tillation there was obtained 11.5 g. (22%) of product, b. p. 155–160° (4 mm.). The free base could be crystallized from hexane, m. p. 55–56°.

Anal. Calcd. for $C_{12}H_{11}ON$: C, 77.81; H, 5.98: N, 7.56. Found: C, 78.22; H, 5.84; N, 7.42.

A picrate of the base melted at 150–151°.

Anal. Calcd. for $C_{12}H_{11}ON \cdot C_6H_3O_7N_3$: C, 52.18; H, 3.45. Found: C, 52.22; H, 3.40.

4-Benzyloxypyridine N-Oxide (X).—The oxide was prepared from the base by means of perbenzoic acid as described above for the 2-isomer and melted at 178–179°.

Anal. Calcd. for $C_{12}H_{11}O_2N$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.57; H, 5.42; N, 6.62.

The amine oxide formed a picrate readily in alcoholic solution, m. p. 123–124°.

Anal. Calcd. for $C_{12}H_{11}O_2N \cdot C_6H_3O_7N_3$: C, 50.24: H, 3.30. Found: C, 49.84; H, 3.29.

N-Hydroxy-4-pyridone (XI–XII).—4-Benzyloxypyridine N-oxide (1 g.) was catalytically reduced with 150 mg. of palladium (5% on charcoal) as described for the 2-isomer. The filtrate was concentrated to a small volume, depositing 345 mg., 68%, m. p. 243–244°. The acid gives no precipitate with ferric chloride but produces an orange color. The preparation of this compound by another method has been described[14] but no m. p. is given.

Anal. Calcd. for $C_5H_5O_2N$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.47; H, 4.81; N, 12.20.

(14) Ost. *J. prakt. Chem.*, [2] **29**, 379 (1884).

N-Benzyloxy-4-pyridone (XIII).—N-Hydroxy-4-pyridone (47 mg.) was added to a solution of sodium (9.7 mg.) in alcohol and refluxed with benzyl chloride (53.6 mg.) for one hour. The mixture was partitioned between ethyl acetate and alkali. The organic layer on evaporation left a residue of 73 mg. After recrystallization from ethyl acetate and hexane, the material melted 112–113°.

Anal. Calcd. for $C_{12}H_{11}O_2N$: C, 71.62; H, 5.51. Found: C, 71.80; H, 5.60.

The picrate of this benzyl ether melted at 164° and depresses the melting point of the picrate of 4-benzyloxypyridine N-oxide.

Anal. Calcd. for $C_{12}H_{11}O_2N \cdot C_6H_3O_7N_3$: C, 50.24; H, 3.30. Found: C, 50.33; H, 3.65.

Acknowledgment.—The author is indebted to Mr. W. A. Lott for his interest and encouragement.

Summary

The synthesis of N-hydroxy-2-pyridone, a cyclic hydroxamic acid, is described. The acid is in tautomeric relationship with 2-hydroxypyridine N-oxide.

Isomeric acids of the 3- and of the 4-pyridyl series also have been prepared.

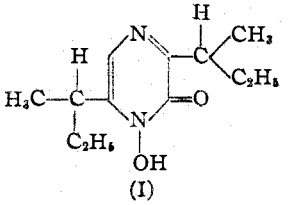
NEW BRUNSWICK, N. J. RECEIVED AUGUST 17, 1948

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

Analogs of Aspergillic Acid. II. Various Antibacterial Heterocyclic Hydroxamic Acids[1]

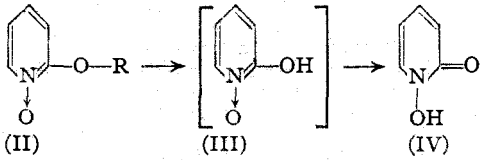
BY W. A. LOTT AND ELLIOTT SHAW

Attempts to develop synthetic methods for introducing into heterocyclic rings the hydroxamic acid grouping present in aspergillic acid (I) led to a



