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Novel annulated products from aminonaphthyridinones

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Abstract—2-(4-Methoxyphenyl)-1-oxo-1,2-dihydro-1,6-naphthyridine-4-carboxamide (**4c**) underwent Hofmann rearrangement with iodobenzene diacetate in methanol to give the corresponding 4-amino compound (**6c**). This, when reacted with 2,4-pentanedione and then hot phosphoryl chloride (attempted Combes synthesis) gave a new heterocyclic system, 6-(4-methoxyphenyl)-2-methylpyrido[3,2-*c*]pyrrolo[2,3-*e*]azocin-7(6*H*)-one (**9c**). This showed typical pyrrole-type reactivity at the 3-position. Alternatively, an attempt to convert the 4-NH_2 in **6c** to 4-OH by diazotization gave, instead, a [1,2,3]triazolo[1,5-*a*]pyridine-3-carboxaldehyde (**16c**). The same series of reactions on a benzo analog, 2-methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxamide (**4a**), gave the same results.

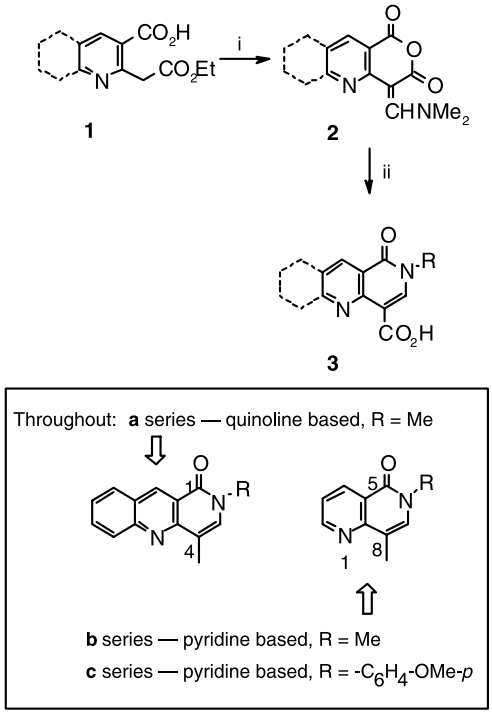
1. Introduction

We have previously demonstrated a useful transformation in which tricyclic dione **2a**, readily prepared by reaction of Vilsmeier reagent on the quinoline derivative **1a**, are converted to acids **3** by reaction with a range of primary amines (Scheme 1), and carboxamides derived from the tricyclic series have revealed potent antitumor activity.[1] As part of a continuing search for new heterocyclic systems as precursors of pharmacologically active derivatives, we sought to convert the carboxyl group in **3** (now extended to bicyclic, pyridine-based analogs) to amino and then build a further ring by any of various well known methods. This paper reports on success with the former and some unexpected findings during the latter.

2. Results and discussion

2.1. Preparation of the amino compounds

Classical methods for the change $-CO_2H \rightarrow -NH_2$ include the Hofmann[2a,3] and Curtius[4] rearrangements. We have concentrated on the former, and the necessary amide intermediates **4** were prepared by standard conversion to the acyl chloride followed by reaction with ammonia (Scheme 2). Many variations on the original bromine/aqueous sodium hydroxide rearrangement conditions have been reported. Of particular interest was a method which used iodobenzene diacetate in methanol under mild conditions.[5] In the present research, this worked well to give methyl carbamates **5**, which were hydrolyzed in alkali to liberate the amines **6**; the procedure was optimized so that it was not necessary to isolate the carbamates.



Scheme 1. (i) DMF–$POCl_3$/0 °C, then 20 °C/2 h; (ii) DMF+2.5 mol $MeNH_2$–THF for a, b; 3 mol anisidine+4 mol NEt_3 for c. All: 20 °C/16 h.

An interesting observation was that, for no obvious reason, the stability of **6** was quite variable. Amine **6b** was quite unstable;

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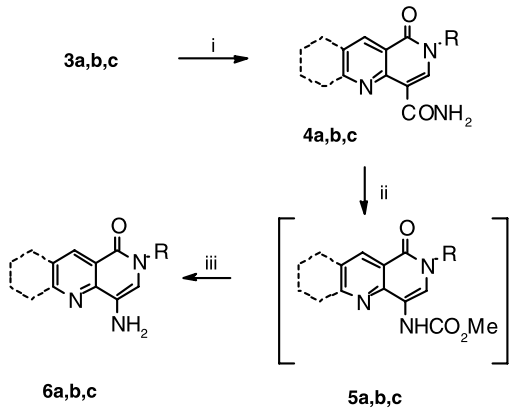
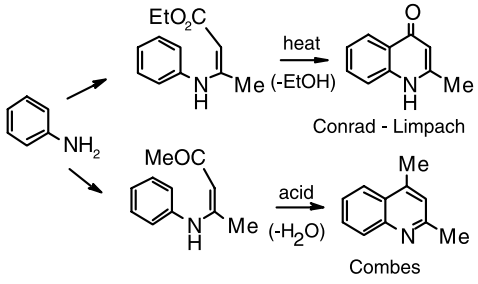


Scheme 2. (i) $SOCl_2$/reflux 0.5 h. Evap, add CH_2Cl_2. Bubble $NH_{3(g)}$; (ii) 1.1 mol $PhI(OAc)_2$/5 mol KOH/MeOH/5 °C, then 20 °C/0.5 h; (iii) Add 10 mol KOH/H_2O/reflux 3 h.

this compound had been previously reported by a different, longer sequence and noted to be unstable.[6] Some other examples not covered in the present paper were also unstable but, on the other hand, **6a** (same NR group as **6b**) and **6c** (same bicyclic system but different R group) were stable solids.

2.2. Attempted Combes synthesis

The construction of a further ring onto aniline is the basis of many classic syntheses of quinoline derivatives. In particular, β-keto esters (or ethoxymethylenemalonates) lead to quinolin-4-ones (Conrad–Limpach synthesis).[7a] The closely related Combes synthesis uses β-diketones as the 3-carbon source and acidic conditions for cyclization of the intermediate[7b] (Scheme 3), and these general pathways are applicable to many other aromatic amines.

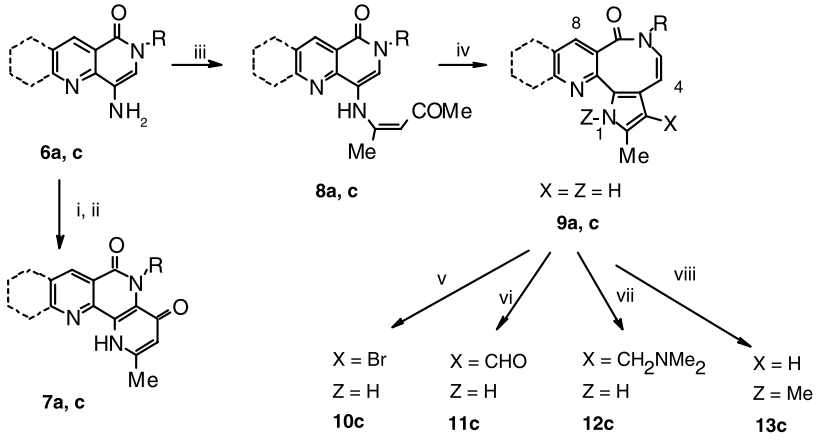


Scheme 3.

