373. *Hydroxamic Acids. Part I. Cyclic Hydroxamic Acids derived from Pyridine and Quinoline.*

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The preparation of the cyclic hydroxamic acids 2-hydroxypyridine 1-oxide (IX) and 2-hydroxyquinoline 1-oxide (XII) is described.

Aspergillic acid has been shown to have a high inhibitory *in vitro* activity against some Gram-negative and Gram-positive organisms (White, *Science*, 1940, **92**, 127; White and Hill, *J. Bact.*, 1942, **43**, 12; Jones, Rake, and Hamre, *ibid.*, 1943, **45**, 461; Menzel, Wintersteiner, and Rake, *ibid.*, 1943, **46**, 109; Dunham, Hamre, McKee, and Rake, *Proc. Soc. Exp. Biol. Med.*, 1943, **54**, 211) and against *M. tuberculosis* (Goth, *J. Lab. Clin. Med.*, 1945, **30**, 899). The toxicity of aspergillic acid is such that it is unlikely to find useful applications in the treatment of systemic infections. Aspergillic acid is a hydroxamic acid related to pyrazine, and although there is some dubiety concerning the nature of the side chains R and R′, it is correctly represented by the structure (I).†

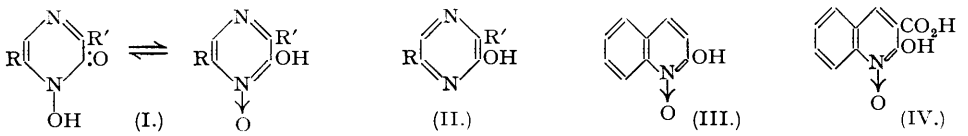
On mild reduction, aspergillic acid is converted into the hydroxypyrazine (II), deoxyaspergillic acid (Dutcher, *J. Biol. Chem.*, 1947, **171**, 321, 341; Newbold and Spring, *J.*, 1947, 373), which is relatively ineffective as an antibacterial agent. It would appear that the activity of aspergillic acid in this respect is to be attributed to the cyclic hydroxamic acid grouping. The work described in this and succeeding communications was undertaken with the object of developing methods for the synthesis of cyclic hydroxamic acids of different types for antibacterial tests.

Very few cyclic hydroxamic acids have been described in the literature. 2-Hydroxyquinoline 1-oxide (" oxycarbostyril ") (III) was obtained by Friedländer and Ostermaier (*Ber.*, 1881, **14**, 1916; 1882, **15**, 332; Friedländer, *Ber.*, 1914, **47**, 3369) as a minor product of the reduction of ethyl *o*-nitrocinnamate. Heller and Wunderlich (*ibid.*, p. 2889) obtained the related oxycarbostyril carboxylic acid (IV) by reduction of *o*-nitrobenzylidenemalonic acid with zinc and acetic acid, and Reissert (*Ber.*, 1908, **41**, 3921; see also Di Carlo, *J. Amer. Chem. Soc.*, 1944, **66**, 1420) obtained 1 : 2-dioxindole (V) by reduction of *o*-nitrophenylacetic acid with zinc and sulphuric acid. Our approach to the synthesis of cyclic hydroxamic acids has been limited in the first place to attempts to oxidise *N*-heterocyclic derivatives directly to the required acid rather than the use of a final ring-closure reaction involving the simultaneous formation of the

* These experiments were made by Mr. A. H. Gowenlock, M.Sc., in the University of Manchester.

† Similar tautomeric structures can be written for the cyclic hydroxamic acids (III), (IV), (VI), (IX), and (XII).

heterocycle and the hydroxamic acid grouping, the method employed for the preparation of the hydroxamic acids mentioned above. The only other cyclic hydroxamic acid known to us,

