40. *Naphthyridines. Part III.* Hydroxynaphthyridines.*

By E. P. Hart.

Nitration and bromination of 2- and 4-hydroxy-1 : 5-naphthyridine have afforded mononitro- and monobromo-derivatives in which by analogies the substituent is regarded as being at position 3. The structure of 4-hydroxy-3-nitro-1 : 5-naphthyridine has been proved by unambiguous synthesis.

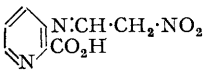
Substitution in the nucleus in hydroxynaphthyridines has been but little studied. No instance of halogenation has been described, and only one of nitration.[1] In the present work nitration of 2- and 4-hydroxy-1 : 5-naphthyridine with fuming nitric and sulphuric acids has given mononitro-derivatives. Likewise bromination in aqueous solution gave monobromo-derivatives, though perbromides are formed in alcohol or carbon tetrachloride. The substituting group in the above derivatives is regarded as being at position 3 by analogy

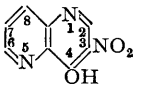
* Part II, *J.*, 1954, 4030.

[1] Mangini, *Boll. sci. Fac. Chim. ind. Bologna*, 1940, 165; *Chem. Zentr.*, 1940, II, 2613; *Chem. Abs.*, 1942, **36**, 5476.

with the corresponding products from hydroxy-pyridines and -quinolines,[2] and the structure of 4-hydroxy-3-nitro-1 : 5-naphthyridine (II) has been established by synthesis.

Several workers [3] have synthesised 4-hydroxy-3-nitroquinolines by reaction of methazonic acid with anthranilic acids, with subsequent cyclisation of the intermediate nitroethylideneamino-compounds. Schofield and Theobald [4] applied this reaction also to the formation of 4-aryl-3-nitroquinolines. With anthranilic acids use of acetic anhydride–sodium acetate was essential for the cyclisation; even then yields were only fair. 3-Aminopyridine-2-carboxylic acid and aqueous methazonic acid gave 3-2′-nitroethylideneaminopyridine-2-carboxylic acid (I) which, when heated in this cyclising medium, afforded 4-hydroxy-3-nitro-1 : 5-naphthyridine (II), identical with the compound obtained by direct nitration of 4-hydroxy-1 : 5-naphthyridine.

(I) 

 (II)

The hydroxynaphthyridines required were obtained by Skraup reactions from amino-hydroxypyridines. 3-Amino-4-hydroxypyridine gave 4-hydroxy-1 : 5-naphthyridine (see Part I [5]); 5-amino-2-hydroxypyridine has previously been obtained, as a red gum, by Petrow and Sturgeon,[6] who reduced 2-hydroxy-5-nitropyridine with iron in acidulated water; in the present work hydrogenation of the nitro-base over palladised charcoal has given a much cleaner product, which is extremely sensitive to oxidation. The overall yield of 2-hydroxy-1 : 5-naphthyridine from 2-hydroxy-5-nitropyridine has been raised by this method to 57%.

Experimental

5-Amino-2-hydroxypyridine.—2-Hydroxy-5-nitropyridine [7] (2 g.), suspended in methano (150 ml.), was hydrogenated in the presences of 10% palladised charcoal (2 g.). After the theoretical volume of hydrogen had been absorbed (2 hr.) the yellow solution was filtered rapidly, and evaporated under reduced pressure. Colourless crystals of the amino-base separated but were extremely sensitive to oxidation and could not be further purified. The dibenzoyl derivative crystallised from aqueous alcohol, m. p. 217°. Petrow and Sturgeon [6] record m. p. 218·5°.

2-Hydroxy-1 : 5-naphthyridine.—The preceding amino-base (from 2 g. of nitro-base), arsenic acid (2 g.), glycerol (4 g.), and concentrated sulphuric acid (6 ml.) were heated to 165°. After the initial violent ebullition had ceased, the temperature was kept thereat for 1 hr., the melt was extracted with dilute hydrochloric acid (2 × 30 ml.), and the extract concentrated to low volume and basified with ammonia solution. The precipitated solids were recrystallised (charcoal) from aqueous alcohol, giving 2-hydroxy-1 : 5-naphthyridine (1·2 g., 57% based on nitro-base) as colourless needles, m. p. 256°.

