704. *Some Derivatives of 2,7-Naphthyridine.*

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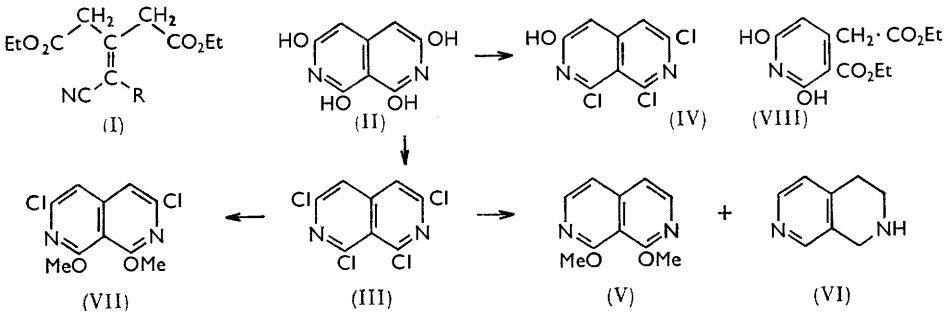
The synthesis of some 2,7-naphthyridine derivatives is described.

Few 2,7-naphthyridine derivatives are known [1] and we now report a simple method for obtaining several hydroxy- and chloro-derivatives. Malononitrile and diethyl acetonedicarboxylate in ethanol, with diethylamine as catalyst, give diethyl β-(dicyanomethylene)-glutarate (I; R = CN), which with sulphuric acid yields 1,3,6,8-tetrahydroxy-2,7-naphthyridine (II), m. p. >350°, insoluble in dilute acids or organic solvents. In dilute alkali this rapidly undergoes aerial oxidation, accelerated by the addition of perhydrol, the oxidation product separating as a high-melting, insoluble blue solid which becomes red on treatment with acid. These properties are reminiscent of the polyhydroxypyridine, -quinoline, and -isoquinoline series,[2] the potassium salt of 4,5,7-trihydroxy-2,3-benzo-1,6-naphthyridine, for instance, becoming violet when dried in air and giving a red compound when a perhydrol solution of the salt is acidified.[3] Aerial oxidation of 4-hydroxyisocarbostyril affords the blue carbindigo [4] and by analogy our oxidation product may have a somewhat similar dimeric structure.



The tetrahydroxynaphthyridine forms a dibenzoyl and a dinitroso-derivative, the latter probably the 4,5-dinitroso-compound, but methylation with Purdie reagents did not give satisfactory results. Attempts to remove the hydroxyl groups by zinc-dust distillation or heating with red phosphorus and iodine in acetic acid were unsuccessful, but heating with phosphoryl chloride at 180° yields 1,3,6,8-tetrachloro-2,7-naphthyridine (III), characterised by the red colour it gives with hydrazine hydrate, and a trichloro-product, probably 1,3,8-trichloro-6-hydroxy-2,7-naphthyridine (IV), since 1,3-dihydroxyisoquinoline with phosphorus pentachloride yields 1-chloro-3-hydroxyisoquinoline along with the dichloro-derivative.[5]

Hydrogenation of the tetrachloronaphthyridine in methanol containing potassium acetate gives a small quantity of a reduction product (as picrate), probably 1,2,3,4-tetrahydro-2,7-naphthyridine (VI) from analogy of the catalytic hydrogenation of quinoline and isoquinoline.[6] Replacement of the potassium acetate by potassium carbonate results in a rapid uptake of hydrogen, to yield the tetrahydro-2,7-naphthyridine (VI), 1,8-dimethoxy-2,7-naphthyridine (V), and a low-melting substance that was not identified. The infrared spectrum of the dimethoxynaphthyridine shows the absence of NH groups and the ultraviolet spectrum resembles that of the tetrachloro-2,7-naphthyridine.

