266. *The Preparation of* 1 : 8-*Naphthyridines from* 2 : 6-*Diaminopyridine.*

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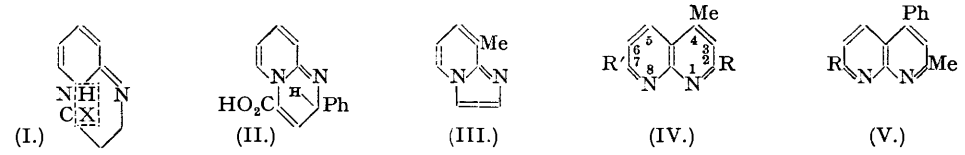
7-Amino-2-hydroxy-4-methyl-1 : 8-naphthyridine (IV; R = OH, R′ = NH_2), prepared by condensation of ethyl acetoacetate or ethyl β-aminocrotonate with 2 : 6-diaminopyridine, has been converted into 2-*chloro*-7-*acetamido*-4-*methyl*-1 : 8-*naphthyridine* (IV; R = Cl, R′ = NHAc), and hence into 2-*anilino*-, 2-p-*chloroanilino*-, 2-*piperidino*-, and 2-*phenoxy*-7-*amino*-4-*methyl*-1 : 8-*naphthyridine*.

Condensation of benzoylacetone with 2 : 6-diaminopyridine gives *7-amino-4-phenyl-2-methyl-1 : 8-naphthyridine* (V; R = NH_2), converted into *7-hydroxy-*, *7-chloro-*, and hence into *7-anilino-*, *7-piperidino-*, and *7-phenoxy-4-phenyl-2-methyl-1 : 8-naphthyridine*. (V; R = NHAc) gives the *1(N)-monoquaternary salt*.

OUR interest in the naphthyridines arose from the chance observation that certain members of the series possessed valuable biological properties (see Petrow, *J.*, 1946, 200), and a comprehensive survey of the field is now in progress in these Laboratories. The present communication describes some new derivatives of 1 : 8-naphthyridine. Biological data will be reported elsewhere.

Although 2-aminopyridine would appear to form the obvious starting point for the synthesis of 1 : 8-naphthyridines, they have not hitherto been prepared from this base. Earlier claims to this effect by Reissert (*Ber.*, 1895, **28**, 119) and Räth (*Annalen*, 1931, **486**, 284; see also E.PP. 319,974, 339,932 and G.PP. 526,630, 522,272) have been conclusively disproved by Bose and Sen (*J.*, 1931, 2840), Seide and Chelinzwen (*J. Gen. Chem. Russia*, 1937, **7**, 2314), Späth and Kuffner (*Ber.*, 1938, **71**, 1657), and Petrow (*J.*, 1945, 928). It would appear that 2-aminopyridine reacts preferentially in the imino-form [partial formula (I)] to give the pyrimidine ring system such as (II) in cases of ring closure. Reactions with ethyl acetoacetate (Crippa and Scevola, *Gazzetta*, 1937, **67**, 330), ethyl benzoylacetate (Seide, *Ber.*, 1925, **58**, 352; cf. Palazzo and Tamburini, *Atti R. Accad. Lincei*, 1911, **20**, I, 37), ethyl malonate (Tschitschibabin, *Ber.*, 1924, **57**, 1169), and ethylene oxide (Knunjanz, *Ber.*, 1935, **68**, 397) have been shown to fall into this category. The recent claim of Mazza and Migliardi (*Atti R. Accad. Sci. Torino*, 1940, **75**, I, 438; see also Migliardi, *ibid.*, p. 548) that reaction of 2-aminopyridine with benzaldehyde and pyruvic acid leads to a 4-carboxy-2-phenyl-1 : 8-naphthyridine cannot be accepted. There seems little doubt that their product should be correctly formulated as the *pyrimidine* derivative (II). Rath (*Ber.*, 1925, **58**, 347; cf. Tschitschibabin, *ibid.*, p. 1704) has described the formation of a " 1 : 2-dihydro-1 : 8-naphthyridine " in low yield from the products of reaction of 2-amino-3-methylpyridine with bromoacetal at 250°. This claim, too, must be accepted with caution, as it seems unreasonable to assume the stability of a 1 : 2-dihydro-structure under the conditions of the experiment. In our view, this reaction leads to the 8-methylpyrimidazole (III). The facile formation of ring systems of this type has been demonstrated by Schmidt and Bangler (*Ber.*, 1926, **59**, 1360), Tschitschibabin (*loc. cit.*), and Allen *et al.* (*J. Amer. Chem. Soc.*, 1944, **66**, 1805). 2-Aminopyridine behaves as a cyclic amidine in these reactions, and on electro-chemical grounds alone its conversion into a 1 : 8-naphthyridine appears highly improbable.