The Conrad–Limpach synthesis with ethyl acetoacetate proceeded as expected. By the standard route, a six-membered ring was added to the bicyclic **6c** and tricyclic **6a** to give **7c** and **7a**, respectively (Scheme 4).

The first step of the Combes synthesis, condensation with 2,4-pentanedione, gave the isolable intermediates **8**, sufficiently pure for direct further use. However, treatment with concentrated sulfuric acid or polyphosphoric acid at 100 °C failed to produce the desired cyclized product. The products were neither purified nor identified, but it was clear from ^{1}H NMR analysis that the sidechains had been lost.

At this point, we noted a literature report where sulfuric acid produced 'unsatisfactory results' but where hot phosphoryl chloride gave the desired product.[8] When applied to **8c**, a substantial amount of a fawn solid was isolated, but early NMR analysis showed this was not the expected product (see Scheme 3); while the carbon count was the same as in **8c**, there was only one methyl signal, and there were three single proton signals in the region 5.9–6.3 ppm, not expected for a fully aromatic product. Elemental analysis was in accord with a formula equivalent to a loss of water from **8c** (giving a yield of 77%), and the novel structure **9c** was assigned from analysis of data from various NMR experiments. Particularly informative were data for these three protons showing in the alkene region of the ^{1}H NMR spectrum, now assigned as H-3 (δ 5.85, s), H-4 (δ 6.27, d, J=8.1 Hz), and H-5 (δ 6.13, d, J=8.1 Hz). $^3J_{CH}$ couplings were crucial; from H–Me to C-3, from H-5 to the low field C-7 (these fixed both ends of the 6 carbon sequence C–Me–C-5), from both H-3 and H-4 to the same quaternary carbon, C-11b. The absence of coupling between H-3 and H-4 was consistent with the intermediacy of the quaternary carbon, C-3a, which did show $^3J_{CH}$ coupling to H-1 and H-5. The mechanism of this overall dehydration reaction, and the reason why the conventional six-membered annulation did not occur, is unclear. The enol form of the side chain, probably as a phosphorus-containing derivative, is a likely initiator of a sequence of ring forming and ring opening steps to create the five- and eight-membered rings.



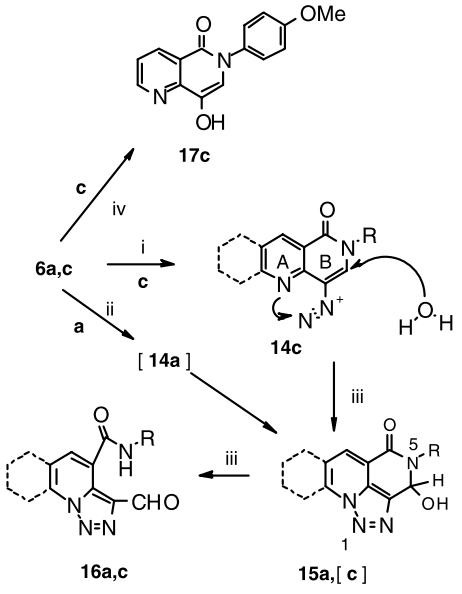
Scheme 4. (i) $AcCH_2CO_2Et/CaSO_4$/HOAc/EtOH/reflux 3.5 h; (ii) Ph_2O/250 °C/15 min; (iii) acac/$CaSO_4$/HOAc/EtOH/reflux 3.5 h, (iv) $POCl_3$/reflux 1 h; (v) Br_2/CH_2Cl_2/20 °C/10 min; (vi) 35 equiv $POCl_3$–DMF/DMF/0 °C/1 h; (vii) $Me_2NH_2^+Cl^-/(CH_2O)n$/EtOH/50 °C/4 h; (viii) MeI/C_6H_6–25%NaOH/TBAHS/stir vigorously 20 °C/24 h.

The tetracyclic analogue **9a** (64%) was formed in the same way from **6a**.

The ready availability of this new system prompted some further chemistry to check out the potential reactivity of the azocine and/or pyrrole rings. It appears that the 4,5-double bond in the former is reasonably stable while the latter readily undergoes typical pyrrole reactions at the available 1- and 3-positions (the work was confined to the more accessible **9c**). Thus, bromination with bromine in chloroform was immediate to give **10c** (92%), Vilsmeier reaction gave the aldehyde **11c** (83%), the Mannich reaction with dimethylamine hydrochloride and paraformaldehyde gave a 64% yield of **12c**, while reaction with methyl iodide under phase transfer conditions, as for indole,[9] gave the anticipated *N*-methyl product **13c** (88%). The ability to readily attach reactive functionalities to the 3-position potentially opens the way to further derivatization, and hence to interesting compounds for pharmacological testing.

2.3. Diazotization of the amines

A second, quite different type of reaction on the amino compounds **6a**, **6c** also led to unexpected annulation products (Scheme 5).



Scheme 5. (i) $NaNO_2$/43% HBF_4/H_2O/0 °C/1 h; (ii) $NaNO_2$/43% HBF_4/H_2O/20 °C/1 h, then MeCN/H_2O/5 min; (iii) 1% NaOH/20 °C/1 h; (iv) 5 mol $Na_2S_2O_5$/H_2O/reflux 4 h, then 10 mol NaOH/reflux 24 h.

The aim was to convert the amino to a hydroxy function, to prepare analogues of 8-hydroxyquinoline. A traditional way of achieving this conversion for aromatic amines is by hydrolysis of an intermediate diazonium salt.[2b] When **6c** in fluoroboric acid at 0 °C was treated with aqueous sodium nitrite,[10] a solid was precipitated. This was unstable in most solvents, for example, DMSO (immediate bubbling) but a ^{1}H NMR spectrum was obtained in acetone. Its general form suggested that the bicyclic system was intact and the compound was most likely the anticipated diazonium salt **14c**. The IR spectrum contained a strong band at 2228 cm^{-1}, consistent with the presence of the N≡N group.[11] When this salt was suspended in water and treated with 10% sodium hydroxide, a white solid resulted, which was not the target hydroxy compound but, rather, the triazolopyrido aldehyde **16c**. The formation of the triazole ring was indirectly suggested by a characteristic change in chemical shifts (proton and carbon) and coupling constants (proton) of the A ring atoms compared with **6c** and **14c**. Cleavage of the B ring was clear from characteristic NMR aldehyde signals [δ 10.22 (^{1}H), 183.3 (^{13}C) ppm], while assignment of the singlet at δ 10.48 ppm as the NH proton was based on its exchange with D_2O and $^3J_{CH}$ coupling with *ortho* protons in the R group (–C_6H_4–OMe-*p*) in the HMBC spectrum.

While the triazolopyridine system is not new, this method of formation is novel. The best standard synthesis appears to be by heating the tosylhydrazone of a pyridine-2-carboxaldehyde in morpholine at 95–100 °C.[12] A plausible mechanism in the present case requires that, reasonably, position 7 in **14c** is more electron deficient than position 8 and hydrolysis occurs here as shown in Scheme 5. In this case, the presumed intermediate **15c** was not isolated. There is precedence for water attack at an alternative highly electron deficient centre in a diazonium derivative of a quinolizinium ion.[13] It is noteworthy that in the sequence of Scheme 5, in contrast to the formation of compounds **9** earlier, cleavage of the naphthyridinone ring occurs at the N-6–C-7 bond.

