303. *Synthesis of 2-Aryl-1′-methylpyrrolo(3′,2′-3,4)-1,8-naphthyridines.*

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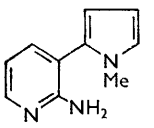
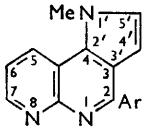
Several compounds containing the above ring system have been obtained by cyclisation of the *N*-acyl derivatives of 2-aminonicotyrine. The structures of the *NN*-diacyl derivatives of 2-aminonicotyrine and 2-aminopyridine are discussed.

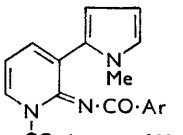
In an investigation of the reactions of certain derivatives of nicotine, we have prepared a number of aryl derivatives of a new heterocyclic ring system, pyrrolo(3′,2′-3,4)-1,8-naphthyridine. 2-Aminonicotyrine (I) was obtained by a Tshitschibabin reaction [1] on nicotyrine, this method being preferred to the dehydrogenation of 2-aminonicotine. Mono- and di-*N*-acyl derivatives of (I) have been cyclised by phosphorus oxychloride in hot toluene, the crystalline 2-aryl-1′-methylpyrrolo(3′,2′-3,4)-1,8-naphthyridines (II) being obtained in good yield. The 2-phenyl- and 2-*p*-methoxy-, 2-*p*-nitro-, 2-*o*-chloro-, and 2-*o*-bromo-phenyl derivatives are described below. The phthalimido-derivative of 2-aminonicotyrine could not be cyclised.



(I)



(II)



(III)

The acylation of 2-aminonicotyrine (I) afforded mono-derivatives with aromatic anhydrides and di-derivatives with aromatic acid chlorides in pyridine. The diaroyl derivatives could be represented either as 2-diaroylaminonicotyrines or 1-aroyl-2-aroylimino-1,2-dihydronicotyrines (III); initially the latter possibility was preferred, for whereas the diaroyl derivatives are insoluble in cold dilute acids the monoaroyl compounds are freely soluble. If structure (III) is the correct representation then different products should result from the anisoylation of 2-benzamidonicotyrine and from the benzoylation of the *N*-monoanisoyl derivative, it being well established that the 2-amino-group is acylated first. Unfortunately neither of the mixed diaroyl compounds could be obtained in a crystalline state.

However, a similar ambiguity exists with the structures of the *NN*-diaroyl derivatives of 2-aminopyridine itself. The two possible structures were mentioned when 2-dibenzoylaminopyridine was first made [2] but later workers [3] have assumed the 2-dibenzoylamino-structure to be correct but without proof. Monoaroylation of 2-aminopyridine offers no difficulty and the second aroyl group is best introduced by the Schotten–Baumann technique. The use of the acid chloride in pyridine for this step leads to exchange with the aroyl group already present; thus treatment of 2-benzamidopyridine with *p*-nitrobenzoyl chloride in boiling pyridine gave 2-*p*-nitrobenzamidopyridine [4] as the main product. The mixed benzoyl–anisoyl derivative of 2-aminopyridine was prepared by the Schotten–Baumann method from either 2-benzamidopyridine or 2-anisamidopyridine; the two compounds afforded the same crystalline diaroylamine, as shown by mixed melting point and infrared spectra. This experiment confirms the assumed structure of 2-dibenzoylaminopyridine, and by analogy the diaroyl derivatives of 2-aminonicotyrine probably also have both aroyl groups on the exocyclic nitrogen atom. In agreement with this

[1] Clemo and Swan, *J.*, 1945, 603.
[2] Tschitschibabin and Bylinken, *Ber.*, 1922, **55**, 998.
[3] Huntress and Walker, *J. Org. Chem.*, 1948, **13**, 735.
[4] Kuhn, Moller, Wendt, and Beener, *Ber.*, 1942, **75**, 711.

conclusion the ultraviolet spectra of mono- and di-benzoylaminonicotyrine are similar, the differences being explicable by the presence of an extra benzoyl group on an unaltered nicotyrine chromophore.

Experimental

2-*Aminonicotyrine*.—This was prepared by the amination of nicotyrine according to Clemo and Swan's directions [1] except that it was found advantageous to grind the sodamide under dry xylene in a slowly rotating ball-mill before use.

2-Aminonicotyrine had m. p. 76—78° (lit.,[5] 77°). 6-Aminonicotyrine had m. p. 90—92° (lit.,[5] 92°). 2-Benzamidonicotyrine [1] in ethanol showed $\lambda_{max.}$ 231 and 296 mμ (log ε 4·20 and 3·88 respectively).

The *dibenzoyl* derivative was prepared by the action of benzoyl chloride (2 mol.) in pyridine, the mixture being heated under reflux for 30 min. The benzoyl compound formed needles, m. p. 174—175° (from aqueous ethanol), raised to 176° by sublimation at 140°/1 mm. (Found: C, 75·2; H, 4·95; N, 10·9. $C_{24}H_{19}N_3O_2$ requires C, 75·55; H, 5·0; N, 11·0%), $\lambda_{max.}$ (in EtOH) 239 mμ (log ε 4·33), infl. 294 mμ (log ε 3·92).

The *mono*-p-*anisoyl derivative* was formed from 2-aminonicotyrine (1·14 g.) and *p*-anisic anhydride (1·8 g.) by heating the reactants together at 120° for 4 hr. Crystallisation of the product from ethanol (charcoal) gave the product as colourless needles, m. p. 190—192° (Found: C, 69·9; H, 5·5. $C_{18}H_{17}N_3O_2$ requires C, 70·3; H, 5·6%).

