Naphthyridines. Part I. The Chemistry of 1 : 5-*Naphthyridine.*

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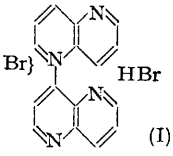
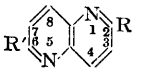
Amination of 1 : 5-naphthyridine has afforded 2-amino-1 : 5-naphthyridine. Use of bromine in chloroform gave the quaternary salt (I), which in water at 100° gave 4-hydroxy-1 : 5-naphthyridine and 1 : 5-naphthyridine. Oxidation of 1 : 5-naphthyridine with peracetic acid afforded the 1-oxide and 1 : 5-dioxide, converted by phosphoryl chloride into mono- and di-chloro-1 : 5-naphthyridine respectively, the dichloro-compound being characterised by conversion into the dianilino-derivative. Mono- and di-chloro-1 : 5-naphthyridine with toluene-*p*-sulphonhydrazide gave adducts, which decomposed in alkali to give 1 : 5-naphthyridine.

There are theoretically six isomeric naphthyridines (diazanaphthalenes) formed by the fusion of two pyridine nuclei, but only the 1 : 5- and the 1 : 8-isomers have been reported, otherwise than as derivatives (Allen, *Chem. Reviews*, 1950, **47**, 275). Moreover, no chemistry of the naphthyridine system itself, except hydrogenation of 1 : 5-naphthyridine (Miyaki, *J. Pharm. Soc. Japan*, 1942, **62**, 257), is recorded although a considerable amount of synthetic work, leading to naphthyridine derivatives, has been published (see particularly Ochiai and Miyaki, *Ber.*, 1937, **70**, 2081; 1941, **74**, 1115; *J. Pharm. Soc. Japan*. 1938, **58**, 764; Miyaki, *loc. cit.*; Price and Roberts, *J. Amer. Chem. Soc.*, 1946, **68**, 1204; Petrow and Sturgeon, *J.*, 1949, 1157; Hauser and Reynolds, *J. Org. Chem.*, 1950, **15**, 1224; Albert and Hampton, *J.*, 1952, 4985). It seemed therefore that a study of the syntheses and chemistry of the naphthyridine bases would be of interest. In this paper are recorded some reactions of 1 : 5-naphthyridine.

The base was prepared by the method of Bobranksi and Sucharda (*Ber.*, 1927, **60**, 1081; *Roczn. Chem.*, 1927, **7**, 241), who do not record the yield; Hauser and Reynolds (*loc. cit.*) record 27%. In the present work the yield has been raised by using a shorter reaction time. Attempted nitration, with a range of concentrated and fuming acids, gave unchanged starting material. Bromine in cold chloroform gave, in high yield, the quaternary 1-(1 : 5-naphthyridin-4-yl)-1 : 5-naphthyridinium bromide hydrobromide (I), hydrolysed



(I)



(II)

in water at 100° to 1 : 5-naphthyridine and 4-hydroxy-1 : 5-naphthyridine. The latter compound has been prepared by decarboxylation of 4-hydroxy-1 : 5-naphthyridine-2 : 3-dicarboxylic acid (Bobranski and Sucharda, *loc. cit.*) and from 3-aminopyridine by the ethoxymethylenemalonic ester method (Adams, Bradsher, Breslow, Amore, and Hauser, *J. Amer. Chem. Soc.*, 1946, **68**, 1317); in the present work it was prepared by a Skraup reaction on 3-amino-4-hydroxypyridine. 1 : 5-Naphthyridine with sodamide in liquid ammonia at room temperature afforded 2-amino-1 : 5-naphthyridine (II; R = NH_2, R′ = H), whence nitrous acid yielded 2-hydroxy-1 : 5-naphthyridine (II; R = OH, R′ = H). This was identical with the hydroxynaphthyridine obtained by Petrow and Sturgeon's method (*loc. cit.*) from a Skraup reaction on 5-amino-2-hydroxypyridine; the structure of (II; R = OH, R′ = H) is thus established.