[1] Allen, *Chem. Rev.*, 1950, **47**, 286; Iselin and Hoffmann, *J. Amer. Chem. Soc.*, 1954, **76**, 3220.
[2] Errera, *Ber.*, 1898, **31**, 1241.
[3] St. Niementowski and Sucharda, *J. prakt. Chem.*, 1916, **94**, 193.
[4] Gabriel and Colman, *Ber.*, 1900, **33**, 996.
[5] Gabriel, *Ber.*, 1886, **19**, 1653, 2335.
[6] " Chemistry of Carbon Compounds," edited by E. H. Rodd, Elsevier, 1957, Vol. IVa, pp. 642, 665.

From a number of experiments it was noted that the tetrachloronaphthyridine undergoes hydrogenation in the presence of bases only when solvents such as methanol or ethanol are used, *i.e.*, only when solvolysis can occur,[7] no hydrogen being absorbed when ether, benzene, or ethyl acetate is the solvent. The ease of solvolysis under basic conditions is shown by the observation that the chloro-compound is unchanged on paper chromatograms in neutral or acidic conditions, whereas no colour due to the tetrachloro-compound can be detected when chromatograms in ethyl acetate, pyridine, or water are sprayed with dilute ethanolic hydrazine hydrate. The tetrachloro-compound is recovered quantitatively by addition of water to methanolic solutions or acidified methanolic solutions, but when solid potassium carbonate is added to a methanolic solution 3,6-dichloro-1,8-dimethoxy-2,7-naphthyridine (VII) separates. This substance is also formed when tetrachloro-2,7-naphthyridine is refluxed with 50% aqueous methanol containing potassium carbonate. Acid-hydrolysis, however, can be effected by boiling dilute hydrochloric acid–dioxan, and gives a chlorine-free product which appears to be 1,3,6,8-tetrahydroxy-2,7-naphthyridine.[8]

Diethylamine catalyses the condensation of diethyl acetonedicarboxylate and ethyl cyanoacetate, previously effected by piperazine acetate.[9] The product (I; R = CO_2Et) with concentrated sulphuric acid undergoes hydration of the cyano-group and cyclisation to yield ethyl 3-ethoxycarbonyl-2,6-dihydroxy-4-pyridylacetate [10] (VIII).

Dimethylamine or morpholine is a useful catalyst for the condensation of malononitrile with ketones, but the best yields occur when the product separates rapidly from solution: otherwise the reaction is complicated by the polymerisation of malononitrile.

Experimental

Ultraviolet spectra were measured for ethanolic solutions by means of a Unicam S.P. 500 spectrophotometer.

1,3,6,8-*Tetrahydroxy*-2,7-*naphthyridine*.—(*a*) Malononitrile (1·1 g.) was kept for 19 days with diethyl acetonedicarboxylate (3 g.) in dry ethanol (25 ml.) containing 4 drops of diethylamine, distilled over sodium directly into the reaction mixture. The solvent was removed under reduced pressure and the residual oil yielded solid *diethyl* β-(*dicyanomethylene*)*glutarate* (2·6 g.), pale yellow needles (from benzene), m. p. 166° (Found: C, 57·1; H, 5·6; N, 11·3%; *M*, 237. $C_{12}H_{14}O_4N_2$ requires C, 57·6; H, 5·6; N, 11·2%; *M*, 250). (*b*) Malononitrile (1·1 g.) was condensed with diethyl acetonedicarboxylate as above; after 24 hr. no ketone could be detected by 2,4-dinitrophenylhydrazine; after a further 24 hr. the solvent was removed under reduced pressure and the residue gently warmed with 70% (by vol.) sulphuric acid (20 ml.) until complete dissolution occurred, whereupon a vigorous exothermic reaction resulted. After 30 sec. the reaction subsided and the solution was boiled for 30 sec., cooled, and poured into water (60 ml.), to yield 1,3,6,8-*tetrahydroxy*-2,7-*naphthyridine* (2·7 g.), m. p. >350°, purified by washing with water and ethanol (Found: C, 48·9; H, 3·6; N, 13·2. $C_8H_6O_4N_2$ requires C, 49·5; H, 3·1; N, 14·4%). (It is hard to get good nitrogen analyses in this series; but this compound and its benzoate could not be recrystallised and may have been impure.) With benzoyl chloride it yielded a *dibenzoate*, m. p. 234—239° after successive washings with dilute hydrochloric acid, sodium carbonate, water, and ethanol (Found: C, 66·4; H, 3·7; N, 6·1. $C_{22}H_{14}O_6N_2$ requires C, 65·7; H, 3·5; N, 7·0%). Solid sodium nitrite (0·5 g.) was added to a solution of the naphthyridine (0·1 g.) in 2N-sodium hydroxide (10 ml.) at 0°. The solution was kept at this temperature and dilute hydrochloric acid was slowly added with stirring until the solution was acid. The *dinitroso-compound* (0·03 g.) separated, and had m. p. >350° after being washed with water and ethanol (Found: N, 21·8. $C_8H_6O_6N_4$ requires N, 22·2%).