While the same final result was obtained from the tricyclic **14a**, some interesting differences emerged. For solubility reasons, the diazotization reaction had to be carried out at room temperature. A pink solid separated immediately but, in this case, it was not the diazonium salt. The NMR resolution was improved following precipitation of a white solid by water addition to an acetonitrile solution. For this compound, the ^{1}H NMR spectrum was able to be obtained in DMSO and contained, in addition to the expected aromatic proton signals, two doublets at δ 6.35 and 7.11 ppm (J= 9.5 Hz). The latter disappeared on addition of D_2O while the former became a singlet. This compound was therefore assigned structure **15a**, the proposed immediate hydrolysis product of the diazonium salt, and apparently more stable in the tricyclic than bicyclic case. Rapid isomerization to the ring-open aldehyde **16a** was brought about by treatment with 1% aqueous NaOH. In this case where R=Me, the methyl signal in the NMR spectrum occurred as a doublet (J=4.4 Hz), providing further evidence for the ring cleavage having resulted in formation of the NH group. Interestingly, the above DMSO/D_2O NMR sample of **15a** quite rapidly changed to a mixture of **15a** and **16a**.

2.4. Corollary

The synthesis of the hydroxy compound **17c** has been achieved by reaction of **6c** with aqueous bisulfite, the Bucherer reaction[14] (Scheme 5). This was interesting as the Bucherer reaction is of limited scope and is typically applied to naphthalene derivatives. However, the yield of **17c** was unaccountably variable, while low yields of unidentified products resulted when the same conditions were applied to some analogs of **6c**.

3. Experimental

3.1. General

NMR spectra were recorded at 300.13 MHz (^{1}H) and 75.47 MHz (^{13}C) on a Bruker Avance 300 spectrometer. Chemical shifts are reported as δ values (ppm) relative to Me_4Si. Standard PENDANT, HSQC, and HMBC spectra were used in making the NMR assignments. Melting points are uncorrected. Microanalyses were performed at the Campbell Microanalytical Laboratory, University of Otago, New Zealand.

3.2. Precursors

Diones **2**[1a,15] and acid **3a**[1a] were prepared as previously reported. Acid **3b**, earlier synthesized from the dione by reaction with hot $POCl_3$,[15] was better prepared by reaction with methylamine,[16] as for **3a**.

3.2.1. 6-(4-Methoxyphenyl)-5-oxo-5,6-dihydro-1,6-naphthyridine-8-carboxylic acid (3c). To a suspension of dione **2b**,**c** (2.26 g, 10.37 mmol) in DMF (34 mL) was added Et_3N (5.65 mL) followed by *p*-anisidine (3.83 g, 31.10 mmol), and the whole was stirred for 16 h. Ice/water (ca. 100 mL) was added and the mixture was taken to pH 1 with 3.3% HCl. The resultant precipitate was filtered and washed with water to give carboxylic acid **3c** (1.86 g, 61%) as a beige solid, mp 245–246 °C, which was used without further purification. ^{1}H NMR (DMSO-d_6): δ 3.80 (s, 3H, O–CH_3), 7.07 (d, J=8.9 Hz, 2H, H-3′, H-5′), 7.44 (d, J=8.9 Hz, 2H, H-2′, H-6′), 7.76 (dd, J=8.1, 4.8 Hz, 1H, H-3), 8.35 (s, 1H, H-7), 8.74 (dd, J=8.1, 1.4 Hz, 1H, H-4), 9.07 (dd, J=4.8, 1.4 Hz, 1H, H-2), 15.18 (br s, 1H, CO_2H). ^{13}C NMR (DMSO-d_6): δ 55.6 (O–CH_3), 104.6 (C-8), 114.5 (C-3′, C-5′), 121.1 (C-4*a*), 123.3 (C-3), 128.2 (C-2′, C-6′), 132.7 (C-1′), 138.8 (C-4), 145.2 (C-7), 150.2 (C-8*a*), 152.6 (C-2), 159.4 (C-4′), 161.1 (C-5), 164.8 (CO_2H).

3.3. Preparation of amides

3.3.1. 2-Methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridine-4-carboxamide (4a). Acid **3a** (2.41 g, 9.49 mmol) in $SOCl_2$ (24 mL) was heated under reflux for 30 min. The excess $SOCl_2$ was removed in vacuo and CH_2Cl_2 (40 mL) was added to the residue. Ammonia gas was bubbled through the mixture for 5 min, which was then evaporated at reduced pressure. Water was added and the mixture was filtered to give **4a** as a pale yellow solid (2.31 g, 96%), mp >300 °C (from 1,4-dioxane). ^{1}H NMR (DMSO-d_6): δ 3.60 (s, 3H, N–CH_3), 7.66 (t, J=7.4 Hz, 1H, H-8), 7.77 (br s, 1H, NH), 7.94 (t, J=7.7 Hz, 1H, H-7), 8.16 (d, J=8.6 Hz, 1H, H-6), 8.27 (d, J=8.3 Hz, 1H, H-9), 8.62 (s, 1H, H-3), 9.37 (s, 1H, H-10), 10.09 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6), 100 °C: δ 36.5 (N–CH_3), 109.1 (C-10*a*), 119.5 (C-4), 125.7 (C-9*a*), 126.8 (C-8), 128.1 (C-6), 129.6 (C-9), 133.2 (C-7), 139.3 (C-10), 144.9 (C-3), 148.7 (C-5*a*), 149.8 (C-4*a*), 162.2 (C-1), 164.9 ($CONH_2$). Anal. Calcd for $C_{14}H_{11}N_3O_2\cdot 0.1H_2O$: C, 65.93; H, 4.43; N, 16.47. Found: C, 65.82; H, 4.51; N, 16.30%.

3.3.2. 6-Methyl-5-oxo-5,6-dihydro-1,6-naphthyridine-8-carboxamide (4b). This was prepared from acid **3b**, as for **4a**, and obtained as a white solid (89%), mp 276–278 °C (from 1,4-dioxane). ^{1}H NMR (DMSO-d_6): δ 3.59 (s, 3H, N–CH_3), 7.59 (dd, J=8.1, 4.5 Hz, 1H, H-3), 7.68 (br s, 1H, NH), 8.57 (s, 1H, H-7), 8.62 (dd, J=8.1, 1.8 Hz, 1H, H-4), 8.98 (dd, J=4.5, 1.8 Hz, 1H, H-2), 9.71 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6), 100 °C: δ 36.7 (N–CH_3), 109.2 (C-8), 120.5 (C-4*a*), 121.9 (C-3), 136.9 (C-4), 143.8 (C-7), 150.7 (C-8*a*), 153.2 (C-2), 161.7 (C-5), 164.7 ($CONH_2$). Anal. Calcd for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.46; N, 20.68. Found: C, 59.11; H, 4.62; N, 20.76%.

