543. *The Synthesis of Quinolylimidazole Alkaloids and the Structure of Normacrorine*

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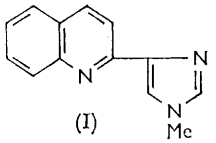
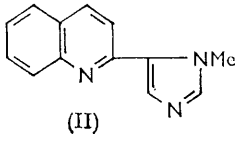
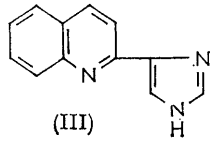
The alkaloidal residue obtained after the separation of macrorine (I), isomacrorine (II), and macrorungine from *Macrorungia longistrobus* C.B. Cl.[1] has now yielded another new alkaloid ($C_{12}H_9N_3$) for which the name normacrorine is suggested. The ultraviolet spectrum, $\lambda_{max.}$ 214, 236, 264, 325, and 336 mμ (ε 42,280, 15,760, 27,230, 10,500, and 10,980, respectively), is very similar to that of macrorine, $\lambda_{max.}$ 217, 238, 265, and 341 mμ (ε 39,170, 15,380, 23,070, and 9370, respectively). A chloroform solution of the alkaloid shows infrared absorption bands at 1595, 1562, and 1495 cm.$^{-1}$ (aromatic) and a band at 3340 cm.$^{-1}$ attributed to an NH group. The n.m.r. spectrum (in acetone with tetramethylsilane as internal standard $\tau = 10{\cdot}0$) showed signals in the aromatic region only ($\tau = 1{\cdot}5$—$2{\cdot}7$). On the basis of the above evidence we suggest structure (III) for normacrorine.


(I)


(II)


(III)

The 4(5)-2′-quinolylimidazole structure for this new alkaloid was confirmed by its synthesis. The method of Clemo [2] for the synthesis of pyridylimidazoles was successfully applied. Conversion of 2-acetylquinoline [3] into 2-ω-aminoacetylquinoline hydrochloride was accomplished by the method of Neber and Huh.[4] Cyclisation of this hydrochloride in the presence of thiocyanate yielded 4(5)-2′-quinolylimidazole-2-thiol hydrochloride which on oxidation with dilute nitric acid afforded 4(5)-2′-quinolylimidazole identical with normacrorine (m. p., mixed m. p., and infrared spectrum).

Methylation of normacrorine with dimethyl sulphate gave a 2 : 1 mixture of macrorine and isomacrorine. According to the mechanism suggested by Ridd and Smith,[5] the negative inductive effect of a quinolyl substituent on the imidazole ring should favour a cross-conjugated system which on methylation in non-basic medium will afford isomacrorine as major product. It has, however, been pointed out by the same authors that, in cases such as 4(5)-phenylimidazole [6] where methylation yields a ratio of isomers not in agreement with that expected, steric hindrance on the nitrogen nearest to the substituent influences the ratio of the *N*-substituted isomers.

[1] R. R. Arndt, A. Jordaan, and V. P. Joynt, *J.*, 1964, 5969.
[2] G. R. Clemo, T. Holmes, and G. C. Leitch, *J.*, 1938, 753.
[3] K. N. Campbell, C. H. Helbing, and J. F. Kerwin, *J. Amer. Chem. Soc.*, 1946, **68**, 1840.
[4] P. W. Neber and G. Huh, *Annalen*, 1935, **515**, 283.
[5] J. H. Ridd and B. V. Smith, *J.*, 1960, 1363.
[6] C. E. Hazeldine, F. L. Pyman, and J. Winchester, *J.*, 1924, **125**, 1431.

Experimental.—Analytical samples were dried *in vacuo* at 60°. The infrared spectra were measured in chloroform solution on a Perkin-Elmer model 21 spectrometer, ultraviolet absorption spectra were obtained on a Unicam model S.P. 500 spectrometer, and the nuclear magnetic resonance spectrum run on a Varian A-60 spectrometer.

