Naphthyridines. Part IV.[1] Preparation of Anthyridines and Pyrimido-[4,5-*b*][1,8]naphthyridines from 2-Amino-1,8-naphthyridines

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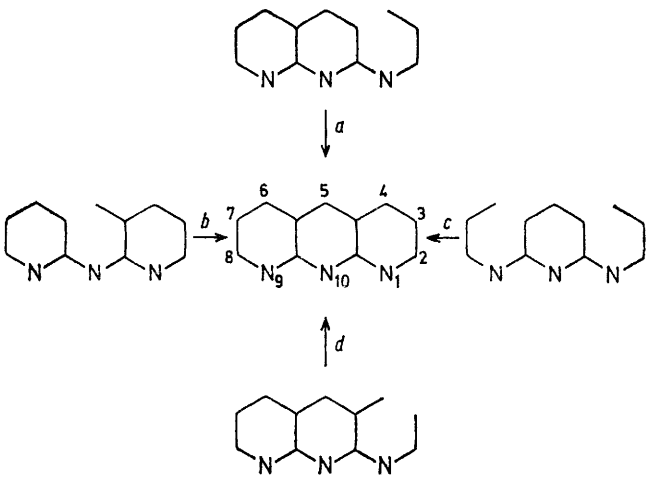
Syntheses of anthyridines by thermal cyclisation of 2-ethoxycarbonylvinylamino-1,8-naphthyridines, from derivatives of 2,6-diaminopyridine, and from 3-substituted 2-amino-1,8-naphthyridines, have been investigated. Pyrimido[4,5-*b*][1,8]naphthyridines have been prepared by cyclisation of 2-acetamido-1,8-naphthyridine-3-carboxamides.

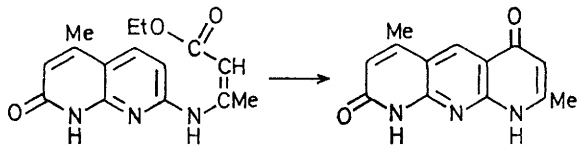
ANTHYRIDINE is the accepted trivial name for 1,8,9-triaza-anthracene or pyrido[2,3-*b*][1,8]naphthyridine. The first three reports [2] of the synthesis of anthyridines (1) are all unsubstantiated and it was not until 1966 that Carboni and his co-workers [3] provided a good general method. This involved a thermally induced intramolecular cyclisation of a 2-ethoxycarbonylvinylamino-1,8-naphthyridinone at the 3-position of the naphthyridine ring (Scheme 1, *a*). The reaction was subject to



SCHEME 1

thermodynamic control; lower temperatures caused cyclisation at the ring nitrogen atom to give the angularly fused pyrimido[1,2-*a*][1,8]naphthyridines. The anthyridines could alternatively be prepared by thermal rearrangement of these angular isomers,[4,5] by treatment of a 2-pyridylaminonicotinic acid with concentrated sulphuric acid at 200° (Scheme 1, *b*),[6] or in one step by the cyclisation of a 2,6-diethoxycarbonylvinylaminopyridine (Scheme 1, *c*).[7] The structures of the anthyridines have been established by both physical (m.p.s, solubilities, u.v. and i.r. spectra) and chemical (oxidation and hydrolysis reactions) methods.

We have investigated three different routes to the anthyridines. In the first, the cyclisation of the 2-ethoxycarbonylvinylamino-1,8-naphthyridines, described in the preceding paper [1] was studied. This did not prove to be a convenient route, the only pure compounds obtained being the known 4,8-dimethylanthyridine-2(1*H*),6(9*H*)-dione (3) [4] derived from 7-(2-