Treatment of 1 : 5-naphthyridine with hydrogen peroxide in acetic acid solution gave the 1 : 5-dioxide. By the use of peracetic acid (Byers and Hickinbottom, *J.*, 1948, 286) the degree of oxidation could be controlled to produce the 1 : 5-dioxide and the 1-oxide. Only one instance of *N*-oxide formation in the naphthyridine series is recorded in the literature (Petrow and Sturgeon, *loc. cit.*). These compounds are of biological interest because of their resemblance to the quinoxaline *N*-oxides (McIlwain, *J.*, 1943, 322; Landquist, *J.*, 1953, 2816). Phosphoryl chloride and the monoxide gave 2-chloro-1 : 5-naphthyridine (II; R = Cl, R′ = H), which on hydrolysis afforded 2-hydroxy-1 : 5-naphthyridine. The 1 : 5-dioxide under similar conditions afforded a dichloro-1 : 5-naphthyridine to which the 2 : 6-structure is assigned, by analogy with the product from the monoxide. For dichloro-1 : 8-naphthyridine, conversion into the dihydrazino-derivative and subsequent treatment with nitrous acid to form a bistetrazolo-derivative established the orientation (Seide, *Ber.*, 1926, **59**, 2465); in the present work repeated attempts to obtain the dihydrazino-derivative failed. Hydrolysis of 2 : 6-dichloro-1 : 5-naphthyridine gave 2 : 6-dihydroxy-1 : 5-naphthyridine (II; R = R′ = OH). The dianilino-derivative was prepared by heating 2 : 6-dichloro-1 : 5-naphthyridine with aniline.

The method used by Albert and Royer (*J.*, 1949, 1148) for the removal of active chlorine atoms from the acridine nucleus was applied to 2-chloro- and 2 : 6-dichloro-1 : 5-naphthyridine, and in both cases yielded adducts which decomposed in alkali, forming 1 : 5-naphthyridine.

1 : 5-Naphthyridine and its 1 : 5-dioxide were found by Dr. A. T. Fuller not to be notably active against *Streptococcus haemolyticus*, *Staphylococcus aureus*, and *B. coli*.

Experimental

All extracts were dried with anhydrous sodium sulphate.

1 : 5-*Naphthyridine*.—3-Aminopyridine (*Org. Synth.*, **30**, 3) (15 g.), anhydrous glycerol (60 g.), arsenic acid (20 g.), and concentrated sulphuric acid (55 g.) were heated to 170° (oil-bath). Vigorous ebullition occurred, after which the temperature was kept at 170° for 2 hr. The mixture was then treated by Bobranski and Sucharda's method (*loc. cit.*). 1 : 5-Naphthyridine, pale yellow needles, m. p. 72° (7·5 g., 36%), separated from light petroleum (b. p. 40—60°) (Found: N, 21·4. Calc. for $C_8H_6N_2$: N, 21·5%).

1-(1 : 5-*Naphthyridin*-4-*yl*)-1 : 5-*naphthyridinium Bromide Hydrobromide* (I).—To a solution of 1 : 5-naphthyridine (0·4 g.) in chloroform (3 ml.) was slowly added, with stirring, bromine

(0·1 ml.) in chloroform (3 ml.). After a short time yellow crystals (0·6 g.) separated. Recrystallisation from alcohol afforded the yellow *quaternary salt*, m. p. 260—262° (Found: C, 45·2; H, 3·0; N, 13·4; Br, 37·9. $C_{16}H_{12}N_4Br_2$ requires C, 45·6; H, 2·9; N, 13·4; Br, 38·0%).

4-*Hydroxy*-1 : 5-*naphthyridine*.—(*a*) The quaternary salt (0·15 g.) was refluxed in water (10 ml.) for 2 hr. The clear solution was basified with potassium hydroxide, concentrated, and extracted with ether (2 × 20 ml.). Removal of solvent gave 1 : 5-naphthyridine, m. p. and mixed m. p. 72°. Acidification of the aqueous extract, evaporation to dryness, and extraction of the residue with hot alcohol gave 4-hydroxy-1 : 5-naphthyridine, colourless prisms, m. p. and mixed m. p. 340°.

