furnishes the expected four possible arabinopyranose tetrabenzoates. X-Ray diffraction measurements and melting point determinations show that the enantiomorphic α-arabinopyranose tetrabenzoates form a racemic mixture, while the β-arabinopyranose tetrabenzoates form a true racemate.

Benzoylation of the long known *rac.* arabinose at 0–4° affords β-D,L-arabinopyranose tetrabenzoate in substantial yield, which demonstrates that ordinary crystalline D,L-arabinose, like its individual components, exists as β-D,L-arabinopyranose.

BETHESDA 14, MARYLAND RECEIVED JANUARY 24, 1947

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

I. Derivatives of Aminopyridines[1]

BY JACK BERNSTEIN, BARBARA STEARNS, MARTIN DEXTER[2] AND W. A. LOTT

Since the common antimalarial agents contain a heterocyclic nitrogen ring, it was thought desirable to prepare and test many of the readily available substituted pyridines as antiparasitic agents. The isomeric aminopyridines and their acetyl derivatives were prepared by known procedures[3] and found to be inactive,[4] as were the isomeric 2-acetylamido-methylpyridines. Alkylated derivatives of 2-aminopyridine, which were also inactive, were prepared by the reaction of 2-bromopyridine with the appropriate amines.[5]

In addition to these compounds, various halogenated aminopyridines were also prepared of which only 2-amino-5-iodopyridine showed slight antiparasitic activity. A number of alkylated and acylated derivatives of this compound were prepared to determine if further modification of the molecule would increase this activity. Alkylated derivatives were prepared by the reaction of 2-chloro-5-iodopyridine[6] with the desired amine. The inertness of a β-halogen as compared with an α- or γ-halogen in the pyridine ring made this method feasible and no replacement of the β-iodine was observed in any case (negative qualitative test). By the reaction of 2-amino-5-iodopyridine with diethylaminoethyl chloride, N-diethylaminoethyl-5-iodo-2-pyridone-imide was prepared. The ultraviolet absorption[7] of this compound in strongly basic solution showed one maximum at 245 mμ (ϵ = 15,900) and a second maximum at 330 mμ (ϵ = 3,180). The absorption of 2-diethylaminoethylamino-5-iodopyridine, also in strongly basic solution, likewise showed two maxima; at 253 mμ (ϵ = 22,000) and at 320 mμ (ϵ = 3,620). The difference in absorption indicates that the compounds are not identical, and since the structure of the latter one is clearly established by the method of synthesis, the alkylation reaction of the 2-amino-5-iodopyridine must have resulted in the N-substituted-2-pyridone-imide structure. The *p*-methoxybenzyl derivative was prepared by the condensation of 2-amino-5-iodopyridine with anisaldehyde in the presence of formic acid.[8] The acylated derivatives of 2-amino-5-iodopyridine were prepared by the usual procedures; reaction with an acyl chloride, acid anhydride or with an isocyanate. None of the derivatives of 2-amino-5-iodopyridine prepared showed the slight activity of the parent compound.

A number of alkoxy derivatives of 2- or 3-aminopyridine were also synthesized. The 2-amino-6-alkoxy derivatives were prepared by the reaction of 2-amino-6-bromopyridine with the sodium derivative of the desired alcohol.[9] The 2-amino-3-alkoxy derivatives were prepared by the procedure of Koenigs[10]; 3-bromopyridine was converted to 3-alkoxypyridine, nitrated to give 2-nitro-3-alkoxypyridine, followed by reduction to the 2-amino-3-alkoxypyridine. 2-Methoxy-5-aminopyridine was prepared by the conversion of 5-nitro-2-chloropyridine to 5-nitro-2-methoxypyridine followed by reduction to the corresponding amino compound.[11] None of these derivatives showed any antimalarial activity.

Condensation of 2-pyridylhydrazine with the appropriate β-keto ester yielded pyrazolones; from ethyl acetoacetate, 1-(2-pyridyl)-3-methyl-5-pyrazolone was formed while from diethyl α,β-diacetylsuccinate, 1,1′-di-(2-pyridyl)-3,3′-dimethyl-4,4′-bipyrazole-5,5′-dione was obtained. An attempt to prepare this latter compound by the reaction of phenylhydrazine with 1-(2-pyridyl)-3-methyl-5-pyrazolone was unsuccessful, although phenylhydrazine does convert 1-phenyl-3-methyl-

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

(2) Present address: Specific Pharmaceuticals, Inc., 329 4th Avenue, New York, N. Y.