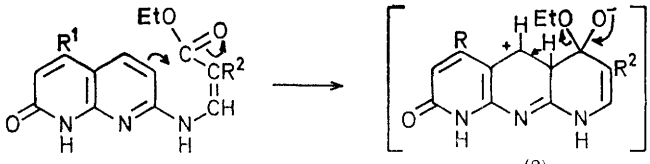
(2) (3)

ethoxycarbonyl-1-methylvinylamino)-4-methyl-1,8-naphthyridin-2(1*H*)-one (2) and 7-acetyl-4-methylanthyridine-2(1*H*),6(9*H*)-dione (9) obtained from 7-(2-acetyl-2-ethoxycarbonylvinylamino)-4-methyl-1,8-naphthyridin-2(1*H*)-one (4). The two anthyridines (3) and (9) showed the expected physical and chemical properties.[3] In addition, the n.m.r. spectra were particularly useful for structure assignments as the 5-protons are in a strongly deshielded environment and give rise to singlets at low field: τ 0·77 [compound (3)] and 0·02 [compound (9)].

The closely related 7-(2-acetyl-2-ethoxycarbonylvinylamino)-4-phenyl-1,8-naphthyridin-2(1*H*)-one (7) gave no tricyclic products when heated in Dowtherm-A or liquid paraffin at 340°. The two nitriles (5) and (6), on

[1] Part III, J. F. Harper and D. G. Wibberley, preceding paper.
[2] W. Schoeller and O. von Schickh, U.S.P. 2,002,280/1935; T. Takahashi, H. Saikachi, and T. Sasaki, *J. Pharm. Soc. Japan*, 1944, **8***A*, 221; C. R. Hauser and M. J. Weiss, *J. Org. Chem.*, 1949, **14**, 453.
[3] S. Carboni, A. Da Settimo, G. Pirisino, and D. Segnini, *Gazzetta*, 1966, **96**, 103; J. F. Harper, Ph.D. Thesis, University of Aston, 1970.
[4] S. Carboni, A. Da Settimo, D. Segnini, and I. Tonetti, *Gazzetta*, 1966, **96**, 1443.
[5] S. Carboni, A. Da Settimo, P. L. Ferrarini, and I. Tonetti, *Gazzetta*, 1967, **97**, 1262.
[6] S. Carboni, A. Da Settimo, and D. Segnini, *J. Heterocyclic Chem.*, 1969, **6**, 369.
[7] S. Carboni, A. Da Settimo, and I. Tonetti, *J. Heterocyclic Chem.*, 1970, **7**, 875.

the other hand, were affected on similar treatment. The insoluble solids which separated in low yield from the hot reaction mixture after 2 min at 340° had the high m.p.s, low solubilities, and i.r. spectra expected of the anthyridine-2(1*H*),6(9*H*)-diones (10) and (11), but were not obtained analytically pure. The other 2-ethoxycarbonylvinylamino-1,8-naphthyridines yielded either pyrimido[1,2-*a*][1,8]naphthyridines,[1] unchanged starting materials, or black tars on similar treatment. This type of ring closure obviously requires a high electron density at the 3-position of the naphthyridine ring (Scheme 2).



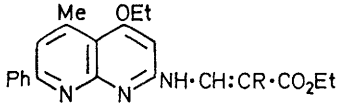
(4) R^1 = Me, R^2 = Ac
(5) R^1 = Me, R^2 = CN
(6) R^1 = Ph, R^2 = CN
(7) R^1 = Ph, R^2 = Ac

(8)

(9) R^1 = Me, R^2 = Ac
(10) R^1 = Me, R^2 = CN
(11) R^1 = Ph, R^2 = CN

SCHEME 2

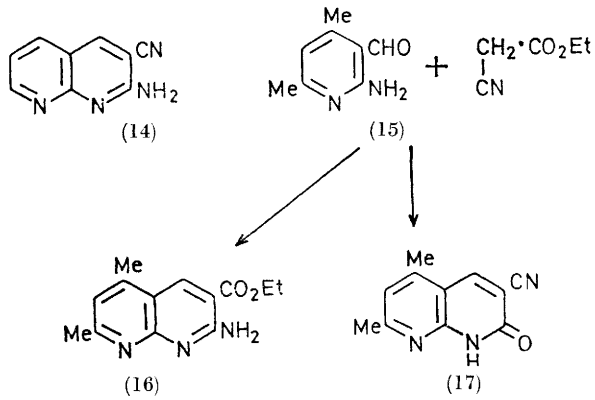
The 4-ethoxy-2-ethoxycarbonylvinylamino-1,8-naphthyridines [(12) and (13)], however, for which n.m.r.