(*b*) 3-Amino-4-hydroxypyridine (2·5 g.) (prepared by Dr. E. Tittensor), glycerol (6 g.), arsenic acid (3 g.), and concentrated sulphuric acid (10 g.) were heated together to 160° (oil-bath). Violent ebullition occurred, after which the temperature was kept at 160° for 2 hr. The cooled melt was extracted with concentrated hydrochloric acid (2 × 40 ml.), filtered, and basified with potassium hydroxide. The precipitated solids were collected and recrystallised from alcohol (charcoal). 4-Hydroxy-1 : 5-naphthyridine (1·2 g., 37%) separated as colourless prisms, m. p. 340° (sinter at 325°) (Found: N, 19·6. Calc. for $C_8H_6ON_2$: N, 19·2%).

2-*Amino*-1 : 5-*naphthyridine*.—Sodium (0·1 g.) was added to a solution of ammonium nitrate (0·1 g.) in liquid ammonia (40 ml.). After the sodium had reacted, 1 : 5-naphthyridine (0·4 g.) was added, and the mixture was set aside until the ammonia had evaporated. Sodium hydroxide solution (20%; 5 ml.) was stirred with the residue, needles of the amino-base (0·35 g.) separating. The picrate, recrystallised from water, formed yellow needles, m. p. 270° (Miyaki, *loc. cit.*, gives m. p. 272°) (Found: N, 22·0. Calc. for $C_8H_7N_3,C_6H_3O_7N_3$: N, 22·4%). The amino-base, on treatment with nitrous acid, did not couple with β-naphthol to give a coloured product.

2-*Hydroxy*-1 : 5-*naphthyridine*.—The amino-base (0·2 g.) in dilute hydrochloric acid (10 ml.) was treated dropwise with sodium nitrite (0·2 g.) in water (10 ml.). Nitrous fumes were removed by boiling, and the solution was concentrated to small volume. 2-Hydroxy-1 : 5-naphthyridine crystallised from alcohol as colourless needles, m. p. 256° alone or mixed with hydroxynaphthyridine prepared by Petrow and Sturgeon's method (*loc. cit.*) (Found: N, 19·7%).

1 : 5-*Naphthyridine* 1-*Oxide*.—1 : 5-Naphthyridine (0·2 g.) and 1·2M-peracetic acid (1·3 ml.) were heated at 55° for 20 hr. The brown mixture was cooled in ice, basified with potassium hydroxide, and extracted with chloroform (3 × 15 ml.). Removal of solvent gave a yellow mixture of mono- and di-oxide. Crystallisation from *cyclo*hexane gave 1 : 5-*naphthyridine* 1-*oxide* (0·05 g.) as a waxy solid, m. p. 125—127° (Found: C, 65·1; H, 4·2. $C_8H_6ON_2$ requires C, 65·6; H, 4·1%).

1 : 5-*Naphthyridine* 1 : 5-*Dioxide*.—(*a*) 1 : 5-Naphthyridine (0·2 g.) and 1·2M-peracetic acid (4·0 ml.) were heated at 55° for 20 hr., an exothermic reaction being at first observed. The clear yellow mixture was cooled in ice, basified with potassium hydroxide, and extracted with chloroform (3 × 15 ml.). Removal of solvent gave yellow crystals (0·2 g., 80%). 1 : 5-*Naphthyridine* 1 : 5-*dioxide* separated from alcohol as yellow clusters, m. p. 299—301° (Found: C, 58·7; H, 4·0; N, 17·5. $C_8H_6O_2N_2$ requires C, 59·2; H, 3·7; N, 17·3%).

(*b*) 1 : 5-Naphthyridine (0·2 g.) in glacial acetic acid (5 ml.) was treated with hydrogen peroxide (100-vol.; 2 ml.) and heated at 50° for 20 hr. Treatment as in the previous oxidation gave yellow clusters (0·2 g.), m. p. 299—301°.

