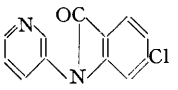
249. *Some Derivatives of* 1 : 5-*Naphthyridine.*

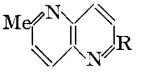
By V. Petrow and B. Sturgeon.

2-Hydroxy-6-methyl-1 : 5-naphthyridine (II; R = OH) has been converted into 2-*chloro*-6-*methyl*-1 : 5-*naphthyridine*, and hence into a number of 2-*substituted* 6-*methyl*-1 : 5-*naphthyridines*. Application of the Doebner–Miller reaction to 5-amino-*N*-methyl-2-pyridone, or methylation of (II; R = OH), gave 2-*keto*-1 : 6-*dimethyl*-1 : 2-*dihydro*-1 : 5-*naphthyridine* (III) which formed a 5-N-*oxide* and a 5-*methiodide*.

The preparation of some derivatives of 1 : 5-naphthyridine was undertaken following the discovery that certain benznaphthyridines (diazaphenanthrenes) synthesised in these laboratories (Petrow, *J.*, 1946, 200, 884, 888) showed outstanding analeptic activity (Thorp, Ph.D. Thesis, London University, 1947, 24). 3-Aminopyridine derivatives formed the starting point of our investigations. Their conversion into 1 : 5-naphthyridines has been described by Bobranski and Sucharda (*Ber.*, 1927, **60**, 1082), who applied the Skraup reaction to 3-aminopyridine, by Adams *et al.* (*J. Amer. Chem. Soc.*, 1946, **68**, 1317), who condensed the same amine with ethyl ethoxymethylenemalonate, and by Räth, whose work is referred to later. The recent claim of Price and Roberts (*J. Org. Chem.*, 1946, **11**, 463) to have converted 5-chloro-*N*-(3′-pyridyl)anthranilic acid, prepared from 3-aminopyridine and 2 : 4-dichlorobenzoic acid, into 2-chloro-5-aza-acridone must be accepted with caution, for earlier attempts (Kermack and Weatherhead, *J.*, 1942, 726; Petrow, *J.*, 1945, 927) to enforce ring closure of *N*-(3′-pyridyl)anthranilic acid were not successful. The chemical properties of their compound,

and in particular its anomalous reaction with phosphorus oxychloride, would appear to indicate its formulation as the corresponding "anthranil" (I).


(I.)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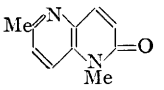
(III.)

Räth (G.P. 507,637) has shown that 5-amino-2-hydroxypyridine hydrochloride undergoes the Skraup and the Doebner–Miller reaction, but the preparation of this intermediate by the published route (G.P. 596,725) is somewhat tedious. We now find that 5-nitro-2-hydroxypyridine is conveniently reduced by the use of reduced iron in acidified water to 5-amino-2-hydroxypyridine, characterised by conversion into both the *mono-* and the *di-benzoyl* derivative. Further, application of the Skraup and the Doebner–Miller reaction to this base has given the corresponding 2-hydroxy-1 : 5-naphthyridine and 2-hydroxy-6-methyl-1 : 5-naphthyridine (II; R = OH) in yields considerably higher than those claimed by Räth. The structure of these compounds is clearly open to question, for ring closure may occur in either the 6- or the 4-position of the pyridine ring. The former alternative was preferred by Räth, and his assumption is supported by the established behaviour of 3-aminopyridine in the Skraup reaction (Bobranski and Sucharda, *loc. cit.*). Numerous attempts on our part rigidly to prove the structure of these compounds have been unsuccessful.

Treatment of (II; R = OH) with phosphorus oxychloride gave 2-*chloro*-6-*methyl*-1 : 5-*naphthyridine* (II; R = Cl), which, by reaction with the appropriate bases, was converted into 2-*anilino*-, 2-p-*chloroanilino*-, 2-*piperidino*-, and 2-*methoxy*-6-*methyl*-1 : 5-*naphthyridine*. The last compound was characterised by conversion into a *mono*-N-*oxide* by McIlwain's method (*J.*, 1943, 324). 2-n-*Butoxy*-6-*methyl*-1 : 5-*naphthyridine* was also prepared as it shows a structural analogy to the tuberculostatic pyridines recently described by Friedman *et al.* (*J. Amer. Chem. Soc.*, 1947, **69**, 1204). Attempts to obtain the amino-derivative by passage of dry ammonia through a solution of (II; R = Cl) in phenol at 180° failed to give the desired compound, 2-*phenoxy*-6-*methyl*-1 : 5-*naphthyridine* being formed in high yield; also (II; R = Cl) failed to react with N^4-acetylsulphanilamide in nitrobenzene solution in the presence of copper bronze and potassium carbonate.