(12) R = Ac
(13) R = CO_2Et

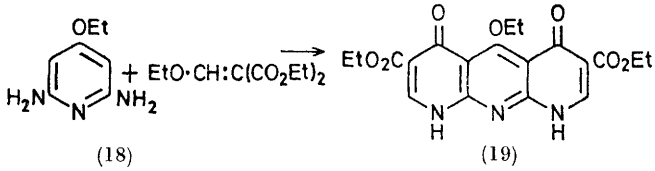
spectra indicate such a charge localisation, when treated at high temperature yield only the pyrimido[1,2-*a*][1,8]-naphthyridines, and isomerisation does not occur on prolonged heating. The only ethoxycarbonylvinylamino-1,8-naphthyridines which cyclised in this linear manner, either in Carboni's work or our own, were the 7-ethoxycarbonylvinylamino-1,8-naphthyridin-2(1*H*)-ones, in which the positive charge of the intermediate complex (8) could be delocalised to N-9.

Two attempts were made to synthesise anthyridines by application of the general Friedländer synthesis to 3-substituted 2-amino-1,8-naphthyridines (Scheme 1, *d*). 2-Amino-1,8-naphthyridine-3-carbonitrile (14) was treated with an excess of acetylacetone with piperidine as catalyst. Only unchanged starting material was isolated, owing presumably either to the low basicity of the exocyclic amino-group or to the weak electrophilicity of the cyano-group. A more reactive precursor would be ethyl 2-amino-5,7-dimethyl-1,8-naphthyridine-3-carboxylate (16), but attempts to synthesise this compound from 2-amino-4,6-dimethylnicotinaldehyde (15) yielded only traces of the required ester (16), together with much larger amounts of the cyano-naphthyridinone (17).



(14) (15) (16) (17)

In the third route to the anthyridines (Scheme 1, *c*) 2,6-diamino-4-ethoxypyridine (18) was heated under reflux in diethyl ethoxymethylenemalonate and a precipitate separated after 6 min. This product had m.p. >340°, and was insoluble in dilute acid and only very sparingly soluble in most organic solvents. Irreproducible analytical results were obtained, but the i.r., n.m.r., and mass spectra confirmed that the product was diethyl 5-ethoxy-1,4,6,9-tetrahydro-4,6-dioxo-1,8-



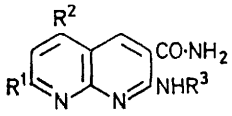
(18) (19)

anthyridine-3,7-dicarboxylate (19). The yield was only 11%, and since 2,6-diamino-4-ethoxypyridine is made by a five-stage synthesis from chelidamic acid [8] in an overall yield of only 10%, this route for the preparation of anthyridines is of limited practical value.

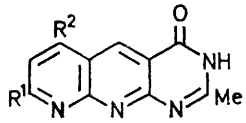
It has previously been found that 2-amino-1,8-naphthyridine-3-carboxamides (20)—(22) show both diuretic and anti-inflammatory activity in rats.[9] For this reason we investigated the preparation of the previously unknown pyrimido[4,5-*b*][1,8]naphthyridin-4(3*H*)-ones in order to compare their pharmacological properties. Mulvey *et al.*[10] have reported the conversion of 2-aminopyridine-3-carboxamides into pyrido-[2,3-*d*]pyrimidin-4(3*H*)-ones by treatment with triethyl orthoformate in acetic anhydride. When this reaction was applied to 2-amino-1,8-naphthyridine-3-carboxamide (20) the only product was the 2-acetamidonaphthyridine (23). The diamides are better prepared by treatment of the amines (20)—(22) with acetic anhydride alone. Cyclisation to the pyrimido[4,5-*b*][1,8]naphthyridin-4(3*H*)-ones (26)—(28) was accomplished by treatment of the diamides (23)—(25) with warm aqueous ammonia solution.