2 : 6-Diaminopyridine, in striking contrast to 2-aminopyridine, forms the most accessible starting material for the synthesis of 1 : 8-naphthyridines, owing probably to the presence of two amino-groupings in the molecule either of which can take part in the prototropic change involved in imine-formation. By direct condensation of the base with ethyl acetoacetate, Seide (*Ber.*, 1926, **59**, 2465) obtained 7-amino-2-hydroxy-4-methyl-1 : 8-naphthyridine (IV; R = OH, R′ = NH_2) in good yield. The reaction has been extended to ethyl benzoylacetate (Mangini and Colonna, *Gazzetta*, 1942, **72**, 183), acetylacetone (Mangini, *Chem. Zentr.*, 1940, II, 2613; Ochiai and Miyaki, *Ber.*, 1941, **74**, 1115), and ethoxymethylene diethylmalonate (Adams *et al.*, *J. Amer. Chem. Soc.*, 1946, **68**, 1317).



(I.) (II.) (III.) (IV.) (V.)

We now find that 7-amino-2-hydroxy-4-methyl-1 : 8-naphthyridine (IV; R = OH, R′ = NH_2) (Seide, *loc. cit.*) passes smoothly under the action of acetic anhydride into 7-acetamido-2-hydroxy-4-methyl-1 : 8-naphthyridine (Mangini and Colonna, *loc. cit.*). The acetamido-grouping in this compound proved stable to phosphorus oxychloride, giving *2-chloro-7-acetamido-4-methyl-1 : 8-naphthyridine* (IV; R = Cl, R′ = NHAc), occasionally mixed with some *2-chloro-7-amino-4-methyl-1 : 8-naphthyridine*. Treatment of (IV; R = Cl, R′ = NHAc) with phenol at 180° gave *7-acetamido-2-phenoxy-4-methyl-1 : 8-naphthyridine*, hydrolysed to the corresponding *amino*-derivative. *7-Amino-2-anilino-*, *7-amino-2-p-chloroanilino-*, and *7-amino-2-piperidino-4-methyl-1 : 8-naphthyridine* were similarly prepared.

Condensation of 2 : 6-diaminopyridine with benzoylacetone in the presence of zinc chloride

gave 7-*amino*-4-*phenyl*-2-*methyl*-1 : 8-*naphthyridine* (V; R = NH_2), characterised by preparation of the *picrate*. The derived *acetamido*-compound (V; R = NHAc) was converted *via* the methosulphate into 7-*acetamido*-4-*phenyl*-2-*methyl*-1 : 8-*naphthyridine*-1-*methiodide*, and hence into the corresponding *methochloride*. The constitution assigned to the monomethiodide followed from the formation of a highly coloured dye on heating the compound with *p*-dimethylaminobenzaldehyde in alcoholic solution containing a trace of piperidine. This colour change is almost certainly due to the formation of the corresponding 2-*p*-dimethylaminostyryl derivative, but attempts to isolate it in a state of analytical purity were unsuccessful. Treatment of (V; R = NH_2) with nitrous acid gave 7-*hydroxy*-4-*phenyl*-2-*methyl*-1 : 8-*naphthyridine* (V; R = OH), from which 7-*chloro*-, and hence 7-*phenoxy*-, 7-*anilino*-, and 7-*piperidino*-4-*phenyl*-2-*methyl*-1 : 8-*naphthyridine* were readily prepared. Attempts to condense (V; R = NH_2) with *p*-acetamidobenzenesulphonyl chloride were unsuccessful.