The *di*-p-*nitrobenzoyl derivative* was obtained from the base by the action of *p*-nitrobenzoyl chloride (2 mol.) in pyridine, the mixture being heated under reflux for 2 hr. Repeated crystallisation of the product from aqueous ethanol gave the di-*p*-nitrobenzoyl derivative as yellow needles, m. p. 208—209° (Found: C, 61·3; H, 4·1; N, 14·7. $C_{24}H_{17}N_5O_6$ requires C, 61·15; H, 3·65; N, 14·85%). Dilution of the hot mother-liquors gave the *mono*-p-*nitrobenzoyl derivative* which formed orange-yellow prisms, m. p. 176°, from aqueous ethanol (Found: C, 63·3; H, 4·3; N, 17·4. $C_{17}H_{14}N_4O_3$ requires C, 63·35; H, 4·4; N, 17·4%).

2-*Phthalimidonicotyrine*, prepared from the amine and phthalic anhydride at 100° for 2 hr., formed rhombs (from ethanol), m. p. 165—175°, resolidifying and then melting at 199° (Found: C, 71·0; H, 4·3. $C_{18}H_{13}N_3O_2$ requires C, 71·3; H, 4·3%).

1′-*Methyl*-2-*phenylpyrrolo*(3′,2′-3,4)-1,8-*naphthyridine*.—2-Dibenzoylaminonicotyrine (0·3 g.) was dissolved in dry toluene (25 c.c.), and phosphorus oxychloride (1 c.c.) was added. The solution was heated under reflux for 3 hr. during which a deep yellow colour developed. The solvents were then removed under reduced pressure (water-pump), and the residual gum was extracted with warm dilute acetic acid (25 c.c.), a crystalline residue of benzoic acid remaining. The yellow extract was cooled and basified with excess of concentrated aqueous ammonia; a colourless precipitate was obtained which was separated and crystallised from aqueous ethanol as prisms (0·18 g.), m. p. 182—183° (Found: C, 78·9; H, 5·15; N, 16·2. $C_{17}H_{13}N_3$ requires C, 78·75; H, 5·05; N, 16·2%), $\lambda_{max.}$ 258 and 345 mμ (log ε 4·62 and 3·91).

By a similar method, 2-*p*-anisamidonicotyrine was cyclised to 2-p-*methoxyphenyl*-1′-*methylpyrrolo*(3′,2′-3,4)-1,8-*naphthyridine* which formed needles (from ethanol), m. p. 212° (Found: C, 74·6; H, 5·2; N, 14·5. $C_{18}H_{15}N_3O$ requires C, 74·7; H, 5·2; N, 14·5%), $\lambda_{max.}$ 259 mμ (log ε 4·36).

A mixture of 2-mono- and 2-di-*p*-nitrobenzoylaminonicotyrine gave 1′-*methyl*-2-p-*nitrophenylpyrrolo*(3′,2′-3,4)-1,8-*naphthyridine* as deep yellow plates (from chloroform–methanol), m. p. 272—273° (Found: C, 66·9; H, 3·8; N, 18·1. $C_{17}H_{12}N_4O_2$ requires C, 67·1; H, 4·0; N, 18·4%), $\lambda_{max.}$ 252 and 360 mμ (log ε 4·47 and 3·97).

2-o-*Chlorophenyl*-1′-*methylpyrrolo*(3′,2′-3,4)-1,8-*naphthyridine* was obtained by cyclisation of 2-*o*-chlorobenzamidonicotyrine (colourless needles, m. p. 132—135°). The product formed colourless needles (from aqueous ethanol), m. p. 238—239° (Found: C, 69·3; H, 4·2; N, 14·0. $C_{17}H_{12}ClN_3$ requires C, 69·5; H, 4·2; N, 14·3%), $\lambda_{max.}$ 216, 256, and 338 mμ (log ε 4·53, 4·75, and 3·81 respectively).

2-o-*Bromophenyl*-1′-*methylpyrrolo*(3′,2′-3,4)-1,8-*naphthyridine* was obtained by cyclisation of 2-*o*-bromobenzamidonicotyrine (colourless needles, m. p. 219—223°). The product formed colourless needles (from aqueous ethanol), m. p. 245—246° (Found: C, 59·9; H, 3·5; N, 12·1. $C_{17}H_{12}BrN_3$ requires C, 60·4; H, 3·6; N, 12·45%), $\lambda_{max.}$ 216, 256, and 337 mμ (log ε 4·59, 4·62 and 3·87 respectively).

[5] Frank, Holley, and Wikholm, *J. Amer. Chem. Soc.*, 1942, **64**, 2835.

2-(N-*Anisoyl*-N-*benzoylamino*)*pyridine*.—2-Benzamidopyridine [2] afforded the *diaroyl derivative* when shaken with anisoyl chloride and aqueous sodium hydroxide. This formed colourless prisms, m. p. 160°, from ethanol (Found: C, 71·8; H, 5·1; N, 8·7. $C_{20}H_{16}N_2O_3$ requires C, 72·3; H, 4·8; N, 8·4%). The same compound was prepared by a similar benzoylation of 2-p-*anisamidopyridine* [colourless plates, m. p. 109°, from aqueous ethanol (Found: C, 68·4; H, 5·1. $C_{13}H_{12}N_2O_2$ requires C, 68·4; H, 5·3%), formed from the amine and anisoyl chloride in warm pyridine].

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