloride which melted at 159–161°. Additional analyses: Calcd.: Cl, 11.04. Found: Cl, 10.86. Analyses on the hydrochloride monohydrate: Calcd : Cl, 10.47. Found: Cl, 10.53. Calcd.: H_2O, 5.3. Found: H_2O, 5.3. [i] *Anal.* Calcd.: Cl, 11.32. Found: Cl, 11.37. [j] *Anal.* Calcd.: C, 50.53; H, 5.05; Cl, 14.95. Found: C, 50.53; H, 5.10; Cl, 14.76. [k] *Anal.* Calcd.: C, 61.31; H, 8.03. Found: C, 61.23; H, 8.10. [l] *Anal.* Calcd.: Cl, 17.62. Found: Cl, 17.20. [m] *Anal.* Calcd.: Cl, 13.79. Found: Cl, 13.67. [n] Isolated as the dihydrochloride. [o] *Anal.* Calcd.: Cl, 24.07. Found: Cl, 23.70. Free base boiled at 169–173° at 5–6 mm. [p] *Anal.* Calcd.: Cl, 10.13. Found: Cl, 10.20. [q] *Anal.* Calcd.: C, 61.80; H, 6.44. Found: C, 61.91; H, 6.65. [r] *Anal.* Calcd.: C, 68.12; H, 6.55. Found: C, 68.12; H, 6.42. [s] Prepared from acetylsalicylyl chloride. Product purified by dissolving in dilute hydrochloric acid and precipitating with dilute alkali, which also caused hydrolysis of the acetyl group. [t] Meyer and Mally reported a m. p. of 127° for the product obtained by the Curtius degradation of the diazide of 2,6-dipicolinic acid, *Monatsh.*, **33**, 407 (1912). [u] Prepared as in example M from 2-nitro-4-methoxyphenylisocyanate. The nitro compound, m. p. 208–210°, after crystallization from acetic acid, was obtained in 73% yield. *Anal.* Calcd. for $C_{13}H_{14}N_6O_4$: N, 23.02. Found: N, 23.28. The nitro compound was then reduced using Adams catalyst. [v] Unable to crystallize. Purified by dissolving in dilute hydrochloric acid and precipitating with dilute sodium hydroxide. [w] Hydrochloride was purified by sublimation. [x] Not crystallized. [s] Activity of quinine on similar scale is 1.0.

Ring substituted derivatives of 2,6-diaminopyridine were obtained in several cases by direct substitution since the β-hydrogen in 2,6-diaminopyridine is quite active. The ring alkylated derivatives were obtained by the amination of the corresponding picoline or by the reaction of a

TABLE II

RING SUBSTITUTED DERIVATIVES OF 2,6-DIAMINOPYRIDINE

Substituents 2,6-di	Other	Procedure[a]	Yield, %	Solvent for crystallization	M. p., °C.	Empirical formula	Analyses, % N Calcd.	Found	Activity[b]
—NH_2	-3-CH_3	T	4	Acetone	149–150	$C_6H_9N_3$	34.15	33.68	0
—NH_2	-4-CH_3	U[c]	71	[d]	110–111[e]	$C_6H_9N_3$	34.15	34.54	0
—$NHCOCH_3$	-3-I	W	33	Alcohol	210–211	$C_9H_{10}IN_3O_2$	13.16	13.12	0
—NH_2	-3-I, -5-I	X	62	Pyridine–water	209–210	$C_5H_5I_2N_3$	11.64	11.85	0
—$NHCOCH_3$	-3-OCH_3	Y	60	Benzene–alcohol	173.5–174.5	$C_{10}H_{13}N_3O_3$	18.63	18.98[f]	0.1

[a] Refers to general preparation described in experimental part. [b] Activity of quinine on similar scale is 1.0. [c] Also prepared by method T. [d] Purified by sublimation. [e] Melting point reverted to 87–88° after standing. [f] *Anal.* Calcd. C, 53.81; H, 5.83. Found: C, 53.70; H, 5.95.

2,6-dihalogenated picoline with ammonia. The 3-methoxy derivative was prepared by the nitration of 3-methoxypyridine to 2,6-dinitro-3-methoxypyridine, followed by reduction of the dinitro body in a mixture of acetic acid and acetic anhydride. Attempts to reduce the dinitro body in alcohol or in alcoholic hydrogen chloride yielded highly colored compounds which could not be purified. Although Koenigs[4] had reported that the nitration of 3-methoxypyridine yielded a dinitro derivative melting at 69°, it was observed that under mild conditions, 3-methoxypyridine yielded a mononitro derivative, 3-methoxy-2-nitropyridine, m. p. 73-74°, while under more vigorous conditions, a dinitro derivative, m. p. 114–115°, was obtained. Various ring-substituted derivatives are listed in Table II.

Several types of fused ring systems were also prepared. From 2,3,6-triaminopyridine, pyridopyrazines were obtained by reaction with glyoxal, diacetyl and ethyl oxalate. Naphthyridines were prepared by the reaction of ethyl acetoacetate[5] or acetylacetone with 2,6-diaminopyridine. Pyridothiazoles were obtained by the reaction of 2,6-diaminopyridine with bromine and potassium thiocyanate in acetic acid solution similar to the procedure used by Kaufmann.[6] These fused ring derivatives are listed in Table III.