(3) Unless otherwise noted, the preparation of known pyridine derivatives is indicated in Maier-Bode and Altpeter, "Das Pyridin und seine Derivative," Wilhelm Knapp, Halle (Saale), 1934; photolithoprint reproduction by Edwards Brothers, Inc., Ann Arbor, Michigan, 1943.

(4) The antiparasitic activity of the compounds as suppressive agents for *Plasmodium lophurae* in ducklings was determined. These determinations were carried out by the Division of Pharmacology of this Institute. Some of the pharmacological results will be described in the forthcoming monograph by the Survey of Antimalarial Drugs.

(5) Subsequently described by Whitmore, Mosher, Goldsmith and Rytina, THIS JOURNAL, **67**, 393 (1945); also British Patent 265,167.

(6) Magidson and Menschikoff, *Ber.*, **58**, 113 (1925).

(7) Absorption spectra were measured by Dr. N. H. Coy of the Biological Laboratories, E. R. Squibb and Sons.

(8) Tschitschibabin and Knunjanz, *Ber.*, **64**, 2839 (1931).

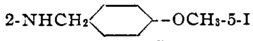
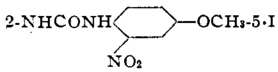
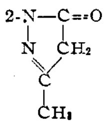
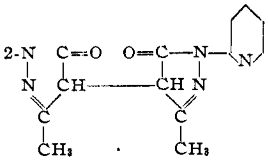
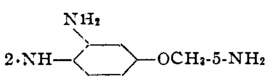
(9) Hertog and Wilbaut, *Rec. trav. chim.*, **55**, 126 (1936).

(10) Koenigs, Gerdes and Sirot, *Ber.*, **61**, 1022 (1928). As indicated by Schickh, Binz and Schulz, *ibid.*, **69**, 2595 (1936), the product described by Koenigs as 2-amino-5-ethoxypyridine was actually 2-amino-3-ethoxypyridine.

(11) U. S. Patent 2,145,579.