Application of the Doebner–Miller reaction to 5-amino-*N*-methyl-2-pyridone gave a compound, readily isolated as the *picrate*, to which the structure of a 2-*keto*-1 : 6-*dimethyl*-1 : 2-*dihydro*-1 : 5-*naphthyridine* (III) has been assigned. This constitution is preferred following its synthesis from 2-hydroxy-6-methyl-1 : 5-naphthyridine by methylation with methyl sulphate. The pyridone (III) has been converted into a *monomethiodide* and into a *mono*-N-*oxide*, both of which undoubtedly have the 5-*N*-structures as *N*-methyl-2-pyridones fail to form true quaternary salts (Borsche and Bonacker, *Ber.*, 1921, **54**, 2678). Attempts to convert (III) into 2-chloro-6-methyl-1 : 5-naphthyridine by heating with phosphorus oxychloride gave a black crystalline solid in very low yield. In appearance it resembled a cyanine dye and was probably a compound of this type, for methincyanines are formed by the reaction of a picoline and an *N*-methylpyridone in the presence of phosphorus pentachloride (Moir, *J.*, 1925, **127**, 2338).

Biological examination of the above compounds failed to reveal outstanding activity.

Experimental.

(M. p.s are corrected. Microanalyses by Drs. Weiler and Strauss, Oxford.)

Dibenzoyl Derivative of 5-Amino-2-hydroxypyridine.—A solution of 5-nitro-2-hydroxypyridine (5 g.) (Caldwell and Kornfeld, *J. Amer. Chem. Soc.*, 1942, **64**, 1696) in water (45 ml.) and concentrated hydrochloric acid (1 ml.) was treated at the boiling point with reduced iron (15 g.) added in portions. When the initial reaction had subsided the mixture was heated under reflux for 1 hour, filtered, and the filtrate and washings taken to dryness under reduced pressure. The red gum so obtained was dissolved in pyridine (40 ml.) and benzoylated by heating with benzoyl chloride (5 g.) for 1 hour at 100°. The *dibenzoyl* derivative of 5-amino-2-hydroxypyridine (3 g.), colourless needles, m. p. 218·5° (Found : C, 71·4; H, 4·9; N, 9·0. $C_{19}H_{14}O_3N_2$ requires C, 71·7; H, 4·4; N, 8·8%), from ethanol–ligroin, separated on addition of water.

5-*Benzamido*-2-*hydroxypyridine.*—The foregoing dibenzoyl derivative (800 mg.), spirit (10 ml.), water (5 ml.), and concentrated hydrochloric acid (10 ml.) were heated under reflux for 30 minutes. The spirit was evaporated, and the product precipitated by the addition of ammonium hydroxide. 5-*Benzamido*-2-*hydroxypyridine* separated from ethanol–light petroleum in colourless needles, m. p. 257° (decomp.) (Found : C, 67·3; H, 4·8; N, 12·8. $C_{12}H_{10}O_2N_2$ requires C, 67·3; H, 4·7; N, 13·1%). The compound was readily soluble in dilute potassium hydroxide solution.

2-*Hydroxy*-1 : 5-*naphthyridine.*—A mixture of 5-amino-2-hydroxypyridine [prepared by reduction

of the nitro-compound (20 g.)], dry glycerol (40 g.), arsenic pentoxide (20 g.), and concentrated sulphuric acid (20 ml.) was heated in an oil-bath at 160° for 45 minutes with occasional stirring. The melt was extracted with boiling 2N-hydrochloric acid (200 ml.), and the filtrate concentrated and basified with ammonium hydroxide. 2-Hydroxy-1 : 5-naphthyridine crystallises from aqueous spirit (charcoal) in colourless needles, m. p. 259° (Found : N, 18·7. Calc. for $C_8H_6ON_2$: N, 19·2%); yield 3·3 g. (15%). Räth (*loc. cit.*) records m. p. 258°.

2-*Hydroxy*-6-*methyl*-1 : 5-*naphthyridine* (II; R = OH).—5-Amino-2-hydroxypyridine, prepared by reduction of 10 g. of the nitro-base, was dissolved in concentrated hydrochloric acid (50 ml.), and the solution treated with acetaldehyde (12 g.) whilst cooled in ice. After 1 hour at 0°, the mixture was heated under reflux for 1 hour. The solids precipitated by basification with ammonium hydroxide were extracted with spirit (50 ml.) and water (300 ml.) (charcoal), and the filtrate concentrated, whereupon almost colourless platelets of 2-hydroxy-6-methyl-1 : 5-naphthyridine separated, m. p. 261—262° (Found : N, 17·3. Calc. for $C_9H_8ON_2$: N, 17·5%). The yield (3·2 g., 27%) was not improved by addition of zinc chloride to the reaction mixture. Räth (*loc. cit.*) gives m. p. 260°.