We have *inter alia* examined the condensation of ethyl β-aminocrotonate with 2 : 6-diaminopyridine in the hope of obtaining the isomeric 7-amino-4-hydroxy-2-methyl-1 : 8-naphthyridine, but the only product isolated as (IV; R = OH, R′ = NH_2) in somewhat better yield. The corresponding nitrile, β-aminocrotononitrile, it may be added, reacts with arylamines with exceptional facility to give the β-aryliminobutyronitriles by loss of the elements of ammonia (Meyer, *J. pr. Chem.*, 1908, **78**, 499). Its behaviour with the aminopyridines will form the subject of a later communication.

Experimental.

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

2-*Chloro*-7-*acetamido*-4-*methyl*-1 : 8-*naphthyridine* (IV; R = Cl, R′ = NHAc).—7-Acetamido-2-hydroxy-4-methyl-1 : 8-naphthyridine was prepared by heating finely powdered (IV; R = OH, R′ = NH_2) (Seide, *Ber.*, 1926, **59**, 2465) (2 g.) with acetic anhydride (30 ml.) under reflux for 30 mins. The heavy yellow solid changed to a flocculent white suspension. When cold, the product was collected and recrystallised from a large volume of glacial acetic acid (charcoal), giving white crystals, m. p. >310° (Found: C, 60·8; H, 5·2; N, 19·0. Calc. for $C_{11}H_{11}O_2N_3$ C, 60·8; H, 5·1; N, 19·3%). Yield 2·2 g. (89%) (Mangini and Colonna, *loc. cit.*, give m. p. ∢285°). The acetamido-compound (10 g.) was heated with phosphorus oxychloride (100 ml.) for 30 minutes under reflux. The product was decomposed with ice-water and made alkaline with sodium hydroxide, and the precipitated solids were recrystallised from spirit. 2-*Chloro*-7-*acetamido*-4-*methyl*-1 : 8-*naphthyridine* formed felted white needles (7·5 g.; 69%), m. p. 240° (Found: C, 55·9; H, 3·8; N, 17·8; Cl, 15·6. $C_{11}H_{10}ON_3Cl$ requires C, 56·1; H, 4·2; N, 17·8; Cl, 15·1%).

If the temperature rose somewhat during the decomposition of the phosphorus oxychloride reaction mixture, 2-*chloro*-7-*amino*-4-*methyl*-1 : 8-*naphthyridine*, white needles, m. p. 258—259°, from alcohol (Found: Cl, 21·3. $C_9H_8N_3Cl$ requires Cl, 21·7%), was also obtained, readily separated from the acetamido-compound by fractionation from alcohol in which it was less soluble. On acetylation it gave the acetamido-derivative, m. p. 240° (above).

7-*Acetamido*-2-*phenoxy*-4-*methyl*-1 : 8-*naphthyridine*.—2-Chloro-7-acetamido-4-methyl-1 : 8-naphthyridine (1 g.) was heated with phenol (3 g.) at 180° for 1 hour. The cooled melt was treated with excess of sodium hydroxide solution, and the insoluble fraction collected and heated with acetic anhydride on the water-bath. 7-*Acetamido*-2-*phenoxy*-4-*methyl*-1 : 8-*naphthyridine*, separated on cooling as long needles from aqueous alcohol, m. p. 205° (Found: C, 69·3; H, 5·2; N, 14·1. $C_{17}H_{15}O_2N_3$ requires C, 69·6; H, 5·1; N, 14·3%). Hydrolysis with alcoholic hydrochloric acid gave 7-*amino*-2-*phenoxy*-4-*methyl*-1 : 8-*naphthyridine*, needles from benzene, m. p. 216—217° (Found: C, 71·6; H, 5·3; N, 16·7. $C_{15}H_{13}ON_3$ requires C, 71·8; H, 5·2; N, 16·7%).

