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SYNTHESIS OF 2,6-NAPHTHYRIDINE

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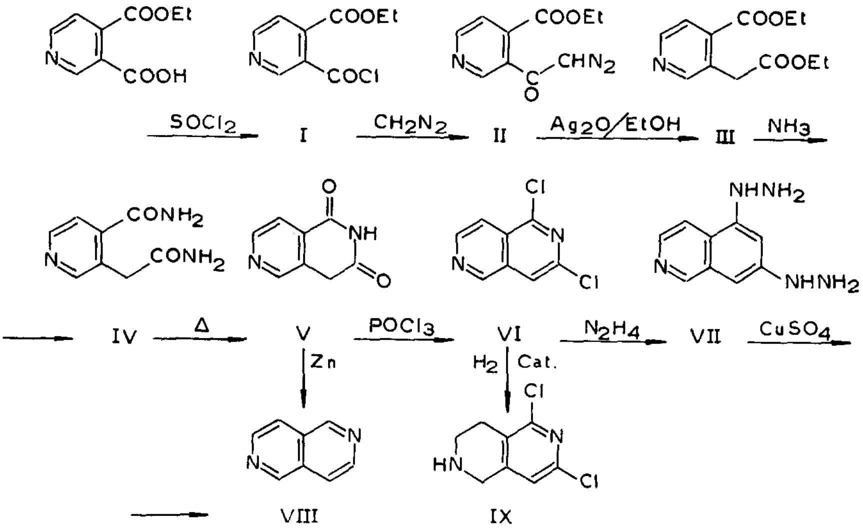
2,6-Naphthyridine is the only member of the naphthyridine group not yet described; just a dibenzo derivative, the 6,12-diazachrysene, was prepared in 1960[1] and found to be identical with "calycanine".

The synthesis, for which other routes have already been attempted[2,3], was possible through the reaction scheme summarized below:



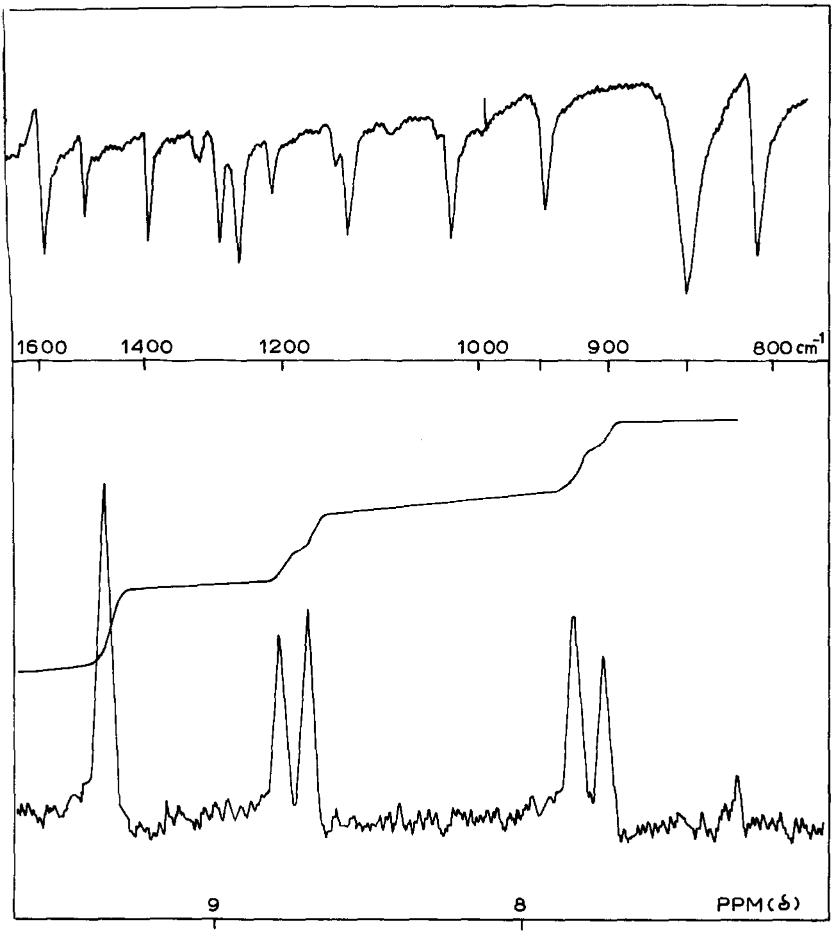
4-Carbethoxy-nicotinic acid[4] was transformed, via acid chloride (I) (b.p. 102°/0.1 mm), to ethyl β-diazoacetyl-isonicotinate (II), m.p. 58-60° from ethyl ether.
Found: C, 54.99; H, 4.16; N, 19.30. Calcd. for $C_{10}H_9N_3O_3$: C, 54.79; H, 4.14; N, 19.17.