(I)

preparation for N-hydroxy-2-pyridone (IV).[2] The



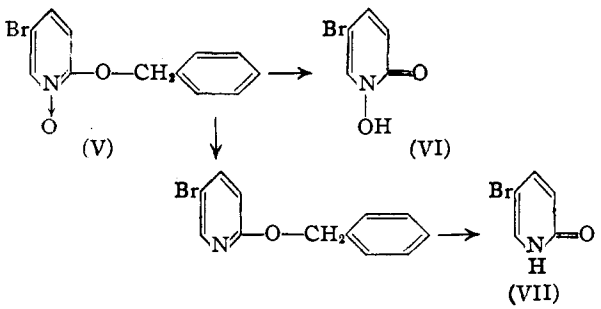
(II) (III) (IV)

synthesis was achieved by conversion of a 2-pyridyl ether to its N-oxide (II), followed by de-alkylation. The 3- and 4-pyridyl derivatives were also prepared[2] but, of these position isomers, only N-hydroxy-2-pyridone showed antibacterial activity, an observation which encouraged the extension of synthetic work to the preparation of additional heterocyclic hydroxamic acids. New methods have been developed. The synthetic acids exceed, in some instances, the *in vitro* antibacterial activity of aspergillic acid.

The hydroxamic acid grouping in N-hydroxy-2-pyridone (IV) is quite stable chemically, resisting the action of boiling aqueous acid or cleavage of the N–O bond by catalytic reduction (Pd), ammonium sulfide, or stannous chloride. In these respects, the grouping bears no resemblance to N-oxides. It is apparent that the amine oxide (II, R = benzyl) is converted to the hydroxamic acid (IV) successfully due to a more rapid initial attack at the ether linkage, by hydrochloric acid or catalytic reduction, than at the N–O bond which subsequently gains increased resistance to reduction by a tautomeric shift (III → IV) to the hydroxamic acid structure.[2] A similar series of reactions led to a 4-methyl derivative of (IV) in good yields. However, when the substituent was bromine in the 5-position, reduction or treatment of the N-oxide (V) with hydrochloric acid led to 5-bromopyridone (VII) as the main product. In the hydrochloric acid debenzylation, for example, the ratio of pyridone to hydroxamic acid isolated (VI) was 3:1. In this case, in contrast to

(1) Presented before the Division of Organic Chemistry at the 112th Meeting of the American Chemical Society, New York, N. Y., September, 1947.

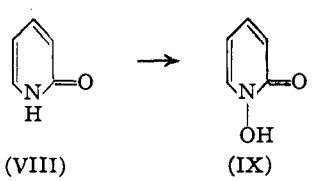
(2) Shaw, THIS JOURNAL, 71, 67 (1949).



those cited above, the initial attack is mainly at the amine oxide bond.

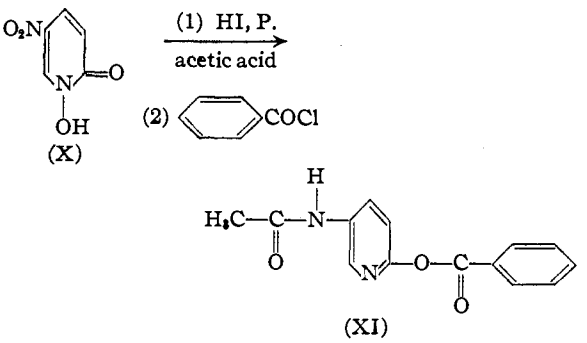
When attempts were made to apply the above synthesis to the preparation of cyclic quinoline hydroxamic acids, difficulty was encountered in the formation of the intermediate amine oxides. Treatment of 2-benzyloxyquinoline and 2-benzyloxy-4-methylquinoline with perbenzoic acid did not lead to satisfactory oxidations. The problem has been attacked by other methods, to be reported later.