TABLE I

AMINOPYRIDINES AND DERIVATIVES

Substituted pyridine	Procedure[a]	Yield, %	Solvent for crystallization	M. p., °C.[b]	Empirical formula	Analyses, % Calcd.	Found
2-NHCH$_2$CH$_2$CH$_2$CH$_3$	A	80	[c]	40–41[d]	$C_9H_{14}N_2$	N, 18.67	18.61
2-N(C$_2$H$_5$)$_2$·HCl	A[e]	66	Alcohol–ether	124–127	$C_9H_{15}ClN_2$	N, 15.01	14.73
2-NHCOCH$_3$-3-CH$_3$	B	85	Hexane	92–93[f]	$C_8H_{10}N_2O$	C, 64.00	63.64
						H, 6.67	6.95
2-NHCOCH$_3$-5-CH$_3$	B	88	Hexane–benzene	103–104	$C_8H_{10}N_2O$	C, 64.00	64.17
						H, 6.67	6.94
2-NH$_2$-5-I	[g]	48	50% Alcohol	126–128	$C_5H_5IN_2$	...	...
	C	12	Benzene	192.5–193.5	$C_{13}H_{13}IN_2O$	N, 8.24	8.40
2-N(C$_2$H$_5$)$_2$·5-I·HCl	A	37	Abs. alcohol–ether	166–168[h]	$C_9H_{14}ClIN_2$	Cl, 11.36	10.95
2-NHCH$_2$CH$_2$N(C$_2$H$_5$)$_2$-5-I·HCl	A	50	Abs. alcohol–ether	154–156[i]	$C_{11}H_{19}ClIN_3$	Cl, 9.99	10.09
1-CH$_2$CH$_2$N(C$_2$H$_5$)$_2$-2=NH·5-I·2HCl	D	36	95% Alcohol	267–269	$C_{11}H_{20}Cl_2IN_3$	Cl, 18.11	17.83
2-NHCOCH$_3$-5-I	[j]	70	50% Alcohol	153–154	$C_7H_7IN_2O$	N, 10.68	10.77
2-NHCOCH$_3$-5-IO$_2$	E	17	[c]	110 (explodes)	$C_7H_7IN_2O_3$	N, 9.52	9.30
	G	20	[c]	Does not melt below 300°	$C_{11}H_8I_2N_4O$	N, 12.02	12.02
2-NHCOOC$_2$H$_5$-5-I	F	22	95% Alcohol	192–194	$C_8H_9IN_2O_2$	N, 9.59	9.70
	H	47	Acetic acid	231–233	$C_{13}H_{11}IN_4O_4$	N, 13.53	13.71
2-NHSO$_2$C$_2$H$_5$-5-I	I	42	95% Alcohol	175–177	$C_7H_9IN_2O_2S$	N, 8.97	9.12
2-NHNH$_2$-5-I	[k]	83	Water	120.5–121	$C_5H_6IN_3$	N, 17.87	17.78
2-NH$_2$-4-I	[l]	43	Water	158–160	$C_5H_5IN_2$	...	...
2-NH$_2$-5-CONH$_2$	J	83	95% Alcohol	239–240	$C_6H_7N_3O$	N, 30.65	30.37
2-NH$_2$-3-OCH$_3$	[m]	15	[n]	78–80	$C_6H_8N_2O$	N, 22.58	21.81
5-NH$_2$-2-OCH$_3$.HCl	[o]	68	Abs. alcohol	167–168 (dec.)	$C_6H_9ClN_2O$	Cl, 22.12	21.99
2-NH$_2$-3,5-di-I-6-ONa	K	63	[c]	182 (dec.)	$C_5H_3I_2N_2NaO$	N, 7.29	7.10
2-NH$_2$-6-OCH$_3$.HCl	L	73	Abs. alcohol	150–152[p]	$C_6H_9ClN_2O$	N, 17.44	17.66
2-NH$_2$-6-OCH$_2$CH$_2$N(C$_2$H$_5$)$_2$·2HCl	L	69	Abs. alcohol–ether	157–159[q]	$C_{11}H_{21}Cl_2N_3O$	Cl, 25.18	25.11
2-NH$_2$-6-O(CH$_2$)$_3$N(C$_2$H$_5$)$_2$·C$_6$H$_5$COOH	L	55	Ether	84–85[r]	$C_{19}H_{27}N_3O_3$	C, 66.09	65.91
						H, 7.83	7.65
		54	Hexane	109.5–111	$C_9H_9N_3O$	...	...
	M	63		257–258	$C_{18}H_{16}N_6O_2$	N, 24.14	24.25
3,4-di-NH$_2$·2HCl	[u]	18	Abs. alcohol	Does not melt below 300°	$C_5H_9Cl_2N_3$	Cl, 39.01	39.20
2,4-di-NH$_2$	[v]	73	Benzene	106–107	$C_5H_7N_3$	...	...
2,4-di-NHCOCH$_3$	[w]	60	Water	200–202	$C_9H_{11}N_3O_2$	C, 55.95	55.80
						H, 5.69	5.59
2,4-di-NH$_2$-6-CH$_3$	N	57	Chloroform	117–118	$C_6H_9N_3$	N, 34.15	34.00
2,5-di-NH$_2$·2HCl	[x]	60	Aqueous alcohol	Does not melt below 300°	$C_5H_9Cl_2N_3$	N, 23.08	23.01
	O	49	95% Alcohol	132–133	$C_{12}H_{14}N_4O$	N, 24.35	24.18
2,6-di-NH$_2$·HCl	[y]	..	Abs. alcohol	81–83	$C_5H_8ClN_3$	...	...