3.3.3. 6-(4-Methoxyphenyl)-5-oxo-5,6-dihydro-1,6-naphthyridine-8-carboxamide (4c). This was prepared from acid **3c**, as for **4a**, and obtained as white needles (98%), mp 285–286 °C (from 1,4-dioxane). ^{1}H NMR (DMSO-d_6): δ 3.80 (s, 3H, O–CH_3), 7.06 (d, J=8.6 Hz, 2H, H-3′, H-5′), 7.43 (d, J=8.6 Hz, 2H, H-2′, H-6′), 7.65 (dd, J=8.0, 4.6 Hz, 1H, H-3), 7.79 (br s, 1H, NH), 8.31 (s, 1H, H-7), 8.65 (d, J=8.0 Hz, 1H, H-4), 9.03 (d, J=4.6 Hz, 1H, H-2), 9.73 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 55.6 (O–CH_3), 109.1 (C-8), 114.5 (C-3′, C-5′), 121.2 (C-4*a*), 122.5 (C-3), 128.2 (C-2′, C-6′), 133.1 (C-1′), 137.6 (C-4), 143.2 (C-7), 150.6 (C-8*a*), 153.7 (C-2), 159.3 (C-4′), 161.5 (C-5), 164.5 ($CONH_2$). Anal. Calcd for $C_{16}H_{13}N_3O_3$: C, 65.08; H, 4.44; N, 14.23. Found: C, 64.84; H, 4.49; N, 14.20%.

3.4. Hofmann rearrangement

3.4.1. 4-Amino-2-methylbenzo[*b*][1,6]naphthyridin-1(2*H*)-one (6a). A solution of KOH (1.11 g, 19.78 mmol) in MeOH (10 mL) was cooled to approximately 5 °C. To this mixture was added iodobenzene diacetate (1.40 g, 4.35 mmol) and carboxamide **4a** (1.00 g, 3.95 mmol). The mixture was allowed to warm to room temperature and was then stirred vigorously for 30 min to make the intermediate carbamate **5a**. A solution of KOH (2.22 g, 39.57 mmol) in MeOH (10 mL) and water (2 mL) was added, and the whole was heated under reflux for 3 h. The dark red solution was cooled, and the solid, which separated was collected by filtration and washed with water to give amine **6a** as orange needles (0.54 g, 61%), mp 197–199 °C (dec) (from EtOH). Extraction of the filtrate with CH_2Cl_2 (2×20 mL) gave a further 0.08 g. ^{1}H NMR (DMSO-d_6): δ 3.44 (s, 3H, N–CH_3), 4.76 (br s, 2H, NH_2), 6.96 (s, 1H, H-3), 7.63 (t, J=7.4 Hz, 1H, H-8), 7.91 (t, J=7.7 Hz, 1H, H-7), 8.10 (d, J=8.6 Hz, 1H, H-6), 8.25 (d, J=8.4 Hz, 1H, H-9), 9.27 (s, 1H, H-10). ^{13}C NMR (DMSO-d_6): δ 35.8 (N–CH_3), 116.4 (C-3), 120.0 (C-10*a*), 126.0 (C-4), 126.3 (C-9*a*), 126.4 (C-8), 128.4 (C-6), 129.8 (C-9), 132.5 (C-7), 138.3 (C-10), 146.7 (C-4*a*), 149.1 (C-5*a*), 159.1 (C-1). Anal. Calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.65. Found: C, 69.04; H, 5.12; N, 18.48%.

3.4.2. 8-Amino-6-methyl-1,6-naphthyridin-5(6*H*)-one (6b). This was prepared from **4b**, as for **6a**. Water was added to the red reaction solution, which was then neutralized with AcOH and evaporated to dryness at reduced pressure. The residue was boiled with chloroform and filtered. Evaporation of the chloroform from the filtrate gave amine **6b** as a brown solid (86%), which was unstable and rapidly decomposed. ^{1}H NMR (DMSO-d_6): δ 3.42 (s, 3H, N–CH_3), 4.68 (br s, 2H, NH_2), 6.93 (s, 1H, H-7), 7.52

(dd, J=8.0, 4.5 Hz, 1H, H-3), 8.51 (dd, J=8.0, 1.7 Hz, 1H, H-4), 8.90 (dd, J=4.5, 1.7 Hz, 1H, H-2). ^{13}C NMR (DMSO-d_6): δ 36.1 (CH_3), 116.2 (C-7), 120.9 (C-4*a*), 122.1 (C-3), 126.3 (C-8), 136.0 (C-4), 147.0 (C-8*a*), 153.1 (C-2), 158.5 (C-5).

3.4.3. 8-Amino-6-(4-methoxyphenyl)-1,6-naphthyridin-5(6*H*)-one (6c). This was prepared from **4c**, as for **6a**, and obtained as yellow needles (68%), mp 164–165 °C (from EtOH). ^{1}H NMR (DMSO-d_6): δ 3.78 (s, 3H, O–CH_3), 4.72 (br s, 2H, NH_2), 6.91 (s, 1H, H-7), 7.02 (d, J=8.8 Hz, 2H, H-3′, H-5′), 7.35 (d, J=8.8 Hz, 2H, H-2′, H-6′), 7.58 (dd, J=8.0, 4.5 Hz, 1H, H-3), 8.55 (d, J=8.0 Hz, 1H, H-4), 8.96 (d, J=4.5 Hz, 1H, H-2). ^{13}C NMR (DMSO-d_6): δ 55.5 (O–CH_3), 114.3 (C-3′, C-5′), 115.9 (C-7), 121.5 (C-4*a*), 122.5 (C-3), 126.6 (C-8), 128.0 (C-2′, C-6′), 134.3 (C-1′), 136.5 (C-4), 147.4 (C-8*a*), 153.5 (C-2), 158.4 (C-4′), 158.5 (C-5). Anal. Calcd for $C_{15}H_{13}N_3O_2$: C, 67.41; H, 4.90; N, 15.72. Found: C, 67.10; H, 5.07; N, 15.45%.

3.5. Conrad–Limpach synthesis

3.5.1. 2,5-Dimethylquinolino[3,2-*c*][1,6]naphthyridine-4,6(1*H*,5*H*)-dione (7a). To a warm solution of amine **6a** (0.34 g, 1.51 mmol) in EtOH (35 mL) was added ethyl acetoacetate (0.26 g, 1.96 mmol), $CaSO_4$ (1.03 g, 7.56 mmol) and AcOH (3.5 mL). This mixture was heated under reflux for 3.5 h, then filtered while hot and the filtrate was evaporated under reduced pressure to give the crotonate intermediate as an orange solid (0.46 g, 90%). A sample (0.26 g, 0.77 mmol) was added in portions to Ph_2O (2 mL) heated at 250 °C, and the solution was heated for a further 15 min. After being cooling to room temperature, the solution was poured onto Et_2O (50 mL) and the resultant precipitate was filtered and washed thoroughly with hot Et_2O to give **7a** as a brown solid (0.20 g, 89%), mp 159–162 °C [from CH_2Cl_2/petroleum spirit (bp 80–110 °C)]. ^{1}H NMR (DMSO-d_6): δ 2.43 (s, 3H, C–CH_3), 4.01 (s, 3H, N–CH_3), 6.17 (s, 1H, H-3), 7.76 (t, J=7.5 Hz, 1H, H-9), 8.03 (t, J=7.8 Hz, 1H, H-10), 8.30 (d, J=8.7 Hz, 1H, H-11), 8.36 (d, J=8.4 Hz, 1H, H-8), 9.40 (s, 1H, H-7), 11.61 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 18.7 (C–*C*H_3), 33.2 (N–CH_3), 116.1 (C-3), 119.7 (C), 126.8 (C), 127.6 (C-7*a*), 127.7 (C-9), 128.4 (C-4*a*, C-11), 129.9 (C-8), 133.3 (C-10), 138.9 (C-7), 143.7 (C-12*a*), 146.1 (C-2), 149.0 (C-11*a*), 160.4 (C-6), 171.7 (C-4). Anal. Calcd for $C_{17}H_{13}N_3O_2\cdot 0.5H_2O$: C, 67.99; H, 4.70; N, 13.99. Found: C, 68.08; H, 4.73; N, 13.60%.