The direct oxidation of amides to hydroxamic acids by means of hydrogen peroxide and ferric chloride has been reported.[3] The conversion of

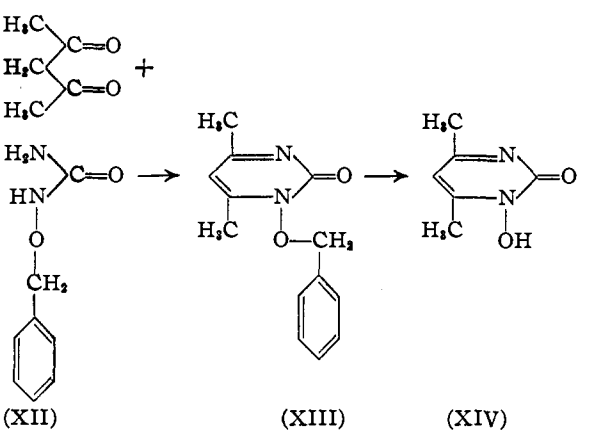


2-pyridone (VIII) to N-hydroxy-2-pyridone (IX) bears a formal resemblance to such a change. This oxidation has been achieved. Persulfuric acid, perbenzoic acid, and performic acid have been tried, but of these only perbenzoic acid gave satisfactory results. 5-Bromopyridone (VII) was also conveniently oxidized in yields of 15–20% to the corresponding hydroxamic acid (VI) and, in view of the poor results obtained in the initial synthetic approach to this acid (V → VI), the direct oxidation offers the best method of preparation. In the quinoline series, however, less than a 1% yield of N-hydroxy-2-quinolone was obtained on treatment of carbostyril with perbenzoic acid.

The stability of the hydroxamic acid grouping in N-hydroxy-2-pyridone (IV) has been described above. It was found that the nucleus in this compound undergoes substitution with ease. Nitration in glacial acetic acid gave a nitro compound identified as N-hydroxy-5-nitro-2-pyridone (X). Reduction with hydriodic acid in glacial acetic acid followed by benzoylation of the product led to the same acetamidopyridyl benzoate (XI) produced from 5-nitro-2-pyridone under similar conditions. Bromination gave a mixture of brominated acids from which was isolated a monobromo derivative different from the known 5- and 6-bromo acids and which is considered to be N-hydroxy-3-bromopyridone. 2-Pyridone itself undergoes substitution in the 3- and 5-positions.[4,5]



For the preparation of a hydroxamic acid in the pyrimidine series, benzyloxyurea (XII) was condensed with acetylacetone and the resultant N-benzyloxypyrimidone (XIII) cleaved by catalytic hydrogenation to 1-hydroxy-4,6-dimethyl-2-pyrimidone (XIV).



The *in vitro* antibacterial activities of a group of the synthetic hydroxamic acids are compared with aspergillic acid in Table I.

The values given indicate the concentrations necessary to prevent growth of the organisms.[6] It is significant that the common structural feature of these antibacterial agents is the cyclic hydroxamic acid grouping capable of chelating metals. A number of structurally related compounds have been tested which have some of the features of the active compounds but are incomplete as hydroxamic acids, *viz.*, pyridine N-oxide and 2-pyridone; these are not active *in vitro*. Furthermore, "vinylogs" of hydroxamic acids such as N-hydroxy-4-pyridone[2] (XV) and N-hydroxy-7-chloro-4-quinolone (XVI) which have an acidity comparable to their isomeric N-hydroxy-2-pyridone and -2-quinolone derivatives but, unlike the latter, do not form precipitates with metallic ions are inactive

(3) Oliveri-Mandala, *Gass. chim. ital.*, **52**, I, 107 (1922).

(4) Tschitschibabin and Schapiro, *J. Russ. Phys.-Chem. Soc.*, **53**, 233 (1921).

(5) Binz and Maier-Bode, *Angew. Chem.*, **49**, 486 (1936).

(6) We are indebted to Drs. Rake and Donovick of the Division of Microbiology, The Squibb Institute for Medical Research, for these results. The activities were measured by a dilution method accurate to ±15%.