Hydroxynitronaphthyridines.—(*a*) 2-Hydroxy-1 : 5-naphthyridine (0·3 g.) was heated with nitric acid (*d* 1·5; 3 ml.) and 20% oleum (3 ml.) on the water-bath for 4 hr. Pouring the cooled mixture into a small volume of water gave yellow-orange crystals. Recrystallisation from aqueous alcohol afforded orange *2-hydroxy-3-nitro-1 : 5-naphthyridine* (0·25 g.), m. p. 272—274° (Found: C, 50·1; H, 2·8; N, 21·7. $C_8H_5O_3N_3$ requires C, 50·4; H, 2·6; N, 22·0%).

(*b*) 4-Hydroxy-1 : 5-naphthyridine (0·3 g.), nitrated as above, gave no precipitate in water. The solution was basified with solid sodium hydrogen carbonate and evaporated to dryness, and the residue extracted with hot alcohol (2 × 25 ml.). Concentration of this extract gave yellow *4-hydroxy-3-nitro-1 : 5-naphthyridine*, m. p. 328—330° (decomp.) (Found: C, 50·2; H, 2·5; N, 21·7%).

Bromohydroxynaphthyridines.—(*a*) To 2-hydroxy-1 : 5-naphthyridine (0·2 g.), dissolved in warm water (5 ml.), was added dropwise saturated bromine water until no further precipitate

[2] Binz and Maier-Bode, *Angew. Chem.*, 1936, **49**, 486; Bishop, Cavell, and Chapman, *J.*, 1952, 439; Koenigs and Geigy, *Ber.*, 1884, **17**, 589; Koenigs and Fulde, *Ber.*, 1927, **60**, 2107; Crowe, *J.*, 1925, 2028; Riegel, Lappin, Albisetti, Adelson, Dodson, Ginger, and Baker, *J. Amer. Chem. Soc.*, 1946, **68**, 1229.
[3] Colonna, *Gazzetta*, 1937, **67**, 46; 1939, **69**, 684; Musajo, *ibid.*, 1937, **67**, 222.
[4] Schofield and Theobald, *J.*, 1950, 395.
[5] Hart, *J.*, 1954, 1879.
[6] Petrow and Sturgeon, *J.*, 1949, 1157.
[7] Caldwell and Kornfeld, *J. Amer. Chem. Soc.*, 1942, **64**, 1696.

formed. Pouring the product into dilute sodium carbonate solution gave 3-*bromo*-2-*hydroxy*-1 : 5-*naphthyridine* (0·22 g.) which crystallised from water as colourless needles, m. p. 295—297° (Found : C, 42·7; H, 2·0; N, 12·5; Br, 35·2. $C_8H_5ON_2Br$ requires C, 42·8; H, 2·2; N, 12·5; Br, 35·6%).

(*b*) 4-Hydroxy-1 : 5-naphthyridine (0·2 g.) similarly afforded 3-*bromo*-4-*hydroxy*-1 : 5-*naphthyridine* (0·2 g.), m. p. 318° (decomp.) (from much water) (Found : C, 43·0; H, 2·3; N, 12·2; Br, 35·6%).

3-2′-*Nitroethylideneaminopyridine*-2-*carboxylic Acid*.—To a solution of 3-aminopyridine-2-carboxylic acid [prepared from quinolinimide [8] (10 g.)], acidified with hydrochloric acid (5 ml.), was added dropwise, with stirring, a solution of potassium methazonate [prepared from nitromethane (5 g.) and 50% aqueous potassium hydroxide (10 ml.)]. After a short time a heavy crystalline precipitate formed, which on recrystallisation from aqueous alcohol (charcoal) afforded the colourless *nitroethylideneamino-compound*, m. p. 255° (decomp.) (Found : C, 45·8; H, 3·5; N, 20·3. $C_8H_7O_4N_3$ requires C, 46·0; H, 3·4; N, 20·2%).

4-*Hydroxy*-3-*nitro*-1 : 5-*naphthyridine*.—The preceding compound (1 g.) was heated with acetic anhydride (10 g.) and anhydrous sodium acetate (1 g.) on the water-bath until dissolution was complete, and then at the b. p. for 1 hr. No precipitate was formed either on cooling or pouring into water; the solution was basified with sodium hydrogen carbonate, and extracted continuously with ether. Evaporation of the dried (Na_2SO_4) extract gave yellow crystals. Crystallisation from a small volume of alcohol gave 4-hydroxy-3-nitro-1 : 5-naphthyridine, m. p. and mixed m. p. 328—330° (decomp.) (Found : C, 50·2; H, 2·5%).

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[8] Sucharda, *Ber.*, 1925, **58**, 1728.