1,3,6,8-*Tetrachloro*-2,7-*naphthyridine*.—The tetrahydroxynaphthyridine (1 g.) was heated with phosphoryl chloride (10 ml.) in a sealed tube at 180° for 24 hr. The product was poured on ice (150 g.), and the mixture was made alkaline with solid potassium carbonate and extracted with ether (3 × 100 ml.). The dried extract (Na_2SO_4), on evaporation, yielded a yellow solid (0·7 g.), which was extracted with boiling light petroleum (b. p. 80—100°) (3 × 10 ml.). The

[7] Hardman and Partridge, *J.*, 1958, 614.
[8] Cf. Tomisek and Christensen, *J. Amer. Chem. Soc.*, 1945, **67**, 2113.
[9] Raha, *J. Indian Chem. Soc.*, 1953, **30**, 129.
[10] Cf. Togerson and Thorpe, *J.*, 1906, **89**, 631.

volume of the extract was halved by distillation under reduced pressure; overnight at 0° there separated 1,3,6,8-*tetrachloro*-2,7-*naphthyridine* (0·5 g.), yellow needles (from aqueous ethanol), m. p. 157—161° (Found: C, 36·0; H, 1·0; N, 10·6; Cl, 52·3. $C_8H_2N_2Cl_4$ requires C, 35·8; H, 0·7; N, 10·4; Cl, 53·0%), $\lambda_{max.}$ 230, 245, 312, 325 mμ (log ε 4·41, 4·44, 3·82, and 3·81). The residue left after the extraction with light petroleum was 1,3,8-*trichloro*-6-*hydroxy*-2,7-*naphthyridine*, needles (0·1 g.), m. p. 295° after crystallisation from benzene and sublimation under reduced pressure (Found: C, 39·0; H, 1·4; N, 12·0; Cl, 42·5. $C_8H_3ON_2Cl_3$ requires C, 38·4; H, 1·2; N, 11·2; Cl, 42·7%).

1,2,3,4-*Tetrahydro*-2,7-*naphthyridine*.—Tetrachloro-2,7-naphthyridine (0·46 g.), fused potassium acetate (1 g.), and palladium chloride (0·2 g.) in dry methanol (40 ml.) were shaken in hydrogen, 190 ml. being absorbed (replacement of 4 chlorine atoms by hydrogen requires 154 ml.). The filtered solution was evaporated and the oily residue dissolved in water (15 ml.), made alkaline with solid potassium carbonate, and extracted with ethyl acetate. The dried extract gave an oil (0·04 g.), yielding 1,2,3,4-*tetrahydro*-2,7-*naphthyridine picrate*, orange-yellow elongated prisms (from water), m. p. 248—250° [Found: C, 39·6; H, 3·2; N, 17·6. $C_8H_{10}N_2,(C_6H_3O_7N_3)_2,H_2O$ requires C, 39·3; H, 3·6; N, 18·4%]. With concentrated aqueous ammonia the picrate gave a rapidly decomposing oil, presumably the parent base.