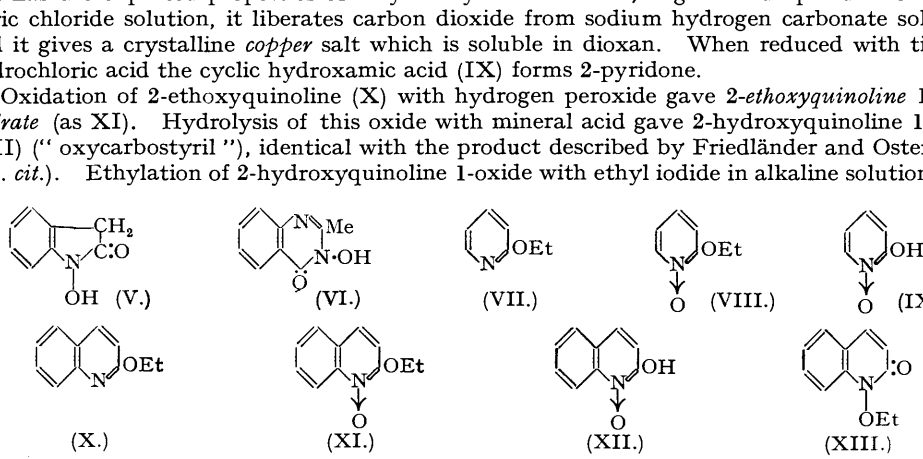


4-hydroxy-2-methylquinazoline 3-oxide (VI) was obtained by treatment of acetylanthranil with hydroxylamine (Anschutz, Schmidt, and Greiffenberg, *Ber.*, 1902, **35**, 3480).

In attempts to prepare a cyclic hydroxamic acid related to quinoxaline, it was found that 2-hydroxyquinoxaline is smoothly oxidised to 2 : 3-dihydroxyquinoxaline and, furthermore, that oxidation of 2-ethoxyquinoxaline gave 3-ethoxyquinoxaline 1-oxide and not 2-ethoxyquinoxaline 1-oxide (Newbold and Spring, this vol., p. 519). Similar oxidation of 2-ethoxy- and 2-chloro-pyrazine derivatives gave the corresponding 4-oxides and not the required 1-oxides (Baxter, Newbold, and Spring, this vol., p. 1859). More successful were attempts to oxidise pyridine and quinoline derivatives.

Treatment of 2-ethoxypyridine (VII) with hydrogen peroxide in acetic acid gives 2-*ethoxypyridine* 1-*oxide* (VIII), characterised by the preparation of its *picrate*. Hydrolysis of 2-ethoxypyridine 1-oxide with dilute hydrochloric acid gives 2-*hydroxypyridine* 1-*oxide* (IX); this has the expected properties of a cyclic hydroxamic acid, it gives a deep red colour with ferric chloride solution, it liberates carbon dioxide from sodium hydrogen carbonate solution, and it gives a crystalline *copper* salt which is soluble in dioxan. When reduced with tin and hydrochloric acid the cyclic hydroxamic acid (IX) forms 2-pyridone.

Oxidation of 2-ethoxyquinoline (X) with hydrogen peroxide gave 2-*ethoxyquinoline* 1-*oxide hydrate* (as XI). Hydrolysis of this oxide with mineral acid gave 2-hydroxyquinoline 1-oxide (XII) (" oxycarbostyril "), identical with the product described by Friedländer and Ostermaier (*loc. cit.*). Ethylation of 2-hydroxyquinoline 1-oxide with ethyl iodide in alkaline solution gives



the ethyl derivative, m. p. 71—72°, previously described by Friedländer and Ostermaier. Although this compound has the same m. p. as 2-ethoxyquinoline 1-oxide it is quite distinct from the latter and it is, probably, 2-keto-1-ethoxy-1 : 2-dihydroquinoline (XIII). Unlike 2-ethoxyquinoline 1-oxide, it is recovered unchanged after being heated with hydrochloric acid.

Antibacterial tests were made on three of the cyclic hydroxamic acids mentioned in this paper; the results are shown below :

Compound.	Minimal inhibitory concentration in mg. per 100 ml. of broth.		
	Strep. hæm.	*Staph. aureus.*	*B. coli.*
2-Hydroxypyridine 1-oxide	1	10	20
2-Hydroxyquinoline 1-oxide.....	0·1	2	1
4-Hydroxy-2-methylquinazoline 3-oxide	1	50	20

The three compounds were also tested against a bovine-type *M. tuberculosis*. With sub-surface culture in Dubos–albumin–Tween medium the first two inhibited growth at a minimum concentration of 1 : 40,000.

We are indebted to Dr. James Walker of the National Institute for Medical Research who arranged the antibacterial tests.