Isolation of normacrorine. The separation of macrorine and isomacrorine and the partial separation of macrorungine from *Macrorungia longistrobus* C.B. Cl. has been described previously.[1] The remaining basic residue (13 g.) was chromatographed on silica (2 kg.). Elution with 9 : 1 and 1 : 1 methylene dichloride–methanol separated macrorungine (4 g.) from normacrorine (6 g.). Normacrorine was purified *via* its monopicrate (see below) from which it could be liberated by passage through basic alumina in acetone solution. The *alkaloid* crystallised from acetone–hexane as colourless plates, m. p. 156—157°, pK_a 5·36 (toluene-*p*-sulphonic acid in 50% MeOH); $\lambda_{max.}$ (in EtOH) 214, 236, 264, 325, and 336 mμ (ε 42·280, 15,760, 27,230, 10,500, and 10,980, respectively); or (in 1% HCl–EtOH) $\lambda_{max.}$ 215, 248, 257, 302, 315, 329, and 355 mμ (ε 31,290, 38,930, 46,340, 7160, 8600, 10,750, and 2750, respectively) (Found: C, 73·7; H, 5·0; N, 21·5. $C_{12}H_9N_3$ requires C, 73·8; H, 4·7; N, 21·5%). The *monopicrate* crystallised from methanol as yellow needles, m. p. 211—212° (decomp.) (Found: C, 51·3; H, 3·2; N, 19·6. $C_{18}H_{12}N_6O_7$ requires C, 51·0; H, 2·9; N, 19·8%).

Methylation of normacrorine. To normacrorine (192 mg.) was added, with cooling, dimethyl sulphate (190 mg.). The mixture was heated on a water-bath for 10 min., diluted with 0·5N-hydrochloric acid (50 ml.), and extracted with methylene dichloride (25 ml.). The aqueous solution was basified with sodium carbonate and extracted with methylene dichloride (100 ml.) to give a basic oil (80 mg.). Chromatography on formamide-impregnated cellulose (36%, 10 g.) and elution with 9 : 1 and 1 : 1 hexane–benzene separated the oil into isomacrorine (23 mg.) and macrorine (40 mg.). Both compounds were recrystallised from acetone–hexane and identified (m. p., and mixed m. p., and infrared spectra).

2-*Acetylquinoline* O-*toluene*-p-*sulphonyl oxime.* To the oxime [7] (7·4 g.) of 2-acetylquinoline (prepared from quinaldic acid by the method of Campbell [3]) dissolved in dry pyridine (15 ml.) was added, slowly, with cooling, toluene-*p*-sulphonyl chloride (8·4 g.). The brown solution was kept at room temperature for 24 hr. and poured into ice–water (1 l.). The crystals (12 g.) which separated were collected by filtration and recrystallised from acetone–hexane to give colourless needles, m. p. 131° (Found: C, 63·4; H, 4·8; N, 8·0. $C_{18}H_{16}N_2O_3S$ requires C, 63·5; H, 4·7; N, 8·2%).

2-ω-*Aminoacetylquinoline hydrochloride.* Potassium (910 mg.) was added to a suspension of the finely powdered toluene-*p*-sulphonyl ester (5·3 g.) in ethanol (150 ml.), and the mixture shaken for 18 hr. The precipitate of potassium toluene-*p*-sulphonate was removed by filtration and the filtrate diluted with ether (2 l.). A further precipitate of the potassium salt was filtered off and the ethereal solution extracted with 1·5N-hydrochloric acid (250 ml.). The combined extracts were evaporated to dryness at 40° under reduced pressure to give 2-ω-*aminoacetylquinoline hydrochloride* (4 g.). Recrystallisation of the hydrochloride from methanol afforded needles, m. p. 216° (decomp.) (Found: C, 59·1; H, 5·1; N, 12·1. $C_{11}H_{10}N_2O$,HCl requires C, 59·3; H, 5·0; N, 12·6%).

4(5)-2′-*Quinolylimidazole*-2-*thiol hydrochloride.* An excess of potassium thiocyanate was added to a solution of 2-ω-aminoacetylquinoline hydrochloride (3·6 g.) in water (20 ml.), and the mixture heated in boiling water for 3 min. It was then cooled, when 4(5)-2′-quinolylimidazol-2-thiol hydrochloride crystallised as fine dark brown needles (2·4 g.). The thiol hydrochloride could not be purified by crystallisation and was used directly for the next step.

Normacrorine. Nitric acid (3 ml.) was added to a dark brown solution of the thiol hydrochloride (800 mg.) in water (30 ml.) and the mixture heated on a water-bath for 1 hr. The now yellow solution was basified with ammonia and extracted with methylene dichloride (100 ml.) to give a brown oil (300 mg.). Chromatography on silica (20 g.) and elution with 20 : 1 methylene dichloride–methanol yielded a crystalline component (180 mg.) which was crystallised from acetone–hexane to give colourless needles, identical in m. p., mixed m. p., and infrared spectrum to authentic normacrorine. The picrate of the synthetic compound was prepared and recrystallised from methanol to give yellow needles, identical in m. p. and mixed m. p. to authentic normacrorine picrate.

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Pretoria, South Africa. [*Received, September 22nd*, 1964.]

[7] T. Nakashima, *Yakugaku Zasshi*, 1957, **77**, 1298 (*Chem. Abs.*, 1958, **52**, 6345i).