1,8-*Dimethoxy*-2,7-*naphthyridine*.—Tetrachloronaphthyridine (0·36 g.), palladium chloride (0·2 g.), and anhydrous potassium carbonate (1 g.) in dry methanol (25 ml.) were shaken in hydrogen. After 1 hr. 141 ml. of hydrogen were absorbed (replacement of 4 chlorine atoms by hydrogen, 120 ml.). The residue in water (3 ml.) was extracted with ether (3 × 5 ml.), which when dried and evaporated gave 1,8-*dimethoxy*-2,7-*naphthyridine* as an oil which solidified and crystallised from methanol (2 drops) and then water in needles (0·014 g.), m. p. 108—110° (Found: C, 63·6; H, 5·8; N, 14·3. $C_{10}H_{10}O_2N_2$ requires C, 63·2; H, 5·3; N, 14·7%), $\lambda_{max.}$ 230, 290, 305, 315 mμ (log ε 4·07, 3·68, 3·72, and 3·86) [picrate, yellow blades (from benzene), m. p. 148—150°]. From the methanolic filtrate tetrahydro-2,7-naphthyridine was isolated as the picrate, m. p. 248—250°.

3,6-*Dichloro*-1,8-*dimethoxy*-2,7-*naphthyridine*.—Tetrachloro-2,7-naphthyridine (0·1 g.) in dry methanol (5 ml.) with anhydrous potassium carbonate (0·1 g.) afforded after 1 hr. 3,6-*dichloro*-1,8-*dimethoxy*-2,7-*naphthyridine*, needles (from methanol), m. p. 155—157° (Found: C, 46·6; H, 3·2; Cl, 26·8. $C_{10}H_8O_2N_2Cl_2$ requires C, 46·3; H, 3·1; Cl, 27·4%). The same product (0·08 g.) was obtained when tetrachloro-2,7-naphthyridine (0·1 g.) was boiled for 1 hr. in methanol (5 ml.) with 10% aqueous potassium carbonate (5 ml.).

Ethyl 3-*Ethoxycarbonyl*-2,6-*dihydroxy*-4-*pyridylacetate*.—Ethyl cyanoacetate (2·5 g.), diethyl acetonedicarboxylate (4 g.), and ethylamine (6 drops); freshly distilled over sodium were kept in dry ethanol (10 ml.) for 7 days. The ethanol was removed by distillation, and at 150°/8 mm. water and unchanged materials distilled. The residue (3·2 g.) was kept overnight in concentrated sulphuric acid (20 ml.), which was then poured into water (60 ml.). *Ethyl* 3-*ethoxycarbonyl*-2,6-*dihydroxy*-4-*pyridylacetate* (1·4 g.) separated, forming orange-yellow needles (from ethanol), m. p. 176·5° (Found: C, 53·0; H, 5·7; N, 5·3. $C_{12}H_{15}O_6N$ requires C, 53·5; H, 5·6; N, 5·2%).

Condensation of Ketones with Malononitrile.—Malononitrile (0·35 g.), diethyl ketone (0·43 g.), and diethylamine (2 drops; freshly distilled over sodium) were kept in absolute ethanol (2 ml.) for 4 days. 2-*Cyano*-3-*ethylpent*-2-*enonitrile* (0·06 g.) separated; it formed needles (aqueous ethanol), m. p. 160—161° (Found: C, 72·5; H, 7·7; N, 19·5. $C_8H_{10}N_2$ requires C, 71·6; H, 7·4; N, 20·9%). Dibenzyl ketone (1·5 g.) similarly gave after 12 hr. 3-*benzyl*-2-*cyano*-4-*phenylbut*-2-*enonitrile* (1·15 g.), plates (from aqueous ethanol), m. p. 49·5° (Found: C, 82·0; H, 5·1; N, 10·8. $C_{18}H_{14}N_2$ requires C, 83·7; H, 5·4; N, 10·8%). Acetone (1 hr.) and fluorenone gave the corresponding products, m. p. 172—173° (lit., 175—180°) and 234° (lit., 213°) respectively.[11]

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[11] Schenck and Finke, *Annalen*, 1928, **462**, 269.