[a] Refers to general procedure given in experimental part. [b] All melting points are uncorrected. [c] Not crystallized. [d] B. p., 124–125° at 15 mm. [e] Preparation of free base is described in British Patent 265,167; reported b. p., 208–214°. Compound existed in two forms, one of which melted at 69–70°. After heating for a short time below this temperature, compound melted at 92–93°. Seide, *Ber.*, **57**, 1802 (1924), reported m. p. of 64°. Magidson and Menschikoff, ref. 6; reported m. p. 129°. [h] B. p. of free base 110–112° at 3 mm. Reported in U. S. Patent 1,793,683, b. p. 125–129° at 2.5 mm. [i] B. p. of free base 158–162° at 1.5 mm. [j] Prepared by reaction of acetic anhydride with 2-amino-5-iodopyridine. Compound is reported in literature, but no m. p. is recorded. [k] British Patent 259,982; m. p. 124°. [l] Graf, *Ber.*, **64**, 21 (1931); reported m. p. 163–164°. [m] Procedure of Koenigs, Gerdes and Sirot, *Ber.*, **61**, 1022 (1928), who prepared 2-amino-3-ethoxypyridine. [n] Purified by sublimation. [o] U. S. Patent 2,145,579. Binz and Rath, *Ann.*, **484**, 52 (1930), reported the dihydrochloride. [p] B. p. of free base, 103–104° at 9 mm. [q] B.p. of free base, 133–135° at 4 mm. [r] B. p. of free base, 146–148° at 3 mm. [s] Fargher and Furness, *J. Chem. Soc.*, **107**, 688 (1915); reported m. p. 110°. [t] Purified by solution in alkali and precipitation with acid. [u] Koenigs, Kinne and Weiss, *Ber.*, **57**, 1172 (1924). [v] Meyer and Tropsch, ref. 14, reported m. p. 107°. [w] Prepared by treatment of 2,4-diaminopyridine with acetic anhydride. [x] Tschitschibabin and Kirsanow, *Ber.*, **60**, 766 (1927). [y] Most of the 2,6-diaminopyridine hydrochloride used in this work was purchased from the Pyridinium Corporation, Nepara Park, New York. After several recrystallizations from alcohol the

product melted at 81–83°. However, heating the solid for two hours at 75° raised the m. p. to 156–157°. Analysis of the material indicated no change in composition. When this high melting sample was recrystallized from alcohol, the m. p. reverted to 81–83°. If the high melting sample was allowed to remain at room temperature, the m. p. slowly reverted to the lower one.

5-pyrazolone to 1,1′-diphenyl-3,3′-dimethyl-4,4′-bipyrazole-5,5′-dione.[12] The product isolated from the reaction of phenylhydrazine with 1-(2-pyridyl)-3-methyl-5-pyrazolone was 1,1′-diphenyl-3,3′-dimethyl-4,4′-bipyrazole-5,5′-dione. This was characterized by analysis and by conversion to 1,1′-diphenyl-3,3′-dimethyl-Δ-4,4′-(Δ²-bipyrazoline)-5,5′-dione. A similar reaction has been observed by Passerini and Ridi.[13]

Finally, several diaminopyridines were synthesized. The 2,5-isomer and the 3,4-isomer were prepared by reduction of 2-amino-5-nitropyridine and 3-nitro-4-aminopyridine, respectively. The 2,4-isomer was obtained via the Curtius degradation of the diazide of 2,4-lutidinic acid.[14] The 2,6-isomer, prepared by the diamination of pyridine, is available commercially. 2,4-Diamino-6-methylpyridine was obtained by the reaction of aqueous ammonia with 2,4-dibromo-6-methylpyridine. Of these compounds, only 2,6-diaminopyridine showed any appreciable activity as an antiparasitic agent. The further modification of the 2,6-diaminopyridine molecule will be described in the following paper of this series.[15]

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

Experimental[16]

A. 2-Diethylaminoethylamino-5-iodopyridine.—A mixture of 24 g. (0.1 mole) of 2-chloro-5-iodopyridine, 23.2 g. (0.2 mole) of diethylaminoethylamine and 50 cc. of absolute alcohol was heated in a bomb tube at 160° for thirty-five hours. The alcohol was then distilled off, the residue poured into water and the solution made strongly alkaline with 40% sodium hydroxide solution. The oil that separated was extracted three times with ether and the combined ether extracts then extracted with 5% hydrochloric acid (most of the unreacted 2-chloro-5-iodopyridine remains in the ether layer). The aqueous layer was then made strongly alkaline, extracted with ether and the ether extract dried over anhydrous potassium carbonate. The residue, after removal of the ether, was distilled under reduced pressure to give 16 g. (50%) of product boiling at 158–162° at 1.5 mm.

Anal. Calcd. for $C_{11}H_{18}IN_3$: N, 13.17. Found: N, 13.24.

The free base was converted to the monohydrochloride by adding one equivalent of ethereal hydrogen chloride to an ether solution of the base. The hydrochloride, after crystallization from a mixture of absolute alcohol and ether, melted at 154–156°.