The diazoketone (II) was converted, by means of silver oxide in absolute ethanol, with rearrangement and loss of nitrogen, to β-homocinchomeronic acid diethylester (III); this ester distils at 132°/0.3 mm and at 116-117°/0.05 mm as a colourless oil. The picrate of (III) melts at 104-106°.
Found: C, 46.65; H, 4.06; N, 12.16. Calcd. for $C_{18}H_{18}N_4O_{11}$: C, 46.36; H, 3.89; N, 12.01.

(III) kept several days in a sealed tube with a solution of ammonia in alcohol and then heated at 100° gave the diamide (IV), white crystals from water which, dried at 55° in vacuo, enclose crystallization water; (IV), after loss of water at 100-110°, melts at 177-182° with decomposition and ammonia evolution, solidifies immediately and melts again at 229-230° with contemporary sublimation. Found: C, 48.31; H, 5.29; N, 21.22. Calcd. for $C_8H_9N_3O_2.H_2O$: C, 48.73; H, 5.62; N, 21.31. (IV), heated over its melting point, gave evidently the imide (V), which can directly be obtained by boiling the reaction mixture of diethyl β-homocinchomeronate (III) with ammonia in amyl alcohol for several hours. The compound (V), crystallized from water and dried, melts at 229-230° and sublimes undecomposed. Found: C, 58.90; H, 3.48; N, 17.45. Calcd. for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28.

The imide (V), kept several hours at 120° in a sealed tube with phosphorus oxychloride, afforded 1,3-dichloro-2,6-naphthyridine (VI), white crystals from petroleum ether melting at 116°; this compound easily sublimes as white needles.
Found: C, 48.10; H, 2.08; N, 14.02; Cl, 35.30. Calcd. for $C_8H_4Cl_2N_2$: 48.27; H, 2.03; N, 14.07; Cl, 35.62.

The hydrogenolysis of the two chlorine atoms was achieved through 1,3-dihydrazino derivative (VII), a light yellow solid which does not melt until 300°. The solution of (VII) in water-acetic acid was added to a 10% $CuSO_4$ solution and heated on a steam bath; the resulting mixture, made alkaline with 5N NaOH, was extracted with CH_2Cl_2. After drying over anhydrous Na_2SO_4, the solvent evaporated leaves a solid which, after sublimation at 60°/0.1 mm, melts at 114-115° (VIII). Found: C, 74.00; H, 4.80; N, 21.70. Calcd. for $C_8H_6N_2$: C, 73.90; H, 4.65; N, 21.55. λ_{max}^{MeOH} mμ (log ε): 247 (3.34); 255 (3.42); 264 (3.33); 318 (3.34) 330 (3.30).