The antiparasitic activity of the compounds as suppressive agents for *Plasmodium lophurae* in ducklings was determined. These determinations were carried out in the Division of Pharmacology of this Institute.[7] The most active of the compounds prepared, 2-amino-6-acetylamidopyridine, 2,6-diacetylamidopyridine, and 2,5-diaminopyrido[2,3-*d*]-thiazole were only one-third as active as quinine as antiparasitic agents for *Plasmodium lophurae* in ducklings.

The authors wish to thank the Dow Chemical Company for their generous gift of 2,6-dibromopyridine used in various phases of this work. They are indebted to Mr. J. F. Alicino of this Institute for the microanalyses reported.

Experimental[8]

A. 2-Amino-6-acetylamidopyridine.—A solution of 23.5 g. (0.3 mole) of acetyl chloride in 50 cc. of dioxane was added dropwise with vigorous stirring to a solution of 66 g. (0.6 mole) of 2,6-diaminopyridine in 300 cc. of dioxane. The temperature was maintained at 25–30°. The addition required one-half hour and the stirring was continued for two hours more. The precipitate of 2,6-diaminopyridine hydrochloride was filtered off, and the dioxane concentrated under reduced pressure. The oily residue crystallized upon cooling to give 45 g. of crude material. This was recrystallized from 600 cc. of benzene and 100 cc. of absolute alcohol to yield 18 g. (40%) of crude product, m. p. 150–152°. Recrystallization raised the melting point to 156–157°.

B. 2-Amino-6-succinylamidopyridine.—A solution of 30 g. (0.3 mole) of succinic anhydride in 200 cc. of warm dioxane was added slowly to a solution of 33 g. (0.3 mole) of 2,6-diaminopyridine in 200 cc. of warm dioxane. The small amount of precipitate of unknown composition which formed immediately was filtered off and the filtrate heated on a steam-bath for three hours. The cooled reaction mixture was filtered to give 36 g. (57%) of crude product, m. p. 170–173° (dec.). Recrystallization from 600 cc. of 75% methyl alcohol raised the melting point to 174–175° (dec.).

C. 2-Acetoacetylamido-6-aminopyridine and 2,6-Diacetoacetylamidopyridine. (a) **Preparation of 2,6-Diacetoacetylamidopyridine Hydrochloride.**—A mixture of 46 g. (0.42 mole) of 2,6-diaminopyridine and 222 cc. of ethyl acetoacetate was heated to 160° and maintained at this temperature for fifteen minutes. The cooled reaction mixture was filtered and 100 cc. of the ethyl acetoacetate removed under reduced pressure. The residue was dissolved in alcohol and an equivalent amount of alcoholic hydrogen chloride added. Upon cooling 52.5 g. (40%) of crude product crystallized. Crystallization from alcohol gave a pure product, m. p. 195–198°.

(b) **Preparation of 2-Acetoacetylamido-6-aminopyridine Hydrochloride.**—The filtrate from the precipitation of the hydrochloride of the disubstituted product was concentrated and upon cooling two additional crops of material were obtained. The first crop, m. p. 152–155°, consisted of a mixture of mono and di-substituted products; the second crop, 9.0 g. (10%), was mainly 2-acetoacetylamido-6-aminopyridine, m. p. 140–143°. Crystallization from alcohol raised the melting point to 146–147°.

D. 2-Amino-6-cyanoacetylamidopyridine.—A mixture of 22 g. (0.2 mole) of 2,6-diaminopyridine and 22.6 g. (0.2 mole) of ethyl cyanoacetate was heated in an oil-bath at 165°. When the internal temperature reached 142°, ethyl alcohol began to distil off. The reaction mixture was heated for two hours and when cool was added to 50 cc. of absolute alcohol. The solid which formed was filtered off and weighed 30 g. (85%). The product, after recrystallization from benzene-alcohol and from 95% alcohol, melted at 152–153°.

E. 2,6-Diglycolylamidopyridine.—A mixture of 282 g. (2.57 moles) of 2,6-diaminopyridine and 390 g. (5.14 moles) of glycolic acid was fused at 120° under reduced pressure for fifteen hours at which time the melt had solidified. One liter of water was added and the insoluble material filtered off. The crude material was crystallized from 50% alcohol to yield 207 g. (35%) of product melting at 214–215°. Recrystallization raised the melting point to 220–221°. (The melting point varied with the rate of heating.)

F. 2,6-Di-diethylaminoacetylamido)-pyridine.—(Attempt to prepare monosubstituted derivative.) A solution of 6.9 g. (0.3 mole) of sodium in 200 cc. of absolute alcohol was heated to reflux, 33 g. (0.3 mole) of 2,6-diaminopyridine added, and then 43 g. (0.27 mole) of ethyl diethylaminoacetate[9] added. The reaction mixture was refluxed for two hours and then 100 cc. of alcohol distilled off. Upon pouring the solution into one liter of water an oil which slowly solidified, precipitated. The solid was purified by dissolving it in dilute hydrochloric acid, filtering, and neutralizing the solution. The product, which weighed 25 g., melted at 105–108° (55% based on ethyl diethylaminoacetate). Crystallization from isopropanol raised the melting point to 109.5–110.5°.