3.5.2. 5-(4-Methoxyphenyl)-2-methylpyrido[3,2-*h*]-[1,6]naphthyridine-4,6(1*H*,5*H*)-dione (7c). This was prepared from amine **6c**, as for **7a**, and obtained as a light brown solid (71%). For microanalysis, a sample on a short bed of silica was washed with EtOAc, then eluted with MeCN. The residue after evaporation of the MeCN was recrystallized from MeCN to give **7c** as a fawn solid, mp 298–300 °C. ^{1}H NMR (DMSO-d_6): δ 2.35 (s, 3H, C–CH_3), 3.76 (s, 3H, O–CH_3), 5.92 (s, 1H, H-3), 6.85 (d, J=8.9 Hz, 2H, H-3′, H-5′), 7.05 (d, J=8.9 Hz, 2H, H-2′, H-6′), 7.81 (dd, J=8.0, 4.5 Hz, 1H, H-8), 8.62 (dd, J=8.0, 1.7 Hz, 1H, H-7), 9.14 (dd, J=4.5, 1.7 Hz, 1H, H-9), 11.80 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 18.6 (C–*C*H_3), 55.3 (O–CH_3), 112.9 (C-3′, C-5′), 115.5 (C-3), 122.4 (C-6*a*), 125.4 (C-8), 126.6 (C-10*b*), 128.2 (C-4*a*), 128.6 (C-2′, C-6′), 133.4 (C-1′), 137.0 (C-7), 145.2 (C-10*a*), 146.1 (C-2), 154.2 (C-9), 157.9 (C-4′), 160.2 (C-6), 169.5 (C-4). Anal. Calcd for $C_{19}H_{15}N_3O_3$: C, 68.46; H, 4.54; N, 12.61. Found: C, 68.04; H, 4.66; N, 12.79%.

3.6. Attempted Combes synthesis

3.6.1. 4-[2-Methyl-1-oxo-1,2-dihydrobenzo[*b*][1,6]naphthyridin-4-yl]aminopent-3-en-2-one (8a). To a solution of **6a** (0.25 g, 1.11 mmol) in EtOH (25 mL), was added 2,4-pentanedione (0.14 g, 1.44 mmol), $CaSO_4$ (0.76 g, 5.56 mmol) and AcOH (2.5 mL). The red mixture was heated under reflux for 3.5 h, then filtered and the filtrate was evaporated under reduced pressure to give **8a** as a red solid (0.33 g, 97%), used in this state in the next reaction. ^{1}H NMR (DMSO-d_6): δ 1.98 (s, 3H, CH_3-5), 2.01 (s, 3H, CH_3-1), 3.52 (s, 3H, N–CH_3), 5.28 (s, 1H, H-3), 7.65 (t, J=7.5 Hz, 1H, H-8′), 7.87 (s, 1H, H-3′), 7.91 (t, J=7.7 Hz, 1H, H-7′), 8.04 (d, J=8.6 Hz, 1H, H-6′), 8.27 (d, J=8.3 Hz, 1H, H-9′), 9.31 (s, 1H, H-10′), 12.25 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 19.6 (CH_3-5), 29.1 (CH_3-1), 36.2 (N–CH_3), 97.6 (C-3), 116.6 (C), 119.6 (C), 126.3 (C-9*a*′), 126.7 (C-8′), 128.6 (C-6′), 129.8 (C-9′), 132.9 (C-7′), 133.3 (C-3′), 138.5 (C-10′), 148.4 (C-4*a*′), 149.5 (C-5*a*′), 160.9 (C-1′), 161.2 (C-4), 194.7 (C-2).

3.6.2. 8-[6-(4-Methoxyphenyl)-5-oxo-5,6-dihydro-1,6-naphthyridin-8-yl]aminopent-3-en-2-one (8c). This was prepared from **6c**, as for **8a**, and obtained as a red solid (87%), used in this state in the next reaction. ^{1}H NMR (DMSO-d_6): δ 1.95 (s, 3H, CH_3-5), 1.96 (s, 3H, CH_3-1), 3.79 (s, 3H, O–CH_3), 5.22 (s, 1H, H-3), 7.02 (d, J=8.8 Hz, 2H, H-3″, H-5″), 7.35 (d, J=8.8 Hz, 2H, H-2″, H-6″), 7.58 (dd, J=8.0, 4.5 Hz, 1H, H-3′), 7.75 (s, 1H, H-7′), 8.55 (d, J=8.0 Hz, 1H, H-4′), 8.99 (dd, J=4.5 Hz, 1H, H-2′). ^{13}C NMR (DMSO-d_6): δ 19.4 (C-5), 29.1 (C-1), 55.6 (O–CH_3), 97.6 (C-3), 114.3 (C-3″, C-5″), 117.2 (C-8′), 121.4 (C-4*a*′), 123.0 (C-3′), 128.3 (C-2″, C-6″), 132.4 (C-7′), 133.3 (C-1″), 136.5 (C-4′), 149.6 (C-8*a*′), 154.6 (C-2′), 158.9 (C-4″), 160.2 (C-5′), 161.3 (C-4) 194.8 (C-2).

3.6.3. 2,6-Dimethylpyrrolo[2′,3′:5,6]azocino[4,3-*b*]-quinolin-7(6*H*)-one (9a). Compound **8a** (0.33 g, 1.07 mmol) was added to $POCl_3$ (10 mL) and the whole was heated under reflux for 1 h. The solvent was evaporated under reduced pressure and water (30 mL) was added. The brown mixture was filtered, and the filtrate was basified with 10% NaOH. The solid, which separated was filtered and washed with water to give **9a** (0.20 g, 64%) as a light brown solid. For microanalysis, a sample on a short bed of silica was eluted with EtOAc–hexane (1/1). The residue after evaporation of the solvents was recrystallized from MeCN to give **9a** as a mustard solid, mp 294–296 °C (after darkening >270 °C). ^{1}H NMR (DMSO-d_6): δ 2.25 (s, 3H, C–CH_3), 3.00 (s, 3H, N–CH_3), 5.78 (d, J=2.0 Hz, 1H, H-3), 6.12 (d, J=8.3 Hz, 1H, H-4), 6.16 (d, J=8.3 Hz, 1H, H-5), 7.53 (t, J=7.5 Hz, 1H, H-10), 7.75 (t, J=7.7 Hz, 1H, H-11), 7.91–7.98 (m, 2H, H-9, H-12), 8.32 (s, 1H, H-8), 11.57 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 12.7 (C–*C*H_3), 35.4 (N–CH_3), 106.9 (C-3), 119.2 (C-3*a*), 120.5 (C-4), 125.7 (C-8*a*), 126.3 (C-10), 128.2 (C-12), 128.3 (C-9), 128.6 (C-5), 128.9 (C-13*b*), 130.8 (C-11), 132.0

(C-2), 132.2 (C-7*a*), 136.1 (C-8), 147.3 (C-12*a*), 148.8 (C-13*a*), 167.3 (C-7). Anal. Calcd for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52. Found: C, 74.50; H, 5.29; N, 14.60%.