2-*Chloro*-6-*methyl*-1 : 5-*naphthyridine* (II; R = Cl).—The hydroxy-compound (II; R = OH) (1·1 g.) and phosphorus oxychloride (10 ml.) were heated under reflux for 45 minutes. The cooled mixture was poured on ice–ammonium hydroxide, and the precipitated solids collected. 2-*Chloro*-6-*methyl*-1 : 5-*naphthyridine* separated from benzene–ligroin in colourless prisms (1·0 g.), m. p. 181—182° (Found : Cl, 19·6. $C_9H_7N_2Cl$ requires Cl, 19·9%).

2-*Anilino*-6-*methyl*-1 : 5-*naphthyridine* (II; R = NHPh).—The foregoing chloro-compound (1·2 g.) was heated with aniline (15 ml.) under reflux for 2 hours. Dilute sodium hydroxide solution was added, and excess of aniline removed in steam. The residue was recrystallised from benzene–ligroin, giving 2-*anilino*-6-*methyl*-1 : 5-*naphthyridine* (1·5 g.) as pale yellow platelets, m. p. 202—203° (Found : C, 76·6; H, 5·5; N, 17·9. $C_{15}H_{13}N_3$ requires C, 76·6; H, 5·5; N, 17·9%).

2-p-*Chloroanilino*-6-*methyl*-1 : 5-*naphthyridine*.—2-Chloro-6-methyl-1 : 5-naphthyridine (1·3 g.), *p*-chloroaniline (2 g.), and nitrobenzene (10 ml.) were heated at the boiling point for 5 minutes and then at 170—180° for 30 minutes. The solids which separated were collected, washed with benzene, and dissolved in alcoholic hydrochloric acid. 2-p-*Chloroanilino*-6-*methyl*-1 : 5-*naphthyridine*, pale yellow plates from aqueous spirit, m. p. 237·5—238° (Found : C, 66·6; H, 4·5; N, 15·3; Cl, 13·7. $C_{15}H_{12}N_3Cl$ requires C, 66·8; H, 4·5; N, 15·6; Cl, 13·2%), separated (66%) on basification with aqueous potassium hydroxide solution.

2-*Piperidino*-6-*methyl*-1 : 5-*naphthyridine*.—The naphthyridine (II; R = Cl) (5 g.) and piperidine (10 ml.) were heated at 175—185° for 7 hours in a sealed tube. Excess of piperidine was removed on the water-bath, and the base liberated with sodium hydroxide and converted into the picrate. 2-*Piperidino*-6-*methyl*-1 : 5-*naphthyridine picrate* (3·8 g. 30%) separated from spirit in silky yellow needles, m. p. 199—199·5° (Found : N, 18·7. $C_{14}H_{17}N_3,C_6H_3O_7N_3$ requires N, 18·4%). The free *base* crystallised from light petroleum (b. p. 40—60°) in pale yellow rhombs, m. p. 62—64° (Found : C, 74·3; H, 7·3; N, 18·5. $C_{14}H_{17}N_3$ requires C, 74·0; H, 7·5; N, 18·5%).

2-*Phenoxy*-6-*methyl*-1 : 5-*naphthyridine*.—Dry ammonia was passed through a solution of 2-chloro-6-methyl-1 : 5-naphthyridine (4·5 g.) in phenol (15 g.) at 180° for 7 hours. Dilute sodium hydroxide solution was stirred into the melt, and the solids were collected and washed with water. 2-*Phenoxy*-6-*methyl*-1 : 5-*naphthyridine* was obtained from light petroleum (b. p. 60—80°) in pearly platelets, m. p. 101·5—103·5° (Found : C, 76·1; H, 5·1; N, 11·7. $C_{15}H_{12}ON_2$ requires C, 76·3; H, 5·1; N, 11·9%).

2-*Methoxy*-6-*methyl*-1 : 5-*naphthyridine* (II; R = OMe).—To a boiling solution of sodium (0·3 g.) in absolute methanol (20 ml.), 2-chloro-6-methyl-1 : 5-naphthyridine (1·5 g.) was added, and the mixture heated under reflux for 7 hours. Addition of water, followed by evaporation of the methanol, gave an oil which was isolated with chloroform and purified by two distillations under 20 mm. pressure. 2-*Methoxy*-6-*methyl*-1 : 5-*naphthyridine* was obtained (75%) as a cream-coloured solid, m. p. 53—54° (Found : C, 69·1; H, 5·9; N, 15·8. $C_{10}H_{10}ON_2$ requires C, 69·0; H, 5·7; N, 16·1%).