G. 2,6-Diacetylamidoacetylamidopyridine.—(Attempt to prepare monosubstituted derivative.) A mixture of 22

(4) Koenigs, Gerdes and Sirot, *Ber.*, **61**, 1022 (1928).

(5) As shown by Tschitschibabin, *Ber.*, **57**, 1168 (1924), and Seide, *ibid.*, **58**, 352 (1925), ring closure of derivatives of 2-aminopyridine occurs on the ring nitrogen through the imino form of the substituted amine. However, Seide, *Ber.*, **59**, 2465 (1926), has indicated that ring closure of derivatives of 2,6-diaminopyridine occurs on the β-carbon, due to the marked reactivity of the β-hydrogen.

(6) Kaufmann, *Arch. Pharm.*, **266**, 215 (1928). By analogy to the experiments of Kaufmann the compounds obtained by this type reaction have been assumed to have the fused ring structure. No absolute proof is offered to substantiate this.

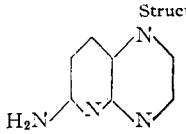
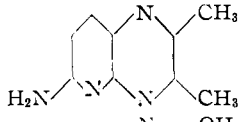
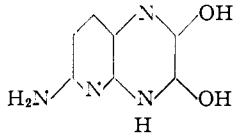
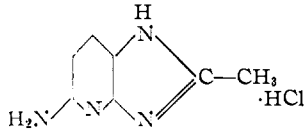
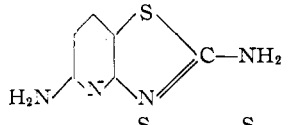
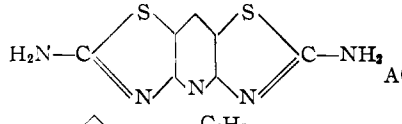
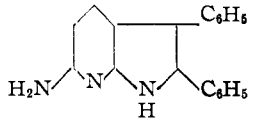
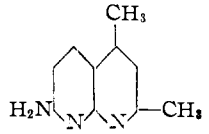
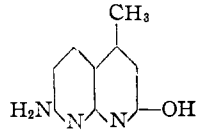
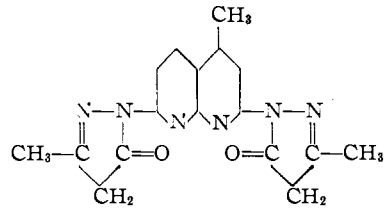
(7) The pharmacological results will be described in the forthcoming monograph by the Survey of Antimalarial Drugs.

(8) All melting points are uncorrected.

(9) Willstätter, *Ber.*, **35**, 600 (1902).

TABLE III

FUSED RING DERIVATIVES OF 2,6-DIAMINOPYRIDINE

Structure	Procedure[a]	Yield, %	Solvent for crystallization	M. p., °C.	Empirical formula	Analyses, % N Calcd.	Found	Activity[b]
	V	62	Water	267	$C_7H_6N_4$	38.36	38.13	0
	V	98	Water	227–228	$C_9H_{10}N_4$	32.18	32.53	0
	Z	68		Does not melt	$C_7H_6N_4O_2$	31.46	31.43	0
	AA	26	[f]	Does not melt	$C_7H_9ClN_4$	30.35	30.45[c]	0
	AB	24	Water	138–139	$C_8H_6N_4S \cdot {}^1/_2H_2O$	32.00	32.22	0.2
	AC	22	[g]	Does not melt	$C_7H_5N_5S_2$	31.39	31.33	0.2
	AD	89	Acetic acid	234.5–235.5	$C_{19}H_{15}N_3$	14.74	14.78	0
	AE	84	Water	216–218	$C_{10}H_{11}N_3$	24.28	24.56	0
	[d]	35	Acetic acid	Does not melt	$C_9H_9N_3O$	24.00	24.10	0
	AF	84	Benzene	260–262 (dec.)	$C_{17}H_{16}N_6O_2$	25.00	25.19	0

[a] Refers to general preparation described in experimental part. [b] Activity of quinine on similar scale is 1.0. [c] *Anal.* Calcd. Cl. 19.24. Found: Cl, 19.20. [d] Seide, *Ber.*, **59**, 2465 (1926). [e] Purified by dissolving in dilute sodium hydroxide and neutralizing with dilute acid. [f] Purified by dissolving in 20% hydrochloric acid and alcohol and adding ether to precipitate the solid. [g] Purified by dissolving in 20% hydrochloric acid and precipitating with aqueous ammonia.

g. (0.2 mole) of 2,6-diaminopyridine and 27 g. (0.2 mole) of acetylamidoacetyl chloride[10] was ground in a mortar and 35 cc. of pyridine added to the finely ground mixture. The reaction mixture became warm and a homogeneous solution was obtained. The product was isolated by dissolving the mixture in tertiary butanol and adding anhydrous ether. The crude hydrochloride was then dissolved in water and normal sodium hydroxide solution added. The precipitate was filtered off and washed with water. The product weighed 6 g. (19% based on acetylamidoacetyl chloride) and melted at 260–261°. Recrystallization from 70% alcohol did not change the melting point.