B. 2-Acetamido-5-methylpyridine.—A solution of 37.4 g. (0.36 mole) of acetic anhydride in 50 cc. of anhydrous benzene was added dropwise, with vigorous stirring, to a solution of 36 g. (0.33 mole) of 2-amino-5-methylpyridine in 400 cc. of benzene. The temperature gradually rose to about 35°. After all the acetic anhydride had been added, the reaction mixture was refluxed for two hours, then cooled and made strongly alkaline. The benzene layer was separated and the aqueous layer extracted with 200 cc. of benzene. The combined benzene extracts were washed with saturated sodium chloride solution, treated with decolorizing carbon, dried over anhydrous magnesium sulfate and concentrated. The addition of hexane precipitated the product as a white solid; 44 g. (88%), melting at 101–102.5°. Crystallization from a mixture of hexane and benzene raised the melting point to 103–104°.

C. 2-(*p*-Methoxybenzylamino)-5-iodopyridine.—A mixture of 22 g. (0.1 mole) of 2-amino-5-iodopyridine, 13.6 g. (0.1 mole) of freshly distilled anisaldehyde and 48 g. of anhydrous formic acid was refluxed in an oil-bath at 140° for sixteen hours. At this time the evolution of carbon dioxide had ceased. The reaction mixture was cooled and 100 cc. of 10% hydrochloric acid added. After extraction with ether to remove unreacted starting material, the aqueous layer was made strongly alkaline. The precipitated solid was filtered, washed with water and with a small amount of absolute alcohol. The crude material was crystallized from benzene to give 4.0 g. (12%) of product, melting at 192.5–193.5°.

D. N-Diethylaminoethyl-5-iodo-2-pyridone-imide Dihydrochloride.—A mixture of 22 g. (0.1 mole) of 2-amino-5-iodopyridine and 17.2 g. (0.1 mole) of diethylaminoethyl chloride hydrochloride was warmed on a steam-bath. At 65°, a clear melt was obtained which solidified when the temperature reached 85°. The solid mass was dissolved in hot alcohol, treated with decolorizing carbon, and cooled. The product, which crystallized out, weighed 14.0 g. (36%) and melted at 266–269°. Recrystallization raised the m. p. to 267–269°.

E. 2-Acetamido-5-iodoxypyridine.—A suspension of 17.0 g. (0.065 mole) of 2-acetamido-5-iodopyridine in 400 cc. of water was cooled in an ice-bath and chlorine bubbled through the reaction mixture for ninety minutes. A heavy yellow precipitate of 2-acetamido-5-iodopyridine dichloride formed. The reaction mixture was made alkaline with dilute sodium hydroxide solution and chlorine bubbled through for an additional forty-five minutes. The suspension was stirred for three hours, made alkaline and filtered. The solid was washed with water, alcohol and ether, and then extracted with chloroform to remove the unreacted starting material. The product, which was a red solid, weighed 3.2 g. (17%) and decomposed violently at 110°.

F. 2-Carbethoxyamido-5-iodopyridine.—A solution of 13.6 g. (0.125 mole) of ethyl chlorocarbonate in 50 cc. of anhydrous ether was added dropwise with vigorous stirring to a solution of 27.5 g. (0.125 mole) of 2-amino-5-iodopyridine and 10 cc. of pyridine in one liter of anhydrous benzene. After all the ethereal solution had been added, the reaction mixture was refluxed for two and one-half hours. The cooled mixture was filtered, and the solid crystallized from 95% alcohol to give 8.0 g. (22%) of product, m. p. 192–194°.

G. *sym*-Di-(5-iodo-2-pyridyl)-urea.—A toluene solution of phosgene (about 5%) was added slowly to a solution of 22 g. (0.1 mole) of 2-amino-5-iodopyridine in 500 cc. of anhydrous ether until no further precipitation occurred. The suspension was then poured into cold water and shaken vigorously. The mixture was made alkaline and the aqueous layer separated. The organic layer was washed again with water and allowed to stand overnight. The precipitated solid was filtered but could not be purified by crystallization. It did not melt below 300°.

H. 2-(2′-Nitro-4′-methoxyphenylureido)-5-iodopyridine.—A mixture of 22 g. (0.1 mole) of 2-amino-5-iodopyridine, 19.4 g. (0.1 mole) of 2-nitro-4-methoxyphenyl isocyanate and one liter of benzene was refluxed for two hours. The precipitated solid was filtered and extracted with hot alcohol to remove unreacted starting material.

(12) Knorr, *Ann.*, **238**, 168 (1887); *Ber.*, **17**, 2044 (1884), and Knorr and Haber, *ibid.*, **27**, 1151 (1894).