2-n-*Butoxy*-6-*methyl*-1 : 5-*naphthyridine*, prepared from (II; R = Cl) and *n*-butanol, formed an ivory-coloured mass, m. p. 37° (Found : C, 72·0; H, 7·8; N, 12·9. $C_{13}H_{16}ON_2$ requires C, 72·2; H, 7·4; N, 13·0%).

2-*Methoxy*-6-*methyl*-1 : 5-*naphthyridine* N-*Oxide*.—The base (2 g.), hydrogen peroxide (2 ml., 100-vol.), and acetic acid (5 ml.) were warmed at *ca.* 70° for 3 hours. Dilution with water precipitated a yellow product which was filtered off, dried, and extracted with boiling light petroleum (b. p. 100—120°). Concentration of the solution deposited thick, colourless rods of 2-*methoxy*-6-*methyl*-1 : 5-*naphthyridine* N-*oxide* (800 mg.), m. p. 154° (Found : C, 63·3; H, 5·2; N, 14·5. $C_{10}H_{10}O_2N_2$ requires C, 63·2; H, 5·3; N, 14·7%).

2-*Keto*-1 : 6-*dimethyl*-1 : 2-*dihydro*-1 : 5-*naphthyridine* (III).—(*a*) A solution of 5-nitro-*N*-methyl-2-pyridone (Räth, *Annalen*, 1930, **484**, 57) (10 g.) in spirit (100 ml.) and concentrated hydrochloric acid (0·5 ml.) was treated with reduced iron (30 g.) at the boiling point. After 1 hour under reflux the filtrate and washings were taken to dryness under reduced pressure. The residual amine was dissolved in concentrated hydrochloric acid (50 ml.), and the solution kept overnight with paraldehyde (7·5 g.). It was then heated under reflux for 2 hours, and the product was isolated by basification with ammonia, extracted with chloroform, and finally converted into the picrate. 2-*Keto*-1 : 6-*dimethyl*-1 : 2-*dihydro*-1 : 5-*naphthyridine picrate* (5·1 g., 30%) separated from spirit (charcoal) in yellow needles, m. p. 189—190° (Found : C, 47·5; H, 3·3; N, 17·1. $C_{10}H_{10}ON_2,C_6H_3O_7N_3$ requires C, 47·6; H, 3·2; N, 17·4%). The *base* formed colourless needles from ligroin, m. p. 136° (Found : C, 68·9; H, 5·9; N, 16·2. $C_{10}H_{10}ON_2$ requires C, 69·0; H, 5·7; N, 16·1%).

(*b*) 2-Hydroxy-6-methyl-1 : 5-naphthyridine (1·5 g.) was dissolved in aqueous potassium hydroxide solution (0·6 g. in 30 ml. water) by warming, and the solution shaken for 8 hours at room temperature with methyl sulphate (1·3 g.). The solution was acidified with dilute hydrochloric acid, basified with ammonium hydroxide, and the product isolated with chloroform. 2-Keto-1 : 6-dimethyl-1 : 2-dihydro-1 : 5-naphthyridine (Found : C, 68·8; H, 5·9; N, 16·0%) was obtained, identical in m. p. and mixed m. p. with the compound prepared by method (*a*).

2-*Keto*-1 : 6-*dimethyl*-1 : 2-*dihydro*-1 : 5-*naphthyridine* 5-*Methiodide*.—The base (1·2 g.) and methyl iodide (1·1 g.) were heated under reflux for 16 hours in ethanol (15 ml.). Dilution of the warm solution with ether precipitated the crude *methiodide* which was purified by washing with benzene; it crystallised from ethanol in yellow micro-needles (400 mg.), m. p. 213·5—215·5° (decomp.) (Found: I, 40·8. $C_{11}H_{13}ON_2I$ requires I, 40·2%).

2-*Keto*-1 : 6-*dimethyl*-1 : 2-*dihydro*-1 : 5-*naphthyridine* 5-N-*Oxide*.—The pyridone (III) (2 g.), hydrogen peroxide (2·5 ml., 100-vol.) and acetic acid (5 ml.) were warmed at 70° for 2 hours. Basification with ammonium hydroxide, followed by extraction with chloroform, gave the N-*oxide* (1·1 g.), cream needles from ethanol, m. p. 246·5° (Found: C, 63·5; H, 5·3; N, 14·5. $C_{10}H_{10}O_2N_2$ requires C, 63·2; H, 5·3; N, 14·7%).

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QUEEN MARY COLLEGE (UNIVERSITY OF LONDON), E.1. [*Received, November 5th,* 1948.]