H. N-[2-(6-Aminopyridyl)]-acetamidine Hydrochloride.—A suspension of 24.6 g. (0.2 mole) of acetimino

(10) Max, *Ann.*, **369**, 286 (1909).

ethyl ether hydrochloride in 100 cc. of absolute alcohol was added with vigorous stirring to a solution of 22 g. (0.2 mole) of 2,6-diaminopyridine in 150 cc. of absolute alcohol. Most of the imino ether went into solution, but after about fifteen minutes a heavy precipitate was obtained. The reaction mixture was stirred for three hours and then allowed to stand overnight at room temperature. The solid was filtered off and crystallized from absolute alcohol to give 14 g. of product (38%) melting at 246–247° (dec.).

I. **2-Amino-6-carbethoxyamidopyridine.**—A solution of 396 g. (3.6 moles) of 2,6-diaminopyridine in eight liters of water was cooled to 5° and 195 g. (1.8 moles) of ethyl chlorocarbonate added dropwise with vigorous stirring over the course of three hours. The temperature was maintained at 5° during the addition. The precipitated solid was filtered and weighed 247 g. (76%). Crystallization of the crude product, m. p. 103–108°, from benzene–hexane raised the melting point to 109–112°.

J. **2,6-Dicarbethoxyamidopyridine.**—(Attempt to prepare monosubstituted derivative.) A vigorously stirred solution of 33 g. (0.3 mole) of 2,6-diaminopyridine in 500 cc. of water was cooled in an ice-bath; 200 cc. of normal hydrochloric acid and 300 g. of cracked ice were added; and then 33 g. (0.3 mole) of ethyl chlorocarbonate added dropwise. The reaction mixture was stirred for two hours and then 200 cc. of normal sodium hydroxide solution added. After standing at 10° overnight, the reaction mixture was filtered to give 21 g. of 2,6-dicarbethoxyamidopyridine (55% based on ethyl chlorocarbonate), which melted at 132.5–133.5° after recrystallization from benzene–hexane mixture. A small amount (12 g.) of 2-amino-6-carbethoxyamidopyridine could be isolated by neutralizing the filtrate.

K. **2-Amino-6-ureidopyridine.**—A solution of 21.6 g. (0.12 mole) of 2-amino-6-carbethoxyamidopyridine in 120 cc. of 3 *N* alcoholic ammonia was heated in a bomb tube at 110° for twelve hours. Upon cooling, the reaction mixture deposited 10.5 g. of product. Concentration of the mother liquor to 40 cc. gave an additional 3.0 g. for a total of 13.5 g. (75%). The product, after recrystallization from absolute alcohol, melted at 175–176° (dec.).

L. **2,6-Diureidopyridine.**—A mixture of 48 g. (0.44 mole) of 2,6-diaminopyridine and 44 g. (0.73 mole) of urea was fused at 130° for thirty-six hours. The cooled melt was triturated with 150 cc. of water, and the crude product, which weighed 35 g. (49%), was filtered off. The 2,6-diureidopyridine, which did not melt below 300°, was purified by extraction with 300 cc. of 3% hydrochloric acid and crystallization of the insoluble residue from water.

M. **2-(*p*-Ethoxyphenylureido)-6-aminopyridine.**—A solution of 17.9 g. (0.1 mole) of *p*-ethoxyphenylisocyanate in 75 cc. of benzene was added dropwise with vigorous stirring to a solution of 12 g. (0.11 mole) of 2,6-diaminopyridine in 1500 cc. of benzene. The reaction mixture was stirred for thirty minutes (a white precipitate formed) and then allowed to stand overnight. The benzene was removed under reduced pressure to leave a residue weighing 25 g. (86%). The product was purified by dissolving it in hot 2% hydrochloric acid, filtering and neutralizing the hot solution. Upon cooling the product crystallized out, m. p. 168–169°.

N. **Di-(6-amino-2-pyridyl)-amine Hydrochloride.**—A mixture of 154 g. (1.4 moles) of 2,6-diaminopyridine and 200 g. (1.37 moles) of 2,6-diaminopyridine hydrochloride was fused at 190° for twelve hours. The cooled melt was triturated with water and the insoluble material filtered off. The product, which weighed 207 g. (60%) was purified by crystallization from alcohol. The free base was obtained by adding one equivalent of dilute sodium hydroxide to a hot aqueous solution of the hydrochloride. Upon cooling the solution, the free base crystallized out. After recrystallization from 50% alcohol the di-(6-amino-2-pyridyl)-amine melted at 172–173°.

Anal. Calcd. for $C_{10}H_{11}N_5$: N, 34.82. Found: N, 35.04.

O. **2,6-Di-(methylamino)-pyridine.** (a) **Reaction of 2,6-Dibromopyridine with Methylamine.**—A mixture of 38 g. (0.16 mole) of 2,6-dibromopyridine and 160 cc. of a 25% aqueous solution of methylamine was heated at 190° for eight hours in a bomb tube. The cooled reaction mixture was diluted with 400 cc. of water, filtered, made strongly alkaline with 40% potassium hydroxide solution and extracted with four 300-cc. portions of ether. The ether extract was dried over anhydrous potassium carbonate and then concentrated on a steam-bath to remove the ether. The residue distilled at 116° at 2 mm. and weighed 13 g. (59%). Upon cooling the distillate solidified and, after recrystallization from hexane, melted at 70–71°.