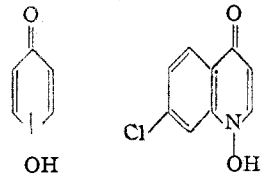
TABLE I

THE *in vitro* ANTIBACTERIAL ACTIVITIES OF SOME SYNTHETIC HYDROXAMIC ACIDS AND THE ANTIBIOTIC, ASPERGILLIC ACID

	Minimal inhibiting concentration mg./ml.		
	Staphylococcus aureus P209[a]	*Klebsiella pneumoniae*[a]	*Mycobacterium smegmatis*[b]
Aspergillic acid	0.021	0.030	0.023
N-Hydroxy-2-pyridone	.003	.043	.035
N-Hydroxy-4-methyl-2-pyridone	.041	.045	.041
N-Hydroxy-3-bromo-2-pyridone	.013	> .25	.05
N-Hydroxy-5-bromo-2-pyridone	.005	.09	.017
N-Hydroxy-6-bromo-2-pyridone	.011	.19	.19
N-Hydroxy-5-nitro-2-pyridone	.14	.90	.45
N-Hydroxy-2-quinolone	.0012	.019	.013
N-Hydroxy-4,6-dimethyl-2-pyrimidone	.21	.95	.44

[a] Tested in yeast beef broth. [b] Tested in modified Kirchner's medium.

in vitro. It seems probable, therefore, that the compounds in Table I are antibacterial due to their ability to combine with, and deprive microorganisms of, metabolically essential metals. A



(XV) (XVI)

correlation between antibacterial activity and chelating power has been demonstrated[7] in a series of 8-hydroxyquinoline derivatives. With respect to aspergillic acid, Goth has observed that the addition of ferric ion diminishes the *in vitro* activity of the antibiotic.[8]

Experimental[9]

2-Bromo-4-methylpyridine and 2,5-Dibromopyridine.—The 2-bromopyridines were prepared from the corresponding 2-aminopyridines by an adaptation of the method of Craig.[10] In an externally cooled 3-neck flask provided with stirrer, thermometer and dropping funnel, 2-amino-4-methylpyridine (81 g.) was dissolved with cooling in 48% hydrobromic acid (630 ml.). After the addition of 115 ml. of bromine, a solution of sodium nitrite (130 g.) in water (190 ml.) was gradually introduced below 0°. Stirring was then continued for an hour after which the solution was made alkaline with 50% sodium hydroxide and treated with sodium sulfite (100 g.). The mixture was steam distilled, and the oily 2-bromo-4-methylpyridine extracted from the distillate with ether. Fractionation of the dried extract gave 99 g., 77%, b. p. 220–222°.[11] When 2-amino-5-bromopyridine[12] was treated in the same way, 2,5-dibromopyridine, m. p. 92–96°, was obtained as a white solid in the steam distillate, 40%.

Pyridyl and Quinolyl Benzyl Ethers.—In the formation of N-hydroxy-2-pyridone (IV) from the N-oxide of a 2-pyridyl ether (II), the ethyl ether was as easily cleaved with hydrochloric acid as the benzyl ether. However, in subsequent applications of the method, the benzyl ether was used because of the additional method of cleavage by hydrogenolysis. The benzyl ethers were prepared from the corresponding bromopyridines and chloroquinolines essentially by the method of Renshaw and Conn.[13] The halogen derivatives were refluxed for two hours with a slight excess of sodium benzylate in benzyl alcohol, poured into water, and extracted with ether. The dried ether–benzyl alcohol layer was concentrated and fractionated *in vacuo*. In those cases resulting in a crystalline product, hexane was used for recrystallization before analysis.

2-Benzyloxy-4-methylpyridine, 50% yield, b. p. 142–145° at 5 mm. *Anal.* Calcd. for $C_{13}H_{13}ON$: C, 78.39; H, 6.53; N, 7.03. Found: C, 78.03; H, 6.85; N, 7.18.

A picrate formed in alcohol, m. p. 140–141°. *Anal.* Calcd. for $C_{19}H_{16}N_4O_8$: C, 53.27; H, 3.73; N, 13.08. Found: C, 53.63; H, 3.68; N, 12.99.