7-*Amino*-2-*anilino*-4-*methyl*-1 : 8-*naphthyridine* (IV; R = NHPh, R′ = NH_2).—2-Chloro-7-acetamido-4-methyl-1 : 8-naphthyridine (4 g.) was heated with aniline (10 ml.) under reflux for 3 hours. Excess of aniline was removed in steam, and the solids were collected and heated under reflux with 2N-hydrochloric acid for 1 hour. The mixture was made alkaline with sodium hydroxide and the product purified from spirit. 7-*Amino*-2-*anilino*-4-*methyl*-1 : 8-*naphthyridine* formed yellow crystals, m. p. 269—270° (Found: C, 71·6; H, 5·4; N, 23·0. $C_{15}H_{14}N_4$ requires C, 72·0; H, 5·6; N, 22·4%).

7-*Amino*-2-p-*chloroanilino*-4-*methyl*-1 : 8-*naphthyridine*.—2-Chloro-7-acetamido-4-methyl-1 : 8-naphthyridine (2·5 g.) and *p*-chloroaniline (2·5 g.) were heated under reflux in nitrobenzene (25 ml.). Vigorous reaction occurred in a few minutes and the mixture set to a semi-solid. Heating at 200° was continued for one hour. The yellow-brown solids were collected and crystallised from alcohol–light petroleum. 7-*Amino*-2-p-*chloroanilino*-4-*methyl*-1 : 8-*naphthyridine* formed ivory needles (1 g.; 33%), m. p. 224—225° (Found: C, 63·1; H, 4·9; N, 19·5; Cl, 12·5. $C_{15}H_{13}N_4Cl$ requires C, 63·3; H, 4·6; N, 19·7; Cl, 12·5%). The *hydrochloride* formed yellow needles from alcohol–light petroleum, m. p. >300° (Found: Cl, 22·8. $C_{15}H_{14}N_4Cl_2$ requires Cl, 22·9%).

7-*Amino*-2-*piperidino*-4-*methyl*-1 : 8-*naphthyridine*.—(IV; R = Cl, R′ = NHAc) (1 g.) was heated with piperidine (5 ml.) at 180° for 8 hours in a sealed tube. Excess of piperidine was removed on the water-bath. The crystalline product, after hydrolysis with concentrated hydrochloric acid (10 ml.) and alcohol (25 ml.) for 1 hour, followed by basification with sodium hydroxide, gave 7-*amino*-2-*piperidino*-4-*methyl*-1 : 8-*naphthyridine*, ivory crystals from light petroleum, m. p. 221·5—222·5° (Found: C, 69·0; H, 7·2; N, 22·7. $C_{14}H_{18}N_4$ requires C, 69·4; H, 7·4; N, 23·1%).

7-*Amino*-4-*phenyl*-2-*methyl*-1 : 8-*naphthyridine* (V; R = NH_2).—2 : 6-Diaminopyridine (20 g.), benzoylacetone (30 g.), and powdered anhydrous zinc chloride (12 g.) were heated in an oil-bath. Reaction

commenced at 135°, after which the temperature was slowly raised to 175° over 3½ hours. Solution in alcohol (200 ml.) followed by gradual precipitation with water (300 ml.) gave a granular product, further purified by solution in 2N-hydrochloric acid (charcoal) and precipitation with sodium hydroxide. For purification, the crude naphthyridine (8 g.) and acetic anhydride (80 ml.) were heated under reflux for 30 minutes. 7-*Acetamido*-4-*phenyl*-2-*methyl*-1 : 8-*naphthyridine*, needles from benzene (30%), m. p. 207—208° (Found: C, 73·4; H, 5·4; N, 15·0. $C_{17}H_{15}ON_3$ requires C, 73·6; H, 5·4; N, 15·2%), separated on cooling. Hydrolysis with boiling 15% hydrochloric acid for 30 minutes gave 7-*amino*-4-*phenyl*-2-*methyl*-1 : 8-*naphthyridine*, pale yellow octahedra from nitrobenzene, m. p. 247·5—248·5° (Found: C, 76·4; H, 5·6; N, 18·1. $C_{15}H_{13}N_3$ requires C, 76·6; H, 5·5; N, 17·9%), characterised as the *picrate*, fine yellow needles from a large volume of alcohol, m. p. 284° (decomp.) (Found: N, 18·1. $C_{15}H_{13}N_3,C_6H_3O_7N_3$ requires N, 18·1%).