(b) **Reaction of 2-Amino-6-bromopyridine with Methylamine.**—A mixture of 27.6 g. (0.16 mole) of 2-amino-6-bromopyridine and 110 cc. of 25% aqueous solution of methylamine was heated at 190° for thirty hours in a bomb tube. The reaction mixture was worked up as above to give 4.5 g. (20%) of 2,6-di-(methylamino)-pyridine melting at 70–71°. Mixed melting point with sample prepared by method (a) was 70–71°.

P. **2-Amino-6-diethylaminopyridine.** (a) **Using 2-Amino-6-bromopyridine.**—A mixture of 80 g. (0.462 mole) of 2-amino-6-bromopyridine and 200 cc. of diethylamine was heated in a bomb tube at 170–180° for thirty-six hours. The cooled tube was opened and the contents poured into 300 cc. of 40% potassium carbonate solution and 200 cc. of water. The oil which separated was extracted with five 300-cc. portions of ether and the ether solution dried over anhydrous potassium carbonate. After removal of the ether and excess diethylamine at atmospheric pressure, the residue was distilled under reduced pressure and boiled at 122–123° at 4.5 mm. The oil solidified upon cooling and melted at 34–35°; wt. 62 g. (81%). The base was converted to the hydrochloride by treating an alcohol solution of the amine with hydrogen chloride and precipitating the hydrochloride by the addition of anhydrous ether. The hydrochloride was purified by dissolving in absolute alcohol and reprecipitating with ether, m. p. 143–144°.

(b) **Using 2-Bromo-6-diethylaminopyridine. Preparation of 2-Bromo-6-diethylaminopyridine.**—A mixture of 45 g. (0.19 mole) of 2,6-dibromopyridine, 27.8 g. (0.38 mole) of diethylamine and 100 cc. of absolute alcohol was heated in a bomb tube at 170–180° for eight hours. A titration with standard silver nitrate solution at the end of this time indicated that 96% of the theoretical ionic bromine had been formed. The alcohol was removed under reduced pressure and the semi-solid residue suspended in 50 cc. of water, causing two layers to form. The aqueous layer was extracted with three 200-cc. portions of ether; the ether extracts combined with the organic layer, and then dried over anhydrous potassium carbonate. The residue, after removal of the ether, was distilled under reduced pressure and boiled at 97–99° at 4 mm., wt. 37 g. (85%).

Preparation of 2-Amino-6-diethylaminopyridine.—A mixture of 24 g. of 2-bromo-6-diethylaminopyridine and 100 cc. of aqueous ammonia (d. 0.9) was heated in a bomb tube at 190° for fifteen hours. A titration with standard silver nitrate solution at the end of this time indicated that only 6% of the theoretical ionic bromine had been formed so the experiment was discontinued.

A solution of 11 g. (0.05 mole) of 2-bromo-6-diethylaminopyridine in 35 cc. of 5 *N* alcoholic ammonia was heated in a bomb tube for twenty-five hours at 170°. A qualitative test for ionic halide was negative so the experiment was discontinued.

A suspension of 18.8 g. (0.082 mole) of 2-bromo-6-diethylaminopyridine in 100 cc. of aqueous ammonia (d. 0.9), containing 1.0 g. of copper sulfate ($CuSO_4 \cdot 5H_2O$) was heated in a bomb tube at 140–145° for thirty-six hours. A titration with standard silver nitrate solution at the end of this time indicated 82% of the theoretical ionic bromine had been formed. The contents of the tube were poured into 200 cc. of 40% potassium hydroxide and the aqueous layer extracted with four 300-cc. portions of ether which was then dried over anhydrous potassium carbonate. The residue, after the removal of the ether, was distilled under reduced pressure, boiling at 122–

124° at 4.5 mm.; wt. 6.0 g. (44%). The product is identical with that obtained by the reverse substitution.

Q. 2,6-Di-diethylaminopyridine Hydrochloride.—A mixture of 35.6 g. (0.15 mole) of 2,6-dibromopyridine and 100 cc. of diethylamine, containing 4 cc. of a 25% aqueous $CuSO_4 \cdot 5H_2O$ solution was heated in a bomb tube at 160° for thirty hours. The reaction mixture was worked up as in example "O" to give 25 g. (76%) of product boiling at 120–122° at 3 mm. The hydrochloride was prepared by adding ethereal hydrogen chloride to an ether solution of the amine, and filtering off the crystals formed. It was purified by sublimation.

R. 2-Methoxy-6-chloro-9-[2'-(6'-aminopyridyl)]-aminoacridine.—A solution of 11.2 g. (0.04 mole) of 2-methoxy-6,9-dichloroacridine in 50 g. of phenol was warmed on a steam-bath and 11 g. (0.10 mole) of 2,6-diaminopyridine added to the deep red solution. The reaction mixture was heated for three hours and then poured into 400 cc. of 10% sodium hydroxide solution. The precipitate was filtered off and crystallized from 50% alcohol to give 8.5 g. (61%) of a yellow product, m. p. 232–233°.

S. 1-[2'-(6'-Aminopyridyl)]-3-methylpyrazolone-5. (a) **Preparation of 2-Nitramino-6-acetamidopyridine.**—To 100 cc. of vigorously stirred fuming nitric acid (d. 1.5), cooled to −5°, there was added in small portions 30.2 g. (0.2 mole) of 2-amino-6-acetamidopyridine. The temperature of the reaction mixture was maintained at −5 to −2° during the addition, which required twenty minutes; and for thirty minutes after the addition was complete. The solution was then poured into 120 cc. of ice and water. The precipitate was filtered off, washed with water and purified by solution in dilute aqueous ammonia followed by acidification with acetic acid. The product, which weighed 25 g. (65%), decomposed violently at 193°. Crystallization from water did not change the decomposition temperature.