2-Benzyloxy-5-bromopyridine, 71% yield, b. p. 178–185° at 14 mm., m. p. 56–58°. *Anal.* Calcd. for $C_{12}H_{10}ONBr$: C, 54.50; H, 3.79; N, 5.30. Found: C, 54.10; H, 3.85; N, 5.30.

A picrate was obtained, m. p. 107–109°. *Anal.* Calcd. for $C_{18}H_{13}O_8N_4Br$: N, 11.34. Found: N, 11.72.

2-Benzyloxyquinoline, 86% yield, b. p. 196–197° at 2 mm., m. p. 46–47°. *Anal.* Calcd. for $C_{16}H_{13}ON$: C, 81.67; H, 5.57; N, 5.95. Found: C, 82.04; H, 6.10; N, 5.76.

2-Benzyloxy-4-methylquinoline, 68% yield, b. p. 174–176° at 1 mm., m. p. 52–56°. *Anal.* Calcd. for $C_{17}H_{15}ON$: C, 81.85; H, 6.02; N, 5.62. Found: C, 81.37; H, 5.94; N, 5.46.

The base gave a picrate, m. p. 149–150°. *Anal.* Calcd. for $C_{23}H_{18}O_8N_4$: C, 57.70; H, 3.76; N, 11.72. Found: C, 57.32; H, 4.04; N, 11.70.

4-Benzyloxy-7-chloroquinoline, 57% yield, m. p. 100–101°, recrystallized from benzene. *Anal.* Calcd. for $C_{16}H_{12}ONCl$: C, 71.24; H, 4.49; N, 5.19. Found: C, 70.92: H, 4.54: N, 5.17

N-Oxides.—The pyridyl and quinolyl benzyl ethers were left standing at room temperature with a chloroform solution containing 1.5 equivalents of perbenzoic acid.[14] After several days, when potassium iodide titration showed disappearance of most of the perbenzoic acid, the solution was washed with aqueous sodium carbonate and water. The chloroform layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to a small volume. The resultant crystals were drained from adhering oil on a filter and recrystallized from ethyl acetate.

2-Benzyloxy-4-methylpyridine N-oxide was thus obtained in a yield of 53%, m. p. 81–82°. *Anal.* Calcd. for $C_{13}H_{13}O_2N$: C, 72.53; H, 6.08; N, 6.51. Found: C, 72.61; H, 6.14; N, 6.72.

2-Benzyloxy-5-bromopyridine N-oxide, 25% yield, m. p. 127–128°. *Anal.* Calcd. for $C_{12}H_{10}O_2NBr$: C, 51.40; H, 3.57; N, 5.00. Found: C, 51.59; H, 4.03; N, 5.02.

4-Benzyloxy-7-chloroquinoline N-oxide required a modification of the above procedure for its isolation. Concentration of the carbonate-washed chloroform solution gave a benzoic acid salt from which the oxide was obtained by trituration with dilute sodium hydroxide and extraction with chloroform, m. p. 163°, 65% yield. *Anal.* Calcd. for $C_{16}H_{12}O_2NCl$: C, 67.25; H, 4.24; N, 4.89. Found: C, 67.11: H, 4.35; N, 5.11.

N-Hydroxy-4-methyl-2-pyridone.—The benzyl ether N-oxide was treated with aqueous hydrochloric acid as previ-

(7) Albert, Rubbo, Goldacre and Balfour, *Brit. J. Exp. Path.*, **28**, 69 (1947).

(8) Goth, *J. Lab. Clin. Med.*, **30**, 899 (1945).

(9) Melting points are uncorrected. Microanalyses were carried out by Mr. J. F. Alicino.

(10) Craig, THIS JOURNAL, **56**, 231 (1934).

(11) Case, THIS JOURNAL, **68**, 2574 (1946).

(12) Tschitschibabin and Tjashelowa, *J. Russ. Phys.-Chem. Soc.*, **50**, 483 (1918).

(13) Renshaw and Conn, THIS JOURNAL, **59**, 297 (1937).