2-*Chloro*-1 : 5-*naphthyridine*.—1 : 5-Naphthyridine 1-oxide (0·05 g.), phosphoryl chloride (2 ml.), and phosphorus pentachloride (0·1 g.) were gently heated to the b. p. and kept at this temperature for 20 min. The cooled mixture was stirred with ice and aqueous ammonia, and the precipitated solids were collected (0·04 g.). Crystallisation from the minimum volume of alcohol (charcoal) gave 2-chloro-1 : 5-naphthyridine as white needles, m. p. and mixed m. p. 112° (Found: N, 17·5; Cl, 21·4. Calc. for $C_8H_5N_2Cl$: N, 17·0; Cl, 21·6%).

2 : 6-*Dichloro*-1 : 5-*naphthyridine*.—1 : 5-Naphthyridine 1 : 5-dioxide (0·15 g.) was added to phosphoryl chloride (4 ml.), cooled in ice. The mixture was refluxed for 20 min., cooled, and poured on ice and aqueous ammonia. The precipitated solids (0·1 g.) were collected and recrystallised from light petroleum (b. p. 40—60°), yielding 2 : 6-*dichloro*-1 : 5-*naphthyridine* as colourless plates, m. p. 236—238° (Found: C, 47·9; H, 1·8; N, 13·9; Cl, 36·1. $C_8H_4N_2Cl_2$ requires C, 48·3; H, 2·0; N, 14·1; Cl, 35·6%).

2 : 6-*Dihydroxy*-1 : 5-*naphthyridine*.—The above dichloro-compound (50 mg.) was suspended in 10% sodium carbonate solution (5 ml.) and refluxed for 2 hr.; evaporation to dryness and extraction of the residue with hot methyl alcohol afforded 2 : 6-*dihydroxy*-1 : 5-*naphthyridine*, colourless clusters, subliming without melting *ca.* 360° (Found: C, 59·5; H, 3·0; N, 17·1.

$C_8H_6O_2N_2$ requires C, 59·2; H, 3·7; N, 17·3%). This gave no colour with ferric chloride solution.

2 : 6-*Dianilino*-1 : 5-*naphthyridine*.—The above dichloro-compound (30 mg.) and aniline (0·1 ml.) were heated at the b. p. for 5 min. and then on the water-bath for 1 hr. Excess of aniline was removed in steam, and the residue recrystallised from light petroleum (b. p. 40—60°). The *dianilino*-derivative separated as yellow prisms, m. p. 278° (Found: C, 76·3; H, 5·1. $C_{20}H_{16}N_4$ requires C, 76·9; H, 5·2%).

Adducts from Chloronaphthyridines.—(*a*) Saturated chloroform solutions of 2-chloro-1 : 5-naphthyridine and toluene-*p*-sulphonhydrazide (Albert and Royer, *loc. cit.*) were mixed, no precipitate forming until dry hydrogen chloride was passed into the mixture. 2-(N′-*Toluene*-p-*sulphonhydrazino*)-1 : 5-*naphthyridine dihydrochloride* separated as colourless needles (Found, by titration: Cl, 18·2. $C_{15}H_{16}O_2N_4SCl_2$ requires Cl, 18·4%). This salt had an indefinite m. p. giving a yellow residue.

(*b*) 2 : 6-Dichloro-1 : 5-naphthyridine, under similar conditions, afforded 2 : 6-*di*-(N′-*toluene*-p-*sulphonhydrazino*)-1 : 5-*naphthyridine dihydrochloride* (Found: Cl, 12·3. $C_{22}H_{24}O_4N_6S_2Cl_2$ requires Cl, 12·4%).

These adducts (0·1 g.) were heated in 10% sodium hydroxide solution (5 ml.). After evolution of nitrogen had ceased, extraction with ether gave yellow needles of 1 : 5-naphthyridine, m. p. and mixed m. p. 72°.

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