3.6.4. 6-(4-Methoxyphenyl)-2-methylpyrido[3,2-*c*]-pyrrolo[2,3-*e*]azocin-7(6*H*)-one (9c). This was prepared from **8c**, as for **9a**, and **9c** (77%) was purified in the same way (elution with acetone) and obtained as a fawn solid, mp 244–246 °C after recrystallization from toluene. ^{1}H NMR (DMSO-d_6): δ 2.24 (s, 3H, C–CH_3), 3.73 (s, 3H, O–CH_3), 5.85 (s, 1H, H-3), 6.13 (d, J=8.1 Hz, 1H, H-5), 6.27 (d, J=8.1 Hz, 1H, H-4), 6.94 (d, J=8.7 Hz, 2H, H-3′, H-5′), 7.16 (d, J=8.7 Hz, 2H, H-2′, H-6′), 7.32 (dd, J=7.7, 4.4 Hz, 1H, H-9), 7.91 (d, J=7.7 Hz, 1H, H-8), 8.59 (d, J=4.4 Hz, 1H, H-10), 11.46 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 12.7 (C–*C*H$_3$), 55.4 (O–*C*H$_3$), 106.4 (C-3), 114.2 (C-3′, C-5′), 118.5 (C-3*a*), 121.2 (C-9), 122.2 (C-4), 127.8 (C-2′, C-6′), 127.9 (C-5), 129.0 (C-11*b*), 130.3 (C-2), 133.1 (C-7*a*), 133.3 (C-1′), 136.1 (C-8), 147.3 (C-11*a*), 149.6 (C-10), 158.1 (C-4′), 167.5 (C-7). Anal. Calcd for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.57; H, 5.00; N, 12.71%.

3.7. Bromination

3.7.1. 3-Bromo-6-(4-methoxyphenyl)-2-methylpyrido-[3,2-*c*]pyrrolo[2,3-*e*]azocin-7(6*H*)-one (10c). To a solution of **9c** (0.14 g, 0.42 mmol) in CH_2Cl_2 (30 mL) was added bromine (0.11 g, 0.69 mmol). The solution was stirred for 10 min, washed with 10% K_2CO_3 (2×20 mL), and the organic phase was dried with $MgSO_4$ and evaporated to give **10c** (0.16 g, 92%) as a fawn solid, mp 227–230 °C [from CH_2Cl_2/petroleum spirit (bp 80–110 °C)]. ^{1}H NMR (DMSO-d_6): δ 2.22 (s, 3H, C–CH_3), 3.73 (s, 3H, O–CH_3), 6.13 (d, J=8.0 Hz, 1H, H-4), 6.27 (d, J=8.0 Hz, 1H, H-5), 6.97 (d, J=8.9 Hz, 2H, H-3′, H-5′), 7.15 (d, J=8.9 Hz, 2H, H-2′, H-6′), 7.40 (dd, J=7.8, 4.8 Hz, 1H, H-9), 7.98 (dd, J=7.8, 1.6 Hz, 1H, H-8), 8.63 (dd, J=4.8, 1.6 Hz, 1H, H-10), 12.05 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 11.5 (C–*C*H$_3$), 55.5 (O–*C*H$_3$), 94.8 (C-3), 114.3 (C-3′, C-5′), 117.7 (C-3*a*), 120.4 (C-4), 122.0 (C-9), 127.6 (C-2′, C-6′), 128.8 (C-11*b*), 129.5 (C-2), 129.7 (C-5), 132.8 (C-1′), 133.4 (C-7*a*), 136.5 (C-8), 146.4 (C-11*a*), 149.8 (C-10), 158.2 (C-4′), 167.0 (C-7). Anal. Calcd for $C_{20}H_{16}BrN_3O_2\cdot 0.5H_2O$: C, 57.29; H, 4.09; N, 10.02. Found: C, 57.70; H, 4.09; N, 10.00%.

3.8. Vilsmeier–Haack formylation

3.8.1. 3-Formyl-6-(4-methoxyphenyl)-2-methylpyrido-[3,2-*c*]pyrrolo[2,3-*e*]azocin-7(6*H*)-one (11c). To DMF (2 mL) at 0 °C was added $POCl_3$ (1 mL), dropwise and with stirring. Azocine **9c** (0.10 g, 0.30 mmol) in DMF (2 mL) was added. The cold solution was stirred for 1 h, then poured onto ice/water (30 mL) and basified to pH 9 with 10% NaOH solution. The resultant brown precipitate was filtered and washed with water to give aldehyde **11c** (0.09 g, 83%) as a brown solid, mp 257–259 °C (from toluene). ^{1}H NMR (DMSO-d_6): δ 2.54 (s, 3H, C–CH_3), 3.73 (s, 3H, O–CH_3), 6.27 (d, J=8.1 Hz, 1H, H-5), 6.51 (d, J=8.1 Hz, 1H, H-4), 6.94 (d, J=8.9 Hz, 2H, H-3′, H-5′), 7.17 (d, J=8.9 Hz, 2H, H-2′, H-6′), 7.45 (dd, J=7.8, 4.8 Hz, 1H, H-9), 8.01 (dd, J=7.8, 1.5 Hz, 1H, H-8), 8.68 (dd, J=4.8, 1.5 Hz, 1H, H-10), 9.91 (s, 1H, CHO), 12.40 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 11.2 (C–*C*H$_3$), 55.4 (O–*C*H$_3$), 114.2 (C-3′, C-5′), 117.6 (C-3*a*), 119.6 (C-3), 121.8 (C-4), 122.4 (C-9), 127.6 (C-2′, C-6′), 128.9 (C-5), 130.2 (C-11*b*), 132.9 (C-1′), 133.8 (C-7*a*), 136.4 (C-8), 142.0 (C-2), 145.6 (C-11*a*), 150.0 (C-10), 158.1 (C-4′), 167.0 (C-7), 185.1 (CHO). Anal. Calcd for $C_{21}H_{17}N_3O_3$: C, 70.18; H, 4.77; N, 11.69. Found: C, 70.59; H, 4.89; N, 11.67%.

3.9. Mannich reaction

3.9.1. 3-(Dimethylamino)methyl-6-(4-methoxyphenyl)-2-methylpyrido[3,2-*c*]pyrrolo[2,3-*e*]azocin-7(6*H*)-one (12c). To a mixture of dimethylamine hydrochloride (0.96 g) and paraformaldehyde (0.48 g) in EtOH (15 mL) was added azocine **9c** (0.12 g, 0.36 mmol) and the whole was heated at 50 °C for 4 h. The mixture was evaporated at reduced pressure and water (30 mL) was added. The solution was basified with 10% NaOH solution and extracted with CH_2Cl_2 (3×10 mL). The combined extracts were washed with water (2×20 mL), dried over $MgSO_4$ and evaporated under reduced pressure to give **12c** (0.09 g, 64%) as a light brown solid, mp 112–114 °C (from toluene). ^{1}H NMR (DMSO-d_6): δ 2.10 [s, 6H, N(CH$_3$)$_2$], 2.21 (s, 3H, C–CH_3), 3.17 (d, J=4.9 Hz, 2H, CH_2), 3.73 (s, 3H, O–CH_3), 6.14 (d, J=8.2 Hz, 1H, H-5), 6.32 (d, J=8.2 Hz, 1H, H-4), 6.92 (d, J=8.9 Hz, 2H, H-3′, H-5′), 7.23 (d, J=8.9 Hz, 2H, H-2′, H-6′), 7.32 (dd, J=7.8, 4.7 Hz, 1H, H-9), 7.90 (dd, J=7.8, 1.5 Hz, 1H, H-8), 8.59 (dd, J=4.7, 1.5 Hz, 1H, H-10), 11.39 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 10.9 (C–*C*H$_3$), 45.0 [N(CH$_3$)$_2$], 53.8 (CH_2), 55.4 (O–*C*H$_3$), 114.0 (C-3′, C-5′), 115.5 (C-3), 118.7 (C-3*a*), 121.1 (C-9), 122.1 (C-4), 127.8 (C-2′, C-6′, C-5), 128.1 (C-11*b*), 129.9 (C-2), 133.2 (C-7*a*, C-1′), 136.0 (C-8), 147.4 (C-11*a*), 149.6 (C-10), 158.0 (C-4′), 167.3 (C-7). Anal. Calcd for $C_{23}H_{24}N_4O_2\cdot 0.25H_2O$: C, 70.29; H, 6.28; N, 14.26. Found: C, 70.32; H, 6.17; N, 14.11%.