[8] D. G. Markees, V. C. Dewey, and G. W. Kidder, *J. Medicin. Chem.*, 1968, **11**, 126.
[9] E. M. Hawes, Ph.D. Thesis, University of London, 1967.
[10] D. M. Mulvey, S. G. Cottis, and H. Tieckelmann, *J. Org. Chem.*, 1963, **29**, 2903.

The pyrimidonaphthyridines were distinguishable from the diamides by their i.r., n.m.r., and mass spectra. Of particular diagnostic value were the deshielding of the 5-proton of the pyrimidonaphthyridines (originally



(20) $R^1 = R^2 = R^3 = H$
(21) $R^1 = Ph$, $R^2 = R^3 = H$
(22) $R^1 = R^2 = Me$, $R^3 = H$
(23) $R^1 = R^2 = H$, $R^3 = Ac$
(24) $R^1 = Ph$, $R^2 = H$, $R^3 = Ac$
(25) $R^1 = R^2 = Me$, $R^3 = Ac$



(26) $R^1 = R^2 = H$
(27) $R^1 = Ph$, $R^2 = H$
(28) $R^1 = R^2 = Me$

the 4-proton of the naphthyridines) (τ 0·37—0·65 lower), and of the 2-Me group of the pyrimidonaphthyridines (originally the *Me*CONH group of the naphthyridines) (τ 0·54—0·62). The mass spectra of the three 2-methylpyrimido[4,5-*b*][1,8]naphthyridin-4(3*H*)-ones (26)—(28) closely resembled those of 2-methylpteridin-4(3*H*)-one [11] and 2-methylpyrido[3,2-*d*]pyrimidin-4(3*H*)-one.[12] The molecular ion was the base peak in all three ring systems, and CO loss was the most important initial fragmentation, to yield ions with relative abundances of 12 [compound (26)], 21 [2-methylpteridin-4(3*H*)-one], and 22% {2-methylpyrido[3,2-*d*]pyrimidin-4(3*H*)-one}. Loss of a methyl group was also common to all three spectra (9, 3, and 3%, respectively) and moderately prominent peaks could be accounted for by $(M - CO - MeCN)^+$ fragmentation ions (35, 21, and 14%, respectively). The diamides (23)—(25), on the other hand, were much less stable to electron impact, the molecular ions carried a much smaller percentage of the ion current, and more prominent peaks were observed for the $(M - Me)^+$, $(M - NH_3)^+$, $(M - H_2O)^+$, and $(M - MeCO)^+$ fragmentation ions.

EXPERIMENTAL

U.v. spectra were recorded on a Unicam SP 800 spectrophotometer, i.r. spectra on a Unicam SP 200 spectrophotometer, n.m.r. spectra on a Varian A60-A spectrometer at 60 MHz using tetramethylsilane as internal standard, and mass spectra on an A.E.I. MS9 spectrometer operating at 50 μA and 70 eV. Light petroleum refers to the fraction of boiling range 60—80°. Dowtherm-A refers to the mixture having the composition diphenyl ether 76%, biphenyl 24%. 4,8-Dimethylanthyridine-2(1*H*),6(9*H*)-dione (3) was prepared [4] from 7-amino-4-methyl-1,8-naphthyridin-2(1*H*)-one; τ (CF_3·CO_2H) 0·77 (1H, s, 5-H), 2·87 (1H, s, 3-H or 7-H), 3·02 (1H, s, 3-H or 7-H), 7·01 (3H, s, 8-Me), and 7·20 (3H, s, 4-Me).