(b) **Preparation of 2-Nitramino-6-amino-pyridine.**—A solution of 127.4 g. (0.65 mole) of 2-nitramino-6-acetamidopyridine in 1800 cc. of normal sodium hydroxide solution was refluxed for one hour, treated with decolorizing carbon and filtered. The cooled filtrate was acidified with acetic acid and the precipitate filtered and washed several times with water, until washings were neutral. The dried product weighed 98 g. (98%). The 2-nitramino-6-aminopyridine, which did not melt but darkened at 240–250°, was crystallized from water for analysis.

Anal. Calcd. for $C_5H_6N_4O_2$: N, 36.36. Found: N, 36.41.

(c) **Preparation of 2-Hydrazino-6-aminopyridine.**—A solution of 15.4 g. (0.1 mole) of 2-nitramino-6-aminopyridine in 300 cc. of 10% sodium hydroxide solution was cooled to 0° in a 1-liter, three-necked flask fitted with a mercury-sealed stirrer and gas inlet tube. To this solution at 0 to 2° there was added with vigorous stirring 31 g. of zinc dust in small portions. (The first portion of zinc dust was activated by suspending it in aqueous copper sulfate solution.) During the addition of the zinc dust a strong stream of nitrogen was passed through the reaction vessel. After all the zinc dust had been added, the reaction mixture was stirred for an additional two hours, during which time nitrogen was continuously bubbled through the solution. The mixture was then filtered under nitrogen and the pale yellow filtrate saturated with hydrated potassium carbonate. A white solid precipitated out. The solid and solution were extracted with 2 × 2 liters of ether which dissolved the precipitated solid and the ether extract was dried over anhydrous potassium carbonate. Upon concentration of the ether at room temperature under reduced pressure a pale yellow solid crystallized out, which weighed 9.0 g. (69%). The 2-hydrazino-6-aminopyridine melted at 93–94° after recrystallization from absolute alcohol–hexane solution.

Anal. Calcd. for $C_5H_8N_4$: N, 45.16. Found: N, 45.46.

(d) **Preparation of 1-[2'-(6'-Aminopyridyl)]-3-methylpyrazolone-5.**—A mixture of 8.3 g. (0.067 mole) of 2-hydrazino-6-aminopyridine and 8.7 g. (0.67 mole) of ethyl acetoacetate was warmed on a steam-bath under nitrogen for two hours. After the first 30 minutes, a solid started to form in the clear melt and soon the whole reaction mixture had solidified. The solid, after crystallization from absolute alcohol, weighed 5.6 g. (44%) and melted at 188–189.5°.

T. 2,6-Diamino-3-methylpyridine.—A mixture of 80 g. (0.86 mole) of 3-methylpyridine, 160 g. of dimethylaniline and 144 g. of sodamide was heated for ten hours at 130–150° followed by about six hours at 170–200°. The mixture was then cooled, the dimethylaniline decanted off and the residual solid decomposed with water. The mixture of solid and alkaline solution thus obtained was extracted with isopropanol, the isopropanol solution dried and concentrated under reduced pressure until all solvent was removed. The residual solid was extracted with chloroform; the extract filtered and concentrated to small volume. On cooling the 2,6-diamino-3-methylpyridine crystallized out. The yield of product recrystallized from acetone was 4.4 g. (4%), m. p. 149–150°.

U. 2,6-Diamino-4-methylpyridine. Preparation of 2,6-Dibromo-4-methylpyridine.—A mixture of 9 g. (0.072 mole) of 2,6-dihydroxy-4-methylpyridine[11] and 30 g. of phosphorus tribromide was heated four and one-half hours at 180° in a bomb tube. The reaction mixture was treated cautiously with ice water and then subjected to steam distillation. The 2,6-dibromo-4-methylpyridine crystallized out in the distillate; wt. 6.5 g. (36%), m. p. 74–75°.

Anal. Calcd. for $C_6H_5Br_2N$: N, 5.58. Found: N, 5.58.

A mixture of 12 g. (0.048 mole) of 2,6-dibromo-4-methylpyridine and 30 cc. of concentrated ammonia (d. 0.9) was heated in a bomb tube at 195° for twenty-seven hours. The contents of the tube were filtered, made strongly alkaline and extracted with chloroform. Evaporation of the chloroform left a crystalline residue of the crude base, 4.2 g. (71%), m. p. 87–88°. Sublimation of a sample produced crystals, m. p. 109–111°, which reverted to the lower melting point on standing.

V. 2,3-Dimethyl-6-aminopyrido[2,3]pyrazine.—A solution of 25 g. (0.3 mole) of diacetyl in 200 cc. of water was added to a solution of 50 g. (0.254 mole) of 2,3,6-triaminopyridine dihydrochloride[12] in 200 cc. of water and the reaction mixture boiled four minutes. An additional 500 cc. of water was then added, the reaction mixture boiled with decolorizing carbon for three minutes more and then filtered. The warm filtrate was made slightly alkaline and allowed to cool. The precipitate was filtered off and recrystallized twice from water. The product melted at 227–228° and weighed 43.5 g. (98%).