3.10. *N*-Methylation

3.10.1. 1-Methyl-6-(4-methoxyphenyl)-2-methylpyrido-[3,2-*c*]pyrrolo[2,3-*e*]azocin-7(6*H*)-one (13c). To a stirred solution of azocine **9c** (0.24 g, 0.73 mmol) in C_6H_6 (20 mL), was added 25% NaOH solution (15 mL), tetra-*n*-butylammonium hydrogen sulfate (0.27 g, 0.80 mmol) and methyl iodide (1 mL). The biphasic mixture was stirred vigorously for 24 h. Water (20 mL) was added and the organic phase was separated, washed with water (3× 20 mL), dried over $MgSO_4$ and evaporated under reduced pressure to give **13c** as a brown solid (0.22 g, 88%), mp 157–160 °C [from petroleum spirit (bp 80–110 °C)]. ^{1}H NMR (DMSO-d_6): δ 2.25 (s, 3H, C–CH_3), 3.60 (s, 3H, N–CH_3), 3.73 (s, 3H, O–CH_3), 5.92 (s, 1H, H-3), 6.13 (d, J=8.1 Hz, 1H, H-5), 6.26 (d, J=8.1 Hz, 1H, H-4), 6.94 (d, J=8.9 Hz, 2H, H-3′, H-5′), 7.17 (d, J=8.9 Hz, 2H, H-2′, H-6′), 7.36 (dd, J=7.8, 4.8 Hz, 1H, H-9), 7.96 (dd, J=7.8, 1.5 Hz, 1H, H-8), 8.65 (dd, J=4.8, 1.5 Hz, 1H, H-10). ^{13}C NMR (DMSO-d_6): δ 12.0 (C–*C*H$_3$), 31.7 (N–*C*H$_3$), 55.4 (CH_3, O–*C*H$_3$), 106.0 (C-3), 114.2 (C-3′, C-5′), 118.3 (C-3*a*), 121.3 (C-9), 122.1 (C-4), 127.7 (C-2′, C-6′), 128.7 (C-5), 129.9 (C-11*b*), 132.9 (C-1′), 133.4 (C-2), 134.7 (C-7*a*), 135.7 (C-8), 146.9 (C-11*a*), 149.4 (C-10), 158.1

(C-4′), 167.0 (C-7). Anal. Calcd for $C_{21}H_{19}N_3O_2$: C, 73.03; H, 5.54; N, 12.17. Found: C, 72.95; H, 5.66; N, 12.12%.

3.11. Diazotization

3.11.1. 6-(4-Methoxyphenyl)-5-oxo-5,6-dihydro-1,6-naphthyridine-8-diazonium tetrafluoroborate (14c). To a solution of amine **6c** (0.20 g, 0.75 mmol) in 43% HBF_4 (2 mL) at 0 °C was added, dropwise, $NaNO_2$ (0.06 g, 0.90 mmol) in water (1 mL). The orange mixture was stirred for 1 h at 0 °C. The yellow solid was filtered and washed with Et_2O to give **14c** (0.20 g, 73%), mp 148–151 °C (dec). ^{1}H NMR (acetone-d_6): δ 3.88 (s, 3H, O–CH_3), 7.13 (d, J=8.9 Hz, 2H, H-3′, H-5′), 7.58 (d, J=8.9 Hz, 2H, H-2′, H-6′), 7.92 (dd, J=8.0, 4.7 Hz, 1H, H-3), 8.76 (dd, J=8.0, 1.0 Hz, 1H, H-4), 9.18 (dd, J=4.7, 1.0 Hz, 1H, H-2), 9.97 (s, 1H, H-7). ^{13}C NMR (acetone-d_6): δ 54.9 (O–CH_3), 90.5 (C-8), 114.3 (C-3′, C-5′), 120.9 (C-4*a*), 125.4 (C-3), 127.7 (C-2′, C-6′), 130.8 (C-1′), 137.5 (C-4), 143.9 (C-8*a*), 156.0 (C-2), 156.5 (C-7), 159.7 (C-5), 160.7 (C-4′). IR (nujol): 2227.7 cm^{-1}.

3.11.2. 3-Formyl[1,2,3]triazolo[1,5-*a*]pyridine-4-(4-methoxyphenyl)carboxamide (16c). Diazonium salt **14c** (0.15 g, 0.41 mmol) was suspended in water (10 mL) and 10% NaOH (1 mL) was added. The mixture was stirred for 1 h, at which time the white solid was filtered and washed with water to give **16c** (0.10 g, 82%), mp 184–185 °C (from MeCN). ^{1}H NMR (DMSO-d_6): δ 3.73 (s, 3H, O–CH_3), 6.93 (d, J=8.8 Hz, 2H, H-3′, H-5′), 7.51 (t, J=7.2 Hz, 1H, H-6), 7.62 (d, J=8.8 Hz, 2H, H-2′, H-6′), 8.02 (d, J=7.2 Hz, 1H, H-5), 9.42 (d, J=7.0 Hz, 1H, H-7), 10.22 (s, 1H, CHO), 10.48 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 55.3 (O–CH_3), 114.0 (C-3′, C-5′), 117.2 (C-6), 121.9 (C-2′, C-6′), 128.2 (C-4), 128.4 (C-7), 130.9 (C-3*a*), 130.9 (C-5), 131.8 (C-1′), 136.9 (C-3), 156.0 (C-4′), 162.8 (CO), 183.3 (CHO). Anal. Calcd for $C_{15}H_{12}N_4O_3$: C, 60.81; H, 4.08; N, 18.91. Found: C, 60.61; H, 4.18; N, 18.89%.

3.11.3. 4-Methyl-5-oxo-5,6-dihydro-3*H*-benzo[*b*][1,2,3]-triazolo[4,5,1-*ij*][1,6]naphthyridin-3-ol (15a). To a solution of amine **6a** (0.36 g, 1.60 mmol) in 43% HBF_4 (5 mL) at room temperature was added, dropwise, a solution of $NaNO_2$ (0.13 g, 1.92 mmol) in water (3 mL). The resultant mixture was stirred for 1 h, then filtered and washed with Et_2O to give a pink solid. This was suspended in MeCN (10 mL) and water was added (1 mL). The mixture was stirred for 5 min, during which time the color changed from pink to white, and filtration gave **15a** as a white solid (0.24 g, 59%), mp 235–239 °C (after darkening >187 °C), which partially changed to **16a** on standing or during attempted recrystallization. ^{1}H NMR (DMSO-d_6): δ 3.14 (s, 3H, N–CH_3), 6.35 (d, J=9.5 Hz, 1H, H-3), 7.11 (d, J=9.5 Hz, 1H, OH), 7.76 (t, J=7.7 Hz, 1H, H-9), 7.96 (t, J=7.5 Hz, 1H, H-8), 8.29 (s, 1H, H-6), 8.33 (d, J=7.8 Hz, 1H, H-10), 8.61 (d, J=8.2 Hz, 1H, H-7). ^{13}C NMR (DMSO-d_6): δ 32.2 (N–CH_3), 80.0 (C-3), 115.5 (C-7), 117.1 (C-5*a*), 125.0 (C-10*a*), 125.9 (C-6), 128.0 (C-9), 128.5 (C-11*a*), 131.7 (C-6*a*), 131.9 (C-10), 132.2 (C-8), 135.3 (C-2*a*), 159.2 (C-5).