7-*Acetyl*-4-*methylanthyridine*-2(1H),6(9H)-*dione* (9).—7-(2-Acetyl-2-ethoxycarbonylvinylamino)-4-phenyl-1,8-naphthyridin-2(1*H*)-one (0·6 g) was added to boiling Dowtherm-A (12 g) and the solution was boiled for 10 min. The hot suspension was filtered through sintered glass and the filtrate cooled to yield the *anthyridinone* (0·3 g) (55%), m.p. >330°. The product was purified by boiling with 2-ethoxyethanol, and washing the solid with hot ethanol (Found: C, 62·2; H, 4·4; N, 15·7%; *M*, 269. $C_{14}H_{11}N_3O_3$ requires C, 62·4; H, 4·1; N, 15·6%; *M*, 269), $\nu_{max.}$ 1680 (ketone C=O) 1660 (amide C=O), 1650 (amide C=O), and 1630 (C=N) cm^{-1}, τ (CF_3·CO_2H) 0·02 (1H, s, 5-H), 0·40 (1H, s, 8-H), 2·87 (1H, s, 3-H), 7·04 (3H, s, 4-Me), 7·13 (3H, s, COMe), *m/e* 271 (1%), 270 (13), 269 (65), 255 (17), 254 (100), 227 (12), 226 (6), 199 (5), 198 (5), 171 (6), 170 (3), 143 (4), 127 (5), 113 (8), 77 (3), 53 (3), and 43 (6), *m** 239·7 (269 → 254), 201·0 (254 → 226), and 173·5 (226 → 198).

Attempted Preparation of 1,4,8,9-*Tetrahydro*-6-*methyl*-4,8-*dioxoanthyridine*-3-*carbonitrile* (10).—7-(2-Cyano-2-ethoxycarbonylvinylamino)-4-methyl-1,8-naphthyridin-2(1*H*)-one (0·25 g) was added to liquid paraffin (40 ml) at 330°. The mixture was heated at 340—350° for 10 min; a precipitate appeared after 2 min. The cooled suspension was centrifuged to collect the precipitate, which was washed thoroughly with light petroleum followed by diethyl ether, and was then dried. The yield (m.p. >330°) was 0·025 g. No suitable solvent for recrystallisation could be found, and a correct analysis for $C_{13}H_8N_4O_2$ was not obtained; $\nu_{max.}$ (KBr) 3100 (NH), 2250 (C≡N), and 1660 (amide C=O) cm^{-1}.

Attempted Preparation of 1,4,8,9-*Tetrahydro*-4,8-*dioxo*-6-*phenylanthyridine*-3-*carbonitrile* (11).—7-(2-Cyano-2-ethoxycarbonylvinylamino)-4-phenyl-1,8-naphthyridin-2(1*H*)-one (0·3 g) was added to liquid paraffin (45 ml) at 330° to yield the crude product, m.p. 300° (decomp.) (0·12 g). No suitable solvent could be found for recrystallisation and a correct analysis for $C_{18}H_{10}N_4O_2$ was not obtained, $\nu_{max.}$ 3450, 3200 (NH), 2250 (C≡N), and 1660 (C=O) cm^{-1}.

Diethyl 5-*Ethoxy*-1,4,6,9-*tetrahydro*-4,6-*dioxoanthyridine*-3,7-*dicarboxylate* (19).—A solution of 2,6-diamino-4-ethoxypyridine (0·3 g) in diethyl ethoxymethylenemalonate (3 g) was refluxed (air-condenser) with collection of distillate for 40 min. The suspension was cooled and filtered; the solid collected was washed with ethanol to yield the anthyridinedione (0·9 g) (11%), m.p. >330°. No suitable solvent could be found for recrystallisation and analysis of the acid-washed material gave incorrect figures for $C_{19}H_{19}N_3O_7$, $\nu_{max.}$ 3150 (NH), 1710 (ester C=O), and 1640 (amide C=O) cm^{-1}, τ (CF_3·CO_2H) 0·72 (2H, s, 2-H and 8-H), 5·06—5·70 (6H, m, 2 × CO_2·CH_2Me and O·CH_2Me), and 8·50 (9H, t, 2 × CO_2·CH_2*Me* and O·CH_2*Me*), *m/e* 401 (1%), 400 (1), 399 (6), 372 (3), 371 (12), 359 (3), 329 (5), 328 (14), 311 (2), 303 (6), 302 (34), 284 (17), 283 (69), 255 (100), 229 (3), 199 (3), 198 (3), 170 (4), 143 (8), 141 (4), 115 (2), 93 (1), 53 (10), and 44 (6).