W. 2,6-Diacetylamido-3-iodopyridine.—To a solution of 23.5 g. (0.1 mole) of 2,6-diamino-3-iodopyridine[13] in 25 cc. of acetic acid there was added 35 cc. of acetic anhydride. The reaction mixture was heated on a steam-bath for one hour and the solution, after cooling, poured into a mixture of ice and water. Since no precipitate was formed, the solution was made strongly alkaline with 40% potassium hydroxide solution. The solid which was filtered off weighed 10.5 g. (33%). After crystallization from alcohol the product melted at 210–211°.

X. 2,6-Diamino-3,5-diiodopyridine.—A solution of 93 g. (0.36 mole) of iodine and 93 g. of potassium iodide in 150 cc. of water was slowly added to a vigorously stirred solution of 38 g. (0.35 mole) of 2,6-diaminopyridine in 550 cc. of water. The reaction mixture was stirred for eight hours and then allowed to stand at room temperature overnight. The supernatant liquid was decanted from the precipitated solid, which was then suspended in 5% potassium hydroxide solution, stirred for two hours and filtered. The crude product weighed 40 g. (36%). For purification the product was dissolved in warm dilute hydrochloric acid from which the hydrochloride of the product precipitated out upon cooling, m. p. 160–165°.

(11) Kon and Nanji, *J. Chem. Soc.*, 566 (1931).

(12) United States Patent 2,136,044.

(13) British Patent 341,598. Best results obtained using 4 moles of 2,6-diaminopyridine to 1 mole of iodine.

Anal. Calcd. for $C_5H_6ClI_2N_3$: N, 10.56. Found: N, 10.32.

The free base was prepared by dissolving the hydrochloride in pyridine and adding water to the solution. In this manner 14 g. (20%) of product, m. p. 209–210°, was obtained.

Y. 3-Methoxy-2,6-diacetylamidopyridine. Preparation of 3-Methoxy-2,6-dinitropyridine. (a) By Dinitration of 3-Methoxypyridine.—To a vigorously stirred solution of 15.8 g. of crude 3-methoxypyridine[14] in 100 cc. of concentrated sulfuric acid there was added dropwise, with cooling, 25 cc. of fuming (d. 1.6) nitric acid. After all the acid had been added, the reaction mixture was warmed on a steam-bath for six hours. The cooled reaction mixture was then poured onto crushed ice and water. The precipitated solid was filtered, washed with water, sodium bicarbonate solution and finally with water. The product, which weighed 12.2 g., melted at 110–114°. Crystallization from alcohol raised the melting point to 114–115°.

Anal. Calcd. for $C_6H_5N_3O_5$: N, 21.11. Found: N, 21.35.

(b) **By Stepwise Nitration of 3-Methoxypyridine. Preparation of 2-Nitro-3-methoxypyridine.**—To 130 cc. of concentrated sulfuric acid, cooled to 5°, there was added slowly 57 g. of crude 3-methoxypyridine. To the vigorously stirred solution there was added 70 cc. of fuming (d. 1.6) nitric acid. The reaction mixture was allowed to warm up slowly and gradually brought up to steam-bath temperature. After the solution had been warmed for one hour on the steam-bath, the reaction mixture was cooled and poured into ice and water. The solid which was filtered off weighed 38 g. and melted at 73–75° after crystallization from alcohol.

Anal. Calcd. for $C_6H_6N_2O_3$: N, 18.18. Found: N, 18.50.

Nitration of 2-Nitro-3-methoxypyridine.—To a vigorously stirred solution of 5 g. of 2-nitro-3-methoxypyridine in 15 cc. of concentrated sulfuric acid, there was added dropwise, with cooling, 4 cc. of fuming (d. 1.6) nitric acid. The reaction mixture was then treated as in the dinitration to give 4.4 g. of product, m. p. 111–114°.

Reduction of 2,6-Dinitro-3-methoxypyridine.—The reduction of 2,6-dinitro-3-methoxypyridine was carried out by dissolving 16.8 g. (0.084 mole) of the nitro body in 500 cc. of glacial acetic acid and 250 cc. of acetic anhydride, adding 0.2 g. of Adams catalyst and treating with hydrogen at atmospheric pressure. The absorption of hydrogen was complete after four hours. The reaction mixture was allowed to stand at room temperature for forty-eight hours, and the solvent then removed under reduced pressure. The residue was poured into 100 cc. of ice-water and 100 cc. of saturated potassium carbonate solution. The precipitate was filtered off and washed with a small amount of water to give 12 g. (60%) of crude product. This was crystallized first from water and then from benzene-chloroform solution, m. p. 173.5–174.5°.

Z. 2,3-Dihydroxy-6-aminopyrido[2,3]pyrazine. A suspension of 80 g. (0.37 mole) of 2,3,6-triaminopyridine oxalate in 150 cc. of ethyl oxalate was heated at 185° for ninety minutes with occasional stirring. The precipitated solid was filtered off, washed with alcohol and purified by dissolving the product in dilute sodium hydroxide and precipitating it with dilute hydrochloric acid. The solid which weighed 44.5 g. (68%) did not melt below 300°.