3.11.4. *N*-Methyl-3-formyl[1,2,3]triazolo[1,5-*a*]quinoline-4-carboxamide (16a). A suspension of **15a** (0.18 g, 7.09 mmol) in water (10 mL) and 10% NaOH (1 mL) was stirred for 1 h. A white solid was filtered to give aldehyde **16a** (0.16 g, 89%), mp 241–243 °C (after darkening >205 °C) [from 1,4-dioxane–DMF (9/1)]. ^{1}H NMR (DMSO-d_6): δ 2.86 (d, J=4.4 Hz, 3H, N–CH_3), 7.83 (t, J=7.4 Hz, 1H, H-7), 8.01 (t, J=7.8 Hz, 1H, H-8), 8.22 (d, J=8.0 Hz, 1H, H-6), 8.35 (s, 1H, H-5), 8.78 (d, 1H, J=8.3 Hz, H-9), 8.83 (br s, 1H, NH), 10.31 (s, 1H, CHO). ^{13}C NMR (DMSO-d_6): δ 26.4 (N–CH_3), 116.1 (C-9), 123.0 (C-5*a*), 124.5 (C-4), 128.7 (C-7), 130.0 (C-6), 130.5 (C-3*a*), 130.8 (C-5), 130.9 (C-9*a*), 132.8 (C-8), 138.5 (C-3), 165.3 (CO), 184.2 (CHO). Anal. Calcd for $C_{13}H_{10}N_4O_2$: C, 61.41; H, 3.96; N, 22.04. Found: C, 61.25; H, 4.16; N, 22.30%.

3.12. Bucherer reaction

3.12.1. 8-Hydroxy-6-(4-methoxyphenyl)-1,6-naphthyridin-5(6*H*)-one (17c). To a solution of sodium metabisulfite (0.85 g, 4.49 mmol) in water (15 mL) was added amine **6c** (0.24 g, 0.90 mmol) and the yellow mixture was heated under reflux for 24 h. After this time, the ensuing orange solution was cooled to room temperature, whereby a yellow solid separated. KOH (0.50 g, 8.99 mmol) was added and the mixture was heated under reflux for 24 h. The solution was then cooled until a yellow precipitate formed, which was collected by filtration to give unreacted **6c** (0.10 g). The filtrate was neutralized with concentrated HCl and the green solid, which separated was filtered and washed with water (0.45 g). Recrystallization from MeCN gave **17c** (0.11 g, 46%) as a yellow solid (which rapidly turned green), mp 174–175 °C. ^{1}H NMR (DMSO-d_6): δ 3.79 (s, 3H, O–CH_3), 7.02 (dd, J=6.8, 2.2 Hz, 2H, H-3′, H-5′), 7.11 (s, 1H, H-7), 7.36 (dd, J=6.8, 2.2 Hz, 2H, H-2′, H-6′), 7.60 (dd, J=8.1, 4.6 Hz, 1H, H-3), 8.55 (dd, J=8.1, 1.7 Hz, 1H, H-4), 8.99 (dd, J=4.6, 1.7 Hz, 1H, H-2), 9.01 (br s, 1H, OH). ^{13}C NMR (DMSO-d_6): δ 55.5 (O–CH_3), 114.3 (C-3′, C-5′), 119.2 (C-7), 121.4 (C-4*a*), 122.8 (C-3), 128.1 (C-2′, C-6′), 133.9 (C-1′), 136.2 (C-8), 136.6 (C-4), 148.0 (C-8*a*), 153.8 (C-2), 158.6 (C-4′), 158.9 (C-5). Anal. Calcd for $C_{15}H_{12}N_2O_3\cdot 0.75H_2O$: C, 63.94; H, 4.83; N, 9.94. Found: C, 63.98; H, 4.36; N, 9.97%.

A yellow solution in EtOH gave an intense green color on addition of Fe^{3+}.

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References and notes

1. (a) Deady, L. W.; Rodemann, T.; Zhuang, L.; Baguley, B. C.; Denny, W. A. *J. Med. Chem.* **2003**, *46*, 1049–1054. (b) Deady, L. W.; Rogers, M. L.; Zhuang, L.; Baguley, B. C.; Denny, W. A. *Bioorg. Med. Chem.* **2005**, *13*, 1341–1355.
2. (a) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley-Interscience: New York, 1992; p 1090. (b) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley-Interscience: New York, 1992; p 669.

3. Wallis, E. S.; Lane, J. F. *Org. React.* **1946**, *3*, 267–306.
4. Smith, P. A. S. *Org. React.* **1946**, *3*, 337–449.
5. Moriarty, R. M.; Chany, C. J.; Vaid, R. K.; Prakash, O.; Tuladhar, S. M. *J. Org. Chem.* **1993**, *58*, 2478–2482. This paper also contains references to other rearrangement conditions.
6. Carroll, F. I.; Berrang, B. D.; Linn, C. P. *J. Heterocycl. Chem.* **1981**, *18*, 941–946.
7. (a) Jones, G. In *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Taylor, E. C., Eds.; Quinolines, Part I; Wiley-Interscience: London, 1977; Vol. 32, pp 139–150. (b) Jones, G. In *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Taylor, E. C., Eds.; Quinolines, Part I; Wiley-Interscience: London, 1977; Vol. 32, pp 119–125.
8. Lempert, H.; Robinson, R. *J. Chem. Soc., Chem. Commun.* **1934**, 1419–1422.
9. Barco, A.; Benetti, S.; Pollini, G. P.; Baraldi, P. G. *Synthesis* **1976**, 124–125.
10. Brown, L. L.; Kulkarni, S.; Pavlova, O. A.; Koren, A. O.; Mukhin, A. G.; Newman, A. H.; Horti, A. G. *J. Med. Chem.* **2002**, *45*, 2841–2849.
11. Aroney, M.; LeFevre, R. J. W.; Werner, R. L. *J. Chem. Soc., Chem. Commun.* **1955**, 276.
12. Jones, G.; Pitman, M. A.; Lunt, E.; Lythgoe, D. J.; Abarca, B.; Ballesteros, R.; Elmasnaouy, M. *Tetrahedron* **1997**, *53*, 8257–8268.
13. Davies, L. S.; Jones, G. *J. Chem. Soc. (C)* **1970**, 688–693.
14. Drake, N. L. *Org. React.* **1942**, *1*, 105–128.
15. Deady, L. W.; Rodemann, T. *J. Heterocycl. Chem.* **2001**, *38*, 1185–1190.
16. Kalkanidis, M. Ph.D. Thesis, La Trobe University, 2003.