2-*Amino*-4,6-*dimethylnicotinohydrazide*.—Ethyl 2-amino-4,6-dimethylnicotinate (7·1 g), hydrazine hydrate (10 g), and 2-ethoxyethanol (70 ml) were heated together under reflux with stirring at 140° for 60 h. The solution was evaporated to dryness, and the solid was washed with ethanol to yield the *hydrazide* (3·6 g) (53%), prisms, m.p. 178—179° (from ethanol) (Found: C, 53·2; H, 6·9; N, 31·2. $C_8H_{12}N_4O$ requires C, 53·3; H, 6·7; N, 31·1%), $\nu_{max.}$ 3450, 3350, 3250, 3150 (NH), and 1620 (C=O) cm^{-1}.

2-*Amino*-4,6-*dimethylnicotinaldehyde* (15).—Toluene-*p*-sulphonyl chloride (3·8 g) in pyridine (10 ml) was added slowly (1 h) to a solution of 2-amino-4,6-dimethylnicotinohydrazide (3·6 g) in pyridine (100 ml) at 10°. The solution was set aside for 1 h, then most of the solvent was removed by distillation under reduced pressure. Addition of acetone

[11] W. J. Irwin and D. G. Wibberley, unpublished work.
[12] I. R. Gelling, W. J. Irwin, and D. G. Wibberley, *J. Chem. Soc.* (*B*), 1969, 513.

to the residue precipitated *N*-(2-amino-4,6-dimethylnicotinoyl)-*N'*-*p*-tolylsulphonylhydrazine (5·2 g) (79%), needles, m.p. 243° (decomp.) (from ethanol), $\nu_{max.}$ 3450, 3350, 3200 (NH), 1690 (C=O), and 1150 (SO_2) cm^{-1}. A suspension of the hydrazide (4·4 g) (recrystallised material only, m.p. 243°) in ethylene glycol (30 ml) was stirred at 170° for 15 min to ensure complete dissolution. Sodium carbonate (1 g) was then added to the hot solution, which was stirred for 1 min and then cooled rapidly. Water (20 ml) was added and the solution was extracted with chloroform. The dried ($MgSO_4$) extracts yielded the *nicotinaldehyde* (0·5 g) (25%), m.p. 161—162° (from water) (Found: C, 63·7; H, 6·8; N, 18·6. $C_8H_{10}N_2O$ requires C, 64·0; H, 6·7; N, 18·7%), $\nu_{max.}$ 3400, 3300, 3250 (NH), and 1660 (C=O) cm^{-1}.

Attempted Preparation of Ethyl 2-Amino-5,7-dimethyl-1,8-naphthyridine-3-carboxylate (16).—2-Amino-4,6-dimethylnicotinaldehyde (0·4 g) was dissolved in ethanol (15 ml) with ethyl cyanoacetate (0·8 g) and piperidine (0·10 ml), and the solution was refluxed on a steam-bath for 4 h. The mixture was cooled to 40° and then filtered. The residue was reserved (see later); the filtrate was set aside for 6 h, and the solid which crystallised was collected and suspended in chloroform (10 ml). This suspension was filtered and the filtrate was evaporated to yield an unknown by-product, m.p. 255—257° (from ethanol). The residue (see before) was washed with chloroform, then dried to yield *1,2-dihydro-5,7-dimethyl-2-oxonaphthyridine-3-carbonitrile* (17) (0·3 g), m.p. 299—300° (decomp.) (from 2-ethoxyethanol) (Found: C, 66·2; H, 4·6; N, 21·2. $C_{11}H_9N_3O$ requires C, 66·3; H, 4·6; N, 21·1%), $\nu_{max.}$ 3250 (NH), 2250 (C≡N), and 1680 (C=O) cm^{-1}.