Experimental.

2-Ethoxyquinoline 1-Oxide.—A solution of 2-ethoxyquinoline (6·0 g.) in glacial acetic acid (50 c.c.) was treated with hydrogen peroxide (100-vol., 50 c.c.) and kept at 56° for 16 hours. The mixture was evaporated under reduced pressure, made alkaline by addition of sodium hydroxide solution, and extracted with chloroform, and the dried (Na_2SO_4) extract evaporated. The residue was dissolved in

light petroleum (b. p. 40—60°), from which the *hydrate* of 2-ethoxyquinoline 1-oxide separated as needles; after two recrystallisations from ether it had m. p. 71—73° (1·8 g.) (Found: C, 63·6; H, 6·5. $C_{11}H_{11}O_2N,H_2O$ requires C, 63·8; H, 6·3%). It is soluble in water, alcohols, chloroform, and benzene. The *picrate* separated from ethanol as yellow needles, m. p. 124—125° (Found: C, 48·8; H, 3·2; N, 13·2. $C_{17}H_{14}O_9N_4$ requires C, 48·8; H, 3·35; N, 13·4%).

2-*Hydroxyquinoline* 1-*Oxide*.—A solution of 2-ethoxyquinoline 1-oxide (0·5 g.) in ethanol (4 c.c.) and 3N-hydrochloric acid (8 c.c.) was refluxed for 2 hours. The ethanol was removed by distillation and the crystalline solid separating was collected and recrystallised from water to yield 2-hydroxyquinoline 1-oxide as plates, m. p. 189—190° not depressed when mixed with a specimen prepared as described by Friedländer and Ostermaier (*loc. cit.*). This oxide dissolves in cold sodium hydrogen carbonate solution with liberation of carbon dioxide and gives a deep red colour with ferric chloride in aqueous-alcoholic solution (Found: C, 67·1; H, 4·5. Calc. for $C_9H_7O_2N$: C, 67·1; H, 4·3%).

2-*Keto*-1-*ethoxy*-1 : 2-*dihydroquinoline*.—A solution of 2-hydroxyquinoline 1-oxide (180 mg.) in ethanol (5 c.c.) was treated with potassium hydroxide solution (7%; 1 c.c.) and ethyl iodide (0·25 c.c.) and heated under reflux for 2 hours. The alcohol was evaporated (reduced pressure), and the mixture diluted with 10% potassium hydroxide solution and extracted with ether. The ether was removed from the dried extract and the residue crystallised from light petroleum (b. p. 60—80°), from which 2-keto-1-ethoxy-1 : 2-dihydroquinoline separated as needles (160 mg.), m. p. 71—72°. A mixture with 2-ethoxyquinoline 1-oxide (m. p. 71—73°) melted between 45° and 55°. 2-Keto-1-ethoxy-1 : 2-dihydroquinoline was recovered unchanged after being heated under reflux for 12 hours with excess of 5N-hydrochloric acid (Found: C, 70·1; H, 5·9. Calc. for $C_{11}H_{11}O_2N$: C, 69·8; H, 5·8%).

2-*Ethoxypyridine* 1-*Oxide*.—2-Ethoxypyridine has been prepared by treatment of 2-pyridone in alkaline solution with ethyl iodide (Pechmann and Baltzer, *Ber.*, 1891, **24**, 3148) and by treatment of 2-aminopyridine with nitrous acid in the presence of ethanol (Tschitschibabin and Rjasanzew, *J. Russ. Phys. Chem. Soc.*, 1915, **47**, 1580). The following method was found to be satisfactory: A solution of 2-bromopyridine (79 g.) in ethanolic sodium ethoxide (13·8 g. of sodium in 250 c.c. of ethanol) was refluxed for 8 hours. The product was distilled and the fraction boiling at 150—170°/755 mm. was treated with ethanolic picric acid, and the picrate recrystallised from ethanol, from which it separated as prismatic needles, m. p. 131—133° (41 g.) (Found: C, 44·7; H, 3·3. Calc. for $C_{13}H_{12}O_8N_4$: C, 44·3; H, 3·4%). The picrate was decomposed with lithium hydroxide to give 2-ethoxypyridine, b. p. 51°/11 mm. (13·5 g.; 33% allowing for recovered 2-bromopyridine).