(13) Passerini and Ridi, *C. A.*, **30**, 3818 (1936).

(14) Meyer and Tropsch, *Monatsh.*, **35**, 189 (1914).

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

(16) All melting points are uncorrected.

The residue was crystallized from acetic acid to give 19.5 g. (47%) of product, m. p. 231-233°.

I. **2-Ethylsulfonamido-5-iodopyridine.**—To a solution of 22.0 g. (0.1 mole) of 2-amino-5-iodopyridine in 12.0 g. (0.15 mole) of pyridine there was slowly added 12.9 g. (0.1 mole) of ethylsulfonyl chloride. The reaction mixture was allowed to stand for fifteen minutes at room temperature and was then heated for three hours on a steam-bath. Water was added to the cooled reaction mixture and after several hours crystallization began. The solid was filtered off, washed several times with water and air-dried to give 19.0 g. (65%) of crude product, m. p. 160-165°. This was purified by dissolving it in 10% sodium hydroxide, treating with decolorizing carbon, and acidifying with 10% hydrochloric acid to *p*H 3. The filtered solid was crystallized from 95% alcohol to give 13.0 g. (42%) of product, m. p. 175-177°.

J. **6-Aminonicotinamide.**—A solution of 2.0 g. (0.0168 mole) of 2-amino-5-cyanopyridine in 7 cc. of 30% hydrogen peroxide, 1 cc. of 6 *N* sodium hydroxide solution and 10 cc. of alcohol was warmed at 40-50° for one hour. The reaction mixture was cooled and the solid filtered, washed with water and air-dried. Crystallization from 95% alcohol gave 1.9 g. (83%) of product, m. p. 239-240°.

K. **Sodium Salt of 2-Amino-3,5-diiodo-6-hydroxypyridine.**—(Attempt to prepare mono-iodo derivative.) To a solution of 16.7 g. (0.14 mole) of 2-amino-6-hydroxypyridine hemihydrate in 100 cc. of 10% hydrochloric acid there was added 22.8 g. (0.14 mole) of iodine monochloride. A precipitate formed immediately. This was filtered off and boiled with 10% sodium hydroxide solution for thirty minutes. The cooled reaction mixture was filtered and the residue washed with alcohol and ether. The product, which weighed 17 g. (63%), melted at 182° (dec.).

Anal. Calcd. for $C_5H_3I_2N_2NaO$: I, 66.15. Found: I, 66.06.

L. **2-Amino-6-diethylaminoethoxypyridine.**—A solution of 15.5 g. (0.09 mole) of 2-amino-6-bromopyridine in 23.4 g. (0.20 mole) of diethylaminoethanol, in which 2.3 g. (0.10 mole) of sodium had been dissolved, was heated in an oil-bath at 170 ± 5° for seven hours. Aqueous potassium hydroxide (20%) was added to the cooled mixture and the oil extracted several times with ether. The combined ether extracts were dried over anhydrous potassium carbonate and the residue, after removal of the ether, distilled under reduced pressure to give 13 g. (69%) of product boiling at 133-135° at 4 mm.

The hydrochloride was prepared by adding two equivalents of an ethereal hydrogen chloride solution to a solution of the free amine in 75 cc. of absolute alcohol. The addition of 200 cc. of anhydrous ether caused no precipitation to take place; but upon scratching the reaction vessel, crystallization of the product occurred. The hydrochloride, after purification by solution in alcohol, addition of ether and seeding to induce crystallization, melted at 157-159°.

M. **1,1'-Di-(2-pyridyl)-3,3'-dimethyl-4,4'-bipyrazole-5,5'-dione.**—A mixture of 25.8 g. (0.1 mole) of diethyl α,β-diacetylsuccinate[17] and 21.8 g. (0.2 mole) of 2-pyridylhydrazine was heated at 100° for one hour and the temperature then gradually raised to 150° and maintained at this temperature for two hours. (The final heating was carried out under reduced pressure in order to complete the removal of the water and alcohol formed in the reaction.) The solid was washed with ether and purified by solution in dilute alkali, treatment with decolorizing carbon, and precipitation with acid. The precipitated solid was washed with water until washings were neutral and then air-dried to give 22.0 g. (63%) of product, m. p. 257-258°.