2-Amino-5,7-dimethyl-1,8-naphthyridine-3-carboxamide (22).—A solution of 2-amino-4,6-dimethylnicotinaldehyde (0·15 g) and cyanoacetamide (0·16 g) in ethanol (10 ml) containing piperidine (0·05 ml) was refluxed on a steam-bath for 1 h. The hot suspension was filtered, and the residue was washed with hot ethanol. The yield of naphthyridine-3-carboxamide was 0·1 g (48%); pale yellow needles, m.p. 262° (decomp.) (from methanol), $\nu_{max.}$ (KBr) 3500, 3460, 3380, 3340 (NH), 1680 (C=O), and 1630 (C=N) cm^{-1}.

2-Acetamido-1,8-naphthyridine-3-carboxamide (23).—A solution of 2-amino-1,8-naphthyridine-3-carboxamide (0·95 g) in acetic anhydride (12 ml) was heated under reflux at 130° for 2 h. The suspension was filtered, and the collected solid was washed with acetone and dried to yield the *acetamidonaphthyridine* (1·1 g) (95%), m.p. >350° (from 2-ethoxyethanol) (Found: C, 57·3; H, 4·5; N, 24·5%; *M*, 230. $C_{11}H_{10}N_4O_2$ requires C, 57·4; H, 4·4; N, 24·3%; *M*, 230), $\nu_{max.}$ 3350, 3200 (NH), 1700 and 1680 (amide I), 1630 (amide II), 1600, and 1570 (amide II) cm^{-1}, τ ($CF_3{\cdot}CO_2H$) 0·61 (1H, s, 4-H), 0·65—1·07 (2H, m, 5-H and 7-H), 1·65—2·41 (2H, m, 6-H and N*H*·COMe), and 7·37 (3H, s, NH·CO*Me*).

2-Acetamido-7-phenyl-1,8-naphthyridine-3-carboxamide (24).—Similarly 2-amino-7-phenyl-1,8-naphthyridine-3-carboxamide and acetic anhydride yielded the *acetamidonaphthyridine* (69%), prisms, m.p. >350°. An analytical sample was prepared by treating the crude product with boiling 2-ethoxyethanol; the hot suspension was filtered and the residue washed with warm ethanol before drying (Found: C, 66·5; H, 4·5; N, 18·5%; *M*, 306. $C_{17}H_{14}N_4O_2$ requires C, 66·7; H, 4·6; N, 18·3%; *M*, 306), $\nu_{max.}$ 3350, 3200 (NH), 1700 and 1670 (amide I), 1630 (amide II), 1600, and 1570 (amide II) cm^{-1}, τ ($CF_3{\cdot}CO_2H$) 0·59 (1H, s, 4-H), 1·08 (1H, d, *J* 9 Hz, 5-H), 1·58 (1H, d, *J* 9 Hz, 6-H), 1·45—2·40 (6H, m, phenyl, and N*H*·COMe), and 7·35 (3H, s, NH·CO*Me*).

2-Acetamido-5,7-dimethyl-1,8-naphthyridine-3-carboxamide (25).— 2-Amino-5,7-dimethyl-1,8-naphthyridine-3-carboxamide and acetic anhydride yielded the *acetamidonaphthyridine* (82%), m.p. 246° (decomp.) (Found: C, 60·3; H, 5·3; N, 21·4%; *M*, 258. $C_{13}H_{14}N_4O_2$ requires C, 60·4; H, 5·5; N, 21·7%; *M*, 258), $\nu_{max.}$ 3400 (NH), 1700 and 1680 (amide I), 1640 (amide II), 1610, and 1570 (amide II) cm^{-1}, τ ($CF_3{\cdot}CO_2H$) 0·72 (1H, s, 4-H), 1·83—2·50br (1H, N*H*·COMe), 2·20 (1H, s, 6-H), 6·93 (6H, s, 5-Me and 7-Me), and 7·40 (3H, s, NH·CO*Me*).