A solution of 2-ethoxypyridine (6 g.) in glacial acetic acid (40 c.c.) was treated with hydrogen peroxide (100-vol., 40 c.c.) and kept at 56° for 20 hours. The mixture was evaporated under reduced pressure, and the residue made alkaline by addition of ice-cold 3N-potassium hydroxide. The mixture was extracted with chloroform (3 × 35 c.c.). The dried (Na_2SO_4) extract was evaporated, and the crystalline residue recrystallised from dioxan–ether to give 2-*ethoxypyridine* 1-*oxide monohydrate* as prismatic needles, m. p. 49—52°. After drying in a vacuum over phosphoric oxide for 24 hours it has m. p. 71—73°; it is extremely hygroscopic, a property which made analysis very difficult (Found: C, 58·8; H, 6·5. $C_7H_9O_2N$ requires C, 60·4; H, 6·5. $C_7H_9O_2N,H_2O$ requires C, 53·2; H, 7·0%). The *picrate* separates from ethanol as yellow needles, m. p. 111—113° (Found: C, 42·5; H, 3·4. $C_{13}H_{12}O_9N_4$ requires C, 42·4; H, 3·3%).

2-*Hydroxypyridine* 1-*Oxide*.—2-Ethoxypyridine 1-oxide (0·6 g.) was heated under reflux with hydrochloric acid (3N, 10 c.c.), and the mixture evaporated under reduced pressure. The residue was kept at 100°/10 mm. until it was solid. Sublimation at 100°/0·001 mm. gave 2-*hydroxypyridine* 1-*oxide* (350 mg.) as a crystalline mass, m. p. 149—151°; when recrystallised from dioxan–benzene it separated as blades. It is readily soluble in hot water and ethanol and insoluble in benzene, chloroform, and ether. An ethanolic solution of the hydroxamic acid gives a deep cherry-red coloration with aqueous ferric chloride solution; it dissolves readily in cold saturated sodium hydrogen carbonate solution with evolution of carbon dioxide (Found: C, 53·7; H, 4·8; N, 12·2; equiv., 114. $C_5H_6O_2N$ requires C, 54·0; H, 4·5; N, 12·6%; equiv., 111).

A concentrated aqueous solution of 2-hydroxypyridine 1-oxide was treated with a slight excess of a saturated solution of copper acetate. The *copper* salt was collected and recrystallised from dioxan, from which it separates as light blue prismatic needles, m. p. 292—294° (decomp.) [Found: C, 42·4; H, 2·8. $(C_5H_4O_2N)_2Cu$ requires C, 42·3; H, 2·8%].

A solution of the copper salt (200 mg.) in hot dioxan was diluted with water (10 c.c.) and saturated with hydrogen sulphide. The mixture was evaporated to dryness, and the residue extracted with hot ethanol. The filtered extract was evaporated to dryness, and the residue sublimed to yield 2-hydroxypyridine 1-oxide (120 mg.), m. p. and mixed m. p. 149—151°.

2-*Pyridone*.—A solution of 2-hydroxypyridine 1-oxide (300 mg.) in hydrochloric acid (*d* 1·19; 3 c.c.) was treated with granulated tin (3 g.) and heated on the water-bath for 5 hours, concentrated hydrochloric acid (1 c.c.) being added every hour. The solution was decanted, and the metal washed with distilled water. The combined solution and washings were evaporated to dryness (reduced pressure) and the solid residue suspended in warm water (30 c.c.) and treated with excess of hydrogen sulphide. The mixture was filtered, and the filtrate evaporated to dryness under reduced pressure. The residual solid was dissolved in water, the solution exactly neutralised by addition of sodium hydrogen carbonate, and again evaporated to dryness. The residue was extracted with boiling benzene, and the extract concentrated and diluted with light petroleum (b. p. 40—60°), from which 2-pyridone (100 mg.) separated as long needles, m. p. 105—107°, either alone or with a specimen prepared as described by Tschitschibabin and Rjasanzew (*J. Russ. Phys. Chem. Soc.*, 1915, **47**, 1571). The mercuric chloride compound had m. p. 196—197° either alone or mixed with an authentic specimen (Pechmann and Baltzer, *loc. cit.*).

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