7-*Acetamido*-4-*phenyl*-2-*methyl*-1 : 8-*naphthyridine*-1-(N)-*methiodide*, prepared *via* the methosulphate, formed silky yellow needles (75%) from alcohol, m. p. 244—245° (Found: I, 31·2. $C_{18}H_{18}ON_3I$ requires I, 30·4%). The *methochloride* formed pale green platelets from alcohol–ether, m. p. 235—236° (Found: Cl, 11·1. $C_{18}H_{18}ON_3Cl$ requires Cl, 10·8%).

7-*Hydroxy*-4-*phenyl*-2-*methyl*-1 : 8-*naphthyridine* (V; R = OH).—The amino-compound (V; R = NH_2) (10 g.) in water (250 ml.) and concentrated hydrochloric acid (5 ml.), mechanically stirred at 0°, was treated simultaneously during 30 minutes with sodium nitrite (4·5 g. in 20 ml. water) and hydrochloric acid (10 ml. in 30 ml. water). After 2 hours the mixture was heated on the water-bath until evolution of nitrogen had ceased. The product was precipitated with ammonium hydroxide (*d* 0·88), giving 7-*hydroxy*-4-*phenyl*-2-*methyl*-1 : 8-*naphthyridine*, needles from alcohol, m. p. 252—253° (Found: C, 76·3; H, 5·2; N, 11·6. $C_{15}H_{12}ON_2$ requires C, 76·2; H, 5·1; N, 11·9%). The compound dissolves in sodium hydroxide solution.

7-*Chloro*-4-*phenyl*-2-*methyl*-1 : 8-*naphthyridine* (V; R = Cl).—The hydroxy-compound (V; R = OH) (2 g.) and phosphorus oxychloride (15 ml.) were heated under reflux at 140—150° for 30 minutes. The product, isolated in the usual way, gave 7-*chloro*-4-*phenyl*-2-*methyl*-1 : 8-*naphthyridine* (70%), felted needles from aqueous methanol (charcoal), m. p. 161° (Found: Cl, 14·4. $C_{15}H_{11}N_2Cl$ requires Cl, 14·0%).

7-*Phenoxy*-4-*phenyl*-2-*methyl*-1 : 8-*naphthyridine* separated from benzene–light petroleum in needles (80%), m. p. 156—157·5° (Found: C, 80·6; H, 5·3; N, 8·9. $C_{21}H_{16}ON_2$ requires C, 80·7; H, 5·2; N, 8·9%).

7-*Anilino*-4-*phenyl*-2-*methyl*-1 : 8-*naphthyridine* formed pale yellow needles from a large volume of alcohol, m. p. 286—287° (Found: C, 80·4; H, 5·6; N, 13·3. $C_{21}H_{17}N_3$ requires C, 81·0; H, 5·5; N, 13·5%).

7-*Piperidino*-4-*phenyl*-2-*methyl*-1 : 8-*naphthyridine*, isolated as the *picrate*, long yellow needles from alcohol, m. p. 220—221° (decomp. at 238°) (Found: N, 15·7. $C_{20}H_{21}N_3,C_6H_3O_7N_3$ requires N, 15·8%), formed pale yellow plates from benzene–light petroleum, m. p. 131—132° (Found: C, 79·0; H, 7·0; N, 14·0. $C_{20}H_{21}N_3$ requires C, 79·2; H, 6·9; N, 13·9%).

7-*Amino*-2-*hydroxy*-4-*methyl*-1 : 8-*naphthyridine* (IV; R = OH, R′ = NH_2).—2 : 6-Diaminopyridine (5 g.) and ethyl β-aminocrotonate (6 g.) were heated at 180—200° for 2 hours, after which the temperature was raised to 220° during 45 minutes, the mixture then solidifying. The grey-green mass was extracted with alcohol, giving (IV; R = OH, R′ = NH_2), m. p. >360°, identified by acetylation and chlorination to (IV; R = Cl, R′ = NHAc), m. p. 240°, alone or in admixture with an authentic specimen (above), further converted into (IV; R = OPh, R′ = NH_2), m. p. 214—215°, alone or in admixture with an authentic specimen.

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