2-Methylpyrimido[4,5-*b*][1,8]*naphthyridin*-4(3H)-*one* (26).—2-Acetamido-1,8-naphthyridine-3-carboxamide (0·23 g) was mixed with water (3 ml) and ammonia (*d* 0·88; 3 ml) and the mixture was warmed on a steam-bath under reflux for 40 min. The cooled mixture was filtered, and the solid collected was washed with water and dried to yield the *pyrimidonaphthyridinone* (0·21 g) (95%). The crude product was treated with boiling 2-ethoxyethanol, filtered off, and washed with ethanol. The pure material had m.p. >350° (Found: C, 61·7; H, 3·8; N, 26·4%; *M*, 212. $C_{11}H_8N_4O$ requires C, 62·3; H, 3·8; N, 26·4%; *M*, 212), $\nu_{max.}$ 3400 (NH), 1700 (C=O), and 1630 (C=N) cm^{-1}, τ ($CF_3{\cdot}CO_2H$) 0·24 (1H, s, 5-H), 0·29—0·51 (2H, m, 6-H and 8-H), 1·33—1·69 (1H, m, 7-H), and 6·80 (3H, s, 2-Me), *m/e* 213 (17%), 212 (100), 197 (9), 184 (12), 171 (22), 171 (4), 154 (4), 144 (16), 143 (35), 128 (4), 116 (13), 112 (5), 75 (50), 63 (50), 42 (10), and 28 (10), *m** 159·7 (212→184).

2-Methyl-8-phenylpyrimido[4,5-b][1,8]*naphthyridin*-4(3H)-*one* (27).—Similarly 2-acetamido-7-phenyl-1,8-naphthyridine-3-carboxamide and ammonia (*d* 0·88) yielded the *pyrimidonaphthyridinone* (95%), yellow needles, m.p. >350° (from dimethylformamide) (Found: C, 70·5; H, 4·4; N, 19·3%; *M*, 288. $C_{17}H_{12}N_4O$ requires C, 70·8; H, 4·2; N, 19·4%; *M*, 288), $\nu_{max.}$ 3150 (NH), 1680 (C=O), and 1630 (C=N) cm^{-1}, τ ($CF_3{\cdot}CO_2H$) 0·13 (1H, s, 5-H), 0·58 (1H, d, *J* 9 Hz, 6-H), 1·33 (1H, d, *J* 9 Hz, 7-H), 1·52—2·30 (5H, m, phenyl), and 6·81 (3H, s, 2-Me), *m/e* 289 (22%), 288 (100), 286 (43), 246 (8), 245 (5), 219 (12), 218 (17), 217 (17), 216 (5), 192 (13), 191 (9), 160 (9), 140 (4), 139 (4), 115 (5), 102 (9), 89 (4), 77 (8), 76 (5), 75 (5), 63 (6), 51 (8), and 42 (27), *m** 210·8 (287→246), 166·5 (219→191).

2,6,8-Trimethylpyrimido[4,5-b][1,8]*naphthyridin*-4(3H)-*one* (28).—2-Acetamido-5,7-dimethyl-1,8-naphthyridine-3-carboxamide and ammonia (*d* 0·88) yielded the *pyrimidonaphthyridinone* (95%), which crystallised as yellow needles of the monohydrate, m.p. >350° (from water) (Found: C, 60·6; H, 5·0; N, 21·7%; *M*, 240. $C_{13}H_{12}N_4O,H_2O$ requires C, 60·4; H, 5·5; N, 21·7%; *M*, 240), $\nu_{max.}$ 1680 (C=O) cm^{-1}, τ ($CF_3{\cdot}CO_2H$) 0·07 (1H, s, 5-H), 1·97 (1H, s, 7-H), 6·78 (6H, s, 6- and 8-Me), and 6·85 (3H, s, 2-Me), *m/e* 241 (18%), 240 (100), 238 (4), 225 (4), 212 (5), 200 (3), 199 (19), 198 (3), 182 (1), 173 (2), 172 (10), 171 (10), 170 (4), 157 (3), 156 (4), 155 (3), 144 (4), 143 (3), 130 (3), 129 (3), 128 (3), 120 (2), 116 (3), 103 (3), 102 (3), 98 (3), 89 (2), 78 (2), 77 (3), 63 (2), 51 (3), 42 (9), and 39 (3), *m** 211·2 (240→225), 187·2 (240→212), and 165·0 (240→199).

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