(14) "Organic Syntheses," Coll. Vol. I, 431 (1941).

ously described[2] and led to the hydroxamic acid, m. p. 129–130°, 75% yield. *Anal.* Calcd. for $C_6H_7O_2N$: C, 57.58; H, 5.63; N, 11.18. Found: C, 57.51; H, 5.89; N, 11.17.

Action of Aqueous Hydrochloric Acid on 2-Benzyloxy-5-bromopyridine N-Oxide.—The oxide (7 g.) was refluxed for ten minutes with 20% hydrochloric acid (35 ml.) during which time the benzyl chloride formed was condensed and removed. The aqueous residue was taken to dryness *in vacuo* and the resultant crystalline mixture, dissolved in ethyl acetate–butanol (1:1), was extracted with aqueous sodium carbonate. When the aqueous layer was acidified and taken to dryness, extraction with absolute alcohol gave the hydroxamic acid, N-hydroxy-5-bromo-2-pyridone, m. p. 137–139°, 13%. *Anal.* Calcd. for $C_5H_4O_2NBr$: C, 31.60; H, 2.12; N, 7.37. Found: C, 31.65; H, 2.59; N, 7.35.

The ethyl acetate–butanol fraction from the above partition on concentration led to 5-bromo-2-pyridone, 40%, m. p. 179–181°, identical with an authentic sample.[16]

N-Hydroxy-7-chloro-4-quinolone.—4-Benzyloxy-7-chloroquinoline N-oxide (10 g.) was reduced with hydrogen at fifty pounds initial pressure in 100 ml. of absolute ethanol and 0.5 g. 5% palladium-on-carbon. The product crystallized out and was separated from the catalyst by solution in dilute sodium hydroxide and reprecipitation with acid, 5 g., m. p. 262°, 73%. Recrystallization from glacial acetic acid did not alter the melting point. The acid gives an orange color with ferric chloride but forms no precipitate. *Anal.* Calcd. for $C_9H_6O_2NCl$: C, 55.26; H, 3.09; N, 7.16. Found: C, 55.53; H, 3.32; N, 7.37.

Direct Oxidation of 2-Pyridones to Hydroxamic Acids.—The 2-pyridone was left standing at room temperature with a chloroform solution of perbenzoic acid containing a 50% excess of the oxidizing agent. After about one week at room temperature, the solution was taken to dryness and desiccated to a dry powder. This residue was triturated with ether and filtered several times to remove benzoic acid. The insoluble portion was recrystallized from benzene. N-Hydroxy-2-pyridone and N-hydroxy-5-bromo-2-pyridone were obtained in this way in yields of 15 and 18%, respectively, and were identical with the acids obtained from the 2-benzyloxypyridyl N-oxides. 6-Bromo-2-pyridone[16] under the above conditions produced N-hydroxy-6-bromo-2-pyridone, m. p. 155–157°, 19% yield. *Anal.* Calcd. for $C_5H_4O_2NBr$: C, 31.60; H, 2.12; N, 7.37. Found: C, 32.02; H, 2.22; N, 7.17.

5-Nitro-2-pyridone was not oxidized by perbenzoic acid at room temperature, judging by the absence of a ferric chloride coloration. Carbostyril (7 g.) produced 0.2 g. of N-hydroxy-2-quinolone, m. p. 189–191°, isolated as the fraction insoluble in aqueous bicarbonate and soluble in carbonate. The acid did not depress the melting point of the material prepared by the method of Friedländer.[17]

N-Hydroxy-5-nitro-2-pyridone.—N-Hydroxy-2-pyridone (3.1 g.) was dissolved in glacial acetic acid (15 ml.); concentrated nitric acid (2 ml., d. 1.42) was added with cooling. The product rapidly crystallized out; 2.8 g., 67% yield, m. p. 198–199°, unchanged on recrystallization from glacial acetic acid. *Anal.* Calcd. for $C_5H_4O_4N_2$: C, 38.47; H, 2.59; N, 17.95. Found: C, 38.09; H, 2.34; N, 17.75.