Reaction of 1-(2-Pyridyl)-3-methyl-5-pyrazolone with Phenylhydrazine.—A mixture of 8.3 g. (0.05 mole) of 1-(2-pyridyl)-3-methyl-5-pyrazolone and 16.2 g. (0.15 mole) of phenylhydrazine was warmed in an oil-bath at 180°. Vigorous reaction occurred and internal temperature rose to 195°. When initial reaction had subsided, temperature of the oil-bath was raised to 205° and maintained at this temperature for two hours. Reaction mixture was cooled, suspended in ether, filtered and residue washed with ether to give 3.8 g. (46%) of product, 1,1'-diphenyl-3,3'-dimethyl-4,4'-bipyrazole-5,5'-dione. A sample was crystallized from pyridine-alcohol mixture for analysis. The product does not melt below 300°.

Anal. Calcd. for $C_{20}H_{18}N_4O_2$: N, 16.18. Found: N, 16.10.

A sample was dissolved in dilute alkali and oxidized by the addition of potassium nitrite solution followed by acidification with dilute sulfuric acid. The blue flocculent precipitate was dissolved in chloroform and the chloroform solution washed with dilute alkali, then water and dried over anhydrous magnesium sulfate. Concentration of the chloroform left a residue which decomposed at 235-240°, reported for "Pyrazole blue," 230-240°.[18]

N. **2,4-Diamino-6-methylpyridine.**—A mixture of 42 g. (0.336 mole) of 2,4-dihydroxy-6-methylpyridine[19] and 120 g. of phosphorus tribromide was heated in a sealed tube at 190° for four hours. The tube was cooled, the contents poured onto crushed ice and the mixture steam-distilled. The oil in the distillate crystallized upon cooling to give 25 g. (30%) of 2,4-dibromo-6-methylpyridine, m. p. 27°; b. p. 230-231°.

Anal. Calcd. for $C_6H_5Br_2N$: N, 5.58. Found: N, 5.85.

A suspension of 19.0 g. (0.0757 mole) of 2,4-dibromo-6-methylpyridine in 55 c. of concentrated aqueous ammonia (d. 0.9) was heated in a sealed tube at 205° for forty hours. The tube was cooled and the reaction mixture filtered. The filtrate was made strongly alkaline by the addition of solid sodium hydroxide and extracted with chloroform. Concentration of the chloroform extract left an oily residue which crystallized upon standing. The solid weighed 5.0 g. (54%) and melted, after recrystallization from chloroform, at 117-118°.[20]

O. **2-(2'-Amino-4'-methoxyanilino)-5-aminopyridine.**—A mixture of 25.0 g. (0.158 mole) of 2-chloro-5-nitropyridine and 26.5 g. (0.158 mole) of 3-nitro-4-aminoanisole was fused at 160° for one hour. The cooled reaction mixture was crystallized from aqueous acetone and then from cellosolve to give 26.4 g. (58%) of 2-(2'-nitro-4'-methoxyanilino)-5-nitropyridine, m. p. 196-197°.

Anal. Calcd. for $C_{12}H_{10}N_4O_5$: N, 19.31. Found: N, 19.32.

A suspension of 17.2 g. (0.059 mole) of the dinitro compound in 1700 cc. of 95% alcohol was reduced at atmospheric pressure using 1.6 g. of catalyst, platinum on carbon (5%). The 2-(2'-amino-4'-methoxyanilino)-5-aminopyridine was isolated by concentration of the solvent. The residue was dissolved in a small amount of absolute alcohol and alcoholic hydrogen chloride added to give 20.3 g. of crude hydrochloride. This was dissolved in water, treated with decolorizing carbon and the solution made alkaline to liberate the free base. The precipitated base was crystallized from 95% alcohol to give 6.6 g. (49%) of product, m. p. 132-133°.

Summary

A number of derivatives of aminopyridines were prepared for testing as antiparasitic agents.

Of the compounds prepared only 2-amino-5-iodopyridine and 2,6-diaminopyridine showed such activity.

Modification of the 2-amino-5-iodopyridine molecule resulted in complete loss of this activity.

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(17) Knorr and Haber, *Ber.*, **27**, 1151 (1894).

(18) Knorr, *Ann.*, **238**, 173 (1887).

(19) Knoevenagel and Fries, *Ber.*, **31**, 767 (1898).

(20) This compound, prepared by the amination of α-picoline, is reported to melt at 52-53°, *Chem. Zentr.*, **108**, I, 2269 (1937).