AA. 2-Methyl-5-amino-1-imidazo[*b*]pyridine.—To a solution of 100 g. of stannous chloride dihydrate in 150 cc. of concentrated hydrochloric acid there was added, in small portions, 23.8 g. (0.1 mole) of 2,6-diacetylamido-3-nitropyridine. The precipitated stannic chloride complex was filtered off, suspended in water and the tin precipitated with hydrogen sulfide. Concentration of the filtrate after removal of the tin sulfide, yielded 9.0 g. of solid which did not melt. The product was dissolved in 20% hydrochloric acid, alcohol added and the hydrochloride, 4.7 g. (26%) precipitated by the addition of ether.

AB. 2,5-Diaminopyrido[2,3-*d*]thiazole.—To a solution of 55 g. (0.5 mole) of 2,6-diaminopyridine and 194 g. of potassium thiocyanate in one liter of 95% acetic acid there was added dropwise with stirring 26 cc. of bromine, keeping the temperature at −5 to −10°. After complete addition of the bromine the solution was filtered, diluted with three volumes of water and neutralized with solid sodium carbonate, and the precipitated solid filtered. After recrystallization from water the compound which weighed 20 g. (24%) melted at 138–139°.

Preparation of 2-Amino-5-acetylamidopyrido[2,3-*d*]-thiazole.—By a similar procedure 2-acetylamido-6-aminopyridine was converted to 2-amino-5-acetylamidopyrido-[2,3-*d*]thiazole. The product, after recrystallization from alcohol, melted at 184–185° with immediate resolidification at 185°.

Anal. Calcd. for $C_8H_8N_4OS$: N, 26.92; S, 15.38. Found: N, 26.85; S, 14.91.

AC. 2,6-Diaminopyrido[2,3-*d*:6,5-*d*^{1}]bis-thiazole.—To a solution of 66 g. (0.6 mole) of 2,6-diaminopyridine in two liters of glacial acetic acid there was added 460 g. of potassium thiocyanate in 100 cc. of water. To this solution at 0 to 3° was added dropwise with stirring 64 cc. of bromine. After complete addition of the bromine, the reaction was stirred for one hour at room temperature and then filtered. The filtrate was diluted with eight liters of water and then neutralized with solid sodium carbonate. The precipitate which formed was filtered, dissolved in 20% hydrochloric acid, treated with activated charcoal, filtered, and the filtrate neutralized with ammonium hydroxide. The precipitate which formed was filtered and washed with water. The compound weighed 30 g. (22%) and did not melt below 300°.

AD. 2,3-Diphenyl-6-amino-1-pyrrolo[2,3-*b*]pyridine.—A mixture of 25 g. (0.23 mole) of 2,6-diaminopyridine, 29 g. (0.2 mole) of 2,6-diaminopyridine hydrochloride and 42 g. (0.2 mole) of benzoin was heated in an oil-bath at 185° for one hour. Water distilled off during the first ten minutes. The melt was ground with 300 cc. of warm 10% hydrochloric acid to remove the soluble bases as hydrochlorides. The insoluble residue was suspended in water containing a slight excess of ammonia, filtered and washed with water. The crude product weighed 51 g. (89%). After recrystallization from glacial acetic acid the product melted at 234.5–235.5°.

AE. 2,4-Dimethyl-7-amino-1,8-naphthyridine. (a) By Ring Closure of 2-Amino-6-(γ-keto-α-methylbutylideneamino)-pyridine.—A suspension of 16 g. (0.084 mole) of 2-amino-6-(γ-keto-α-methylbutylideneamino)-pyridine in 100 cc. of 85% phosphoric acid was warmed for one hour on a steam-bath. The solid slowly dissolved to give a red-colored solution. The cooled reaction mixture was poured into water and the solution made alkaline with 10% sodium hydroxide solution. The precipitated solid, which weighed 12 g. (84%), melted at 216–218° after recrystallization from water.

(b) **By Reaction of 2,6-Diaminopyridine with Acetylacetone in Phosphoric Acid.**—To a suspension of 5 g. (0.045 mole) of 2,6-diaminopyridine in 25 cc. of 85% phosphoric acid there was added 5 cc. of acetylacetone. The mixture was warmed for thirty minutes on a steam-bath and the reaction mixture worked up as in (a) to give 6.5 g. (85%) of product, m. p. 216–218°.

AF. 2,7-Di-(3-methyl-5-keto-1-pyrazolyl)-4-methyl-1,8-naphthyridine.—A solution of 23 g. (0.0735 mole) of 2,7-dihydrazino-4-methyl-1,8-naphthyridine[5] dihydrochloride dihydrate in 200 cc. of 50% alcohol and 18.2 g. (0.14 mole) of ethyl acetoacetate was heated at 70° for five minutes. The reaction mixture was neutralized and the cooled solution extracted with ether. The dried ether extracts were concentrated to give an oil which was then

(14) Prepared by the reaction of 3-bromopyridine with sodium methylate in methanol solution according to the procedure of Koenigs [*Ber.*, **61**, 1022 (1928)]. However, all preparations of 3-methoxypyridine were contaminated with some 3-bromopyridine. The 3-methoxypyridine used in this nitration contained about 20% 3-bromopyridine.

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.

NEW BRUNSWICK, N. J. RECEIVED SEPTEMBER 3, 1946

[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	$C_{16}H_{20}N_4O_2S$	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.