The nitro derivative (1.5 g.) was refluxed in glacial acetic acid (20 ml.) with concentrated hydriodic acid (1.5 ml., sp. gr. 1.7) and red phosphorus (1 g.). Since the hydroxamic acid grouping was not completely reduced (ferric chloride color) after three hours, a second portion of hydriodic acid was added and the refluxing continued for an hour longer. On concentration of the filtrate, yellow crystals of an hydriodide were obtained, 0.95 g. The hydriodide was dissolved in pyridine (15 ml.) and shaken in a stoppered flask with benzoyl chloride (1 ml.). After fifteen minutes, the mixture was poured into water and concentrated under reduced pressure. The derivative, 0.2 g., was recrystallized from ethyl acetate and hexane and melted at 149–150°.

When 5-nitro-2-pyridone was treated in the same way, an identical benzoate (XI) was obtained, indicating that nitration of the hydroxamic acid had produced a 5-nitro derivative. 5-Amino-2-pyridone forms di-acyl derivatives.[18] *Anal.* Calcd. for $C_{14}H_{12}N_2O_3$: C, 65.60; H, 4.72; N, 10.93. Found: C, 65.77; H, 4.73; N, 10.60.

N-Hydroxy-3-bromo-2-pyridone.—To a solution of N-hydroxy-2-pyridone (3 g.) in glacial acetic acid (15 ml.) was added a solution of bromine (4.3 g.) in the same solvent (20 ml.). After two hours at room temperature, the solution was filtered and taken to dryness *in vacuo*. The residue was clearly a mixture from which the initial crop of crystals from ethyl acetate, 0.7 g., m. p. 208–209°, was the only pure fraction isolated. *Anal.* Calcd. for $C_5H_4O_2NBr$: C, 31.60; H, 2.12; N, 7.37. Found: C, 31.48; H, 2.27; N, 7.46.

An hydriodic acid reduction was carried out as described above for the nitration product, and led to the pyridone, m. p. 183–184° (alcohol). *Anal.* Calcd. for C_5H_4ONBr: C, 34.51; H, 2.30; N, 8.04. Found: C, 34.74; H, 2.58; N, 7.89.

1-Benzyloxy-4,6-dimethyl-2-pyrimidone.—N-Benzyloxyurea[19] was dissolved in absolute alcohol (200 ml.) in a flask provided with a stirrer; acetylacetone (12.6 g.) and concentrated sulfuric acid (13.8 ml.) were added. After one hour, crystallization was induced by scratching and chilling. With the addition of ether, a 51% yield of the pyrimidine sulfate was obtained. The free base separated on treatment of the salt with aqueous alkali, m. p. 130–131° (from water). *Anal.* Calcd. for $C_{13}H_{14}O_2N_2$: C, 67.80; H, 6.12; N, 12.16. Found: C, 68.03; H, 6.24; N, 12.14.

N-Hydroxy-4,6-dimethyl-2-pyrimidone.—The benzyl ether (11.5 g.) was shaken with palladium-on-charcoal-5% (1.0 g.) in the atmosphere of hydrogen at an initial pressure of 50 lb. Reduction was rapid. When the theoretical amount of hydrogen had been taken up, the shaking was stopped. The hydroxamic acid was crystallized from the filtrate with the addition of ether; 6.5 g., 90%, m. p. 185–186°. There was no change in melting point on recrystallization from ether. *Anal.* Calcd. for $C_6H_8N_2O_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.27; H, 5.88; N, 19.68.

Summary

The synthesis of a number of heterocyclic compounds containing the hydroxamic acid grouping, —N(OH)—C(=O)—, in the ring is described. Such acids have, in general, antibacterial action *in vitro*.

NEW BRUNSWICK, N. J. RECEIVED AUGUST 17, 1948

(15) Tschitschibabin and Tjashelowa, *J. Russ. Phys.-Chem. Soc.*, **50**, 483 (1918).

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

(17) Friedländer and Ostermaier, *Ber.*, **14**, 1916 (1881); **15**, 332 (1882).

(18) Mills and Widdows, *J. Chem. Soc.*, **93**, 1372 (1908).

(19) Behrend and Leuchs, *Ann.*, **257**, 207 (1890).