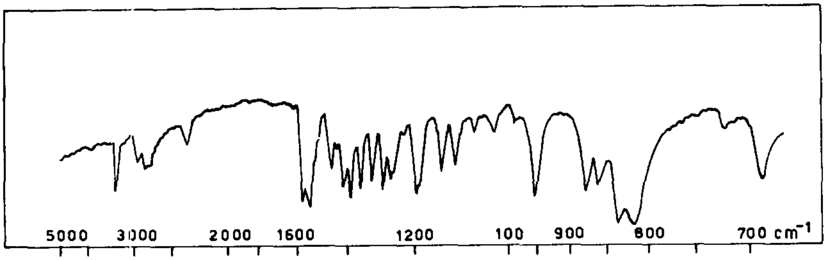


I.R. spectrum (KBr) and P.M.R. spectrum of (VIII)

The p.m.r. spectrum of 2,6-naphthyridine shows three groups of signals of same intensity: the lowest field signal, a singlet with δ= 9.39 p.p.m., has to be assigned to the two protons 1 and 5 (uncoupled); the other two signals appear as an AB system (J_{AB}= 6 c.p.s., normal for ortho aromatic protons). Assignements: δ = 7.78 p.p.m. (protons 4 and 8), δ= 8.75 p.p.m. (protons 3 and 7).

In this manner the compound (VIII) was identified as 2,6-naphthyridine; its monopicrate crystallized from ethanol melts at 206°. Found: C, 47.12; H, 2.86; N, 19.08. Calcd. for $C_{14}H_9N_5O_7$: C, 46.80; H, 2.53; N, 19.50.

An attempted hydrogenolysis of 1,3-dichloro-2,6-naphthyridine (VI) with hydrogen over PtO_2 resulted in absorption of two moles of H_2 in 30 minutes. Removal of catalyst and recrystallization of the residue from petroleum ether gave (IX), m.p. 125-127°. Found: C, 47.44; H, 4.01; N, 14.03; Cl, 34.53. Calcd. for $C_8H_8Cl_2N_2$: C, 47.32; H, 3,97; N, 13.80; Cl, 34.93. λ_{max}^{MeOH} mμ (log ε): 218 (3.95); 273 (3.61).

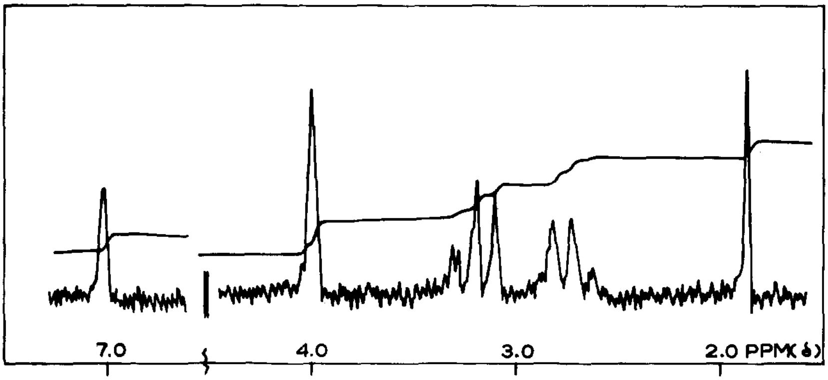


I. R. spectrum of (IX) in KBr

The p.m.r. spectrum of the hydrogenation compound shows a singlet (one proton) at δ = 7.01 p.p.m. (aromatic proton 4), another singlet (two protons) at δ = 4.00 p.p.m. (methylene group in 5 position), a system consisting roughly of two equally spaced triplets (A_2B_2 system), two protons each, for the two methylene groups in 7 (δ= 3.19 p.p.m.) and 8 (δ = 2.72 p.

p.m.) position and finally a singlet (one proton) at δ = 1.87 p.p.m. (proton of NH group).

The p.m.r. spectra were taken in $CDCl_3$ solution (TMS as internal standard) with a Varian A 60 instrument.



P.M.R. spectrum of (IX)

The compound (V), mixed with zinc dust and heated at 170° in a sealed tube, gave in poorer yields a compound which was identical with the 2,6-naphthyridine obtained above.

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