Formation of New Heterotetracyclic Compounds by Ring Closure of 2-Amino-3-vinylpyridines

Vicente Ojea, Carlos Peinador, Juan Vilar, José M[a] Quintela*

Departamento de Química Fundamental e Industrial, Facultad de Ciencias, Universidad de La Coruña, E-15071 La Coruña, Spain

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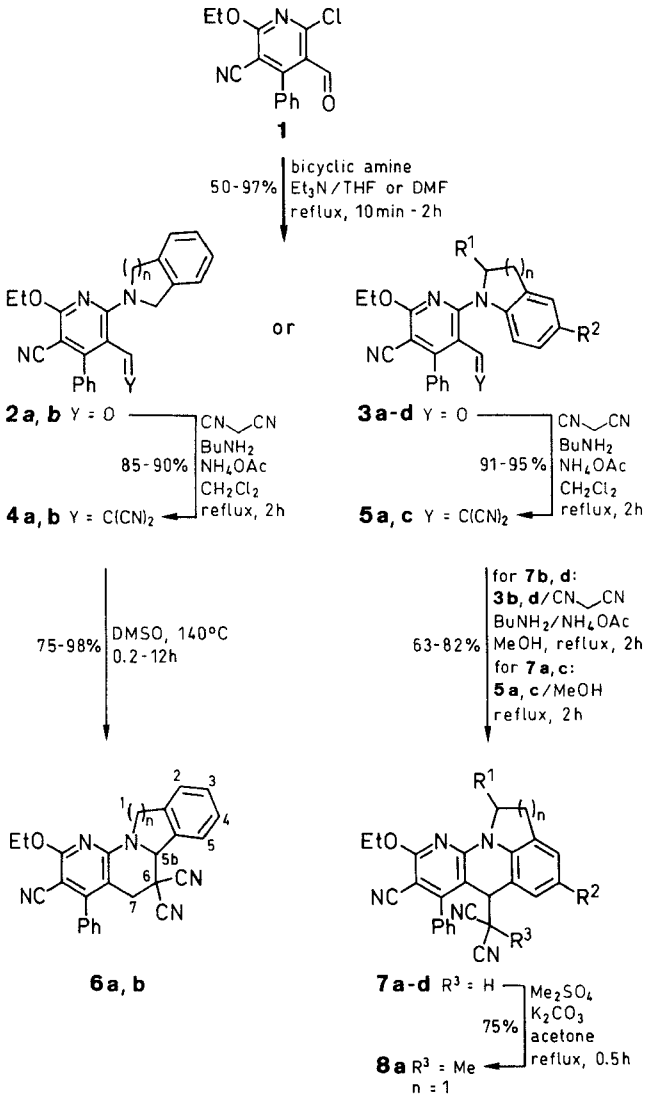
2-(Isoindol-2-yl)- and 2-(isoquinolin-2-yl)-3-(2,2-dicyanovinyl)pyridine derivatives react thermally in polar solvents via [1,5]hydrogen transfer followed by carbon–carbon bond formation to give 1,5b,6,7-tetrahydroisoindolo[2,1-*a*][1,8]naphthyridine-6,6,9-tricarbonitrile and 2,6b,7,8-tetrahydro-1*H*-isoquino[2,1-*a*][1,8]naphthyridine-7,7,10-tricarbonitrile derivatives, respectively. The corresponding 2-(indol-1-yl)- and 2-(quinolin-1-yl)-3-(2,2-dicyanovinyl)pyridine derivatives lend themselves more readily to thermal electrocyclic ring closure followed by aromatization to give 2,6-dihydro-1*H*-indolo[1,8,7-*a,b*][1,8]naphthyridine and 1,2,3,7-tetrahydroquino[1,9,8-*a,b*][1,8]naphthyridine derivatives. Thus, new heterotetracyclic compounds containing the 1,8-naphthyridine group were synthesized in both ways.

In recent work we extended application of the "*tert*-amino effect"[1] to the synthesis of heterotricyclic compounds by thermal isomerization of 2-dialkylamino-3-vinylpyridines.[2] The results obtained prompted us to apply the same methodology to the synthesis of heterotetracyclic compounds. This paper reports a new, convenient route to the synthesis of derivatives of various heterotetracycles, viz. isoindolo[2,1-*a*]- **6a**, isoquino[2,1-*a*]- **6b**, indolo[1,8,7-*a,b*]- **7a,c** and quino[1,9,8-*a,b*][1,8]-naphthyridines **7b**, (Scheme 1). To the best of our knowledge, the synthesis of the latter two compounds involves an unprecedented reaction in the "*tert*-amino effect" chemistry. While 2-dialkylamino-3-vinylpyridines **4a,b** are subject to a "*tert*-amino effect" similar to those reported by Reinhoudt et al.,[3] 2-alkylarylamino-3-vinylpyridines **5a–d** react by an electrocyclization/aromatization sequence to yield **7a–d**, which are new types of heterocycles. The electrocyclization process, which involves a 3-aza-1,3,5-hexatriene system, while scarcely mentioned in the literature, has so far been used in the synthesis of pyridines,[4] quinolines,[5] acridines,[6] and phenanthiridines.[7]

The starting compounds for the thermal isomerization were prepared as required from 2-chloro-3-formylpyridine derivative **1**, the synthesis of which was reported elsewhere.[2] Treatment of compound **1** with the appropriate bicyclic amine and triethylamine in tetrahydrofuran or dimethylformamide yielded the corresponding 2-dialkylamino-**2a,b** or 2-alkylarylamino-3-formylpyridine derivatives **3a–d** in moderate to good yields. Formation of the desired aldehydes was confirmed by ^{1}H NMR [δ =

9.1–9.5 (s, CHO)] and decoupled ^{13}C NMR spectroscopy [δ = 185–188 (CO)] (Table 1). A Knoevenagel condensation of the carbonyl group of **2a,b** or **3a–d** with malononitrile (butylamine and ammonium acetate as catalysts)[8] in dichloromethane under reflux for 2 hours gave rise to the corresponding 2-dialkylamino- **4a,b** or 2-alkylarylamino-3-(2,2-dicyanovinyl)pyridine derivatives **5a, c**. After purification by column chromatography, compounds **4a,b** and **5a,c** were isolated as yellow-orange solids with high yields (Table 2). The $PyHCC(CN)_2$ absorption signal in the ^1H NMR spectra between δ = 7.5–7.7 as a singlet and the $PyHCC(CN)_2$ absorption in the decoupled ^{13}C NMR spectra between δ = 155–157 are typical of the proposed 2-amino-3-vinylpyridine structures **4a,b** and **5a,c** (Table 2). In the case of **5b,d** some of the cyclized product **7b** or **7d** was already present in the reaction crude and only the cyclized product **7b** or **7d** was isolated after purification by flash chromatography.



2–10	n	R^1	R^2	2–10	n	R^1	R^2
a	1	H	H	c	1	Me	H
b	2	H	H	d	2	Me	F

Scheme 1

Heating the 2-dialkylamino derivatives **4a,b** in polar solvents yielded the corresponding heterotetracyclic compounds **6a,b**. The 1,3-dihydroisoindole derivative **4a** yielded **6a** upon heating in dimethyl sulfoxide at 140 °C for 12 hours. The ^1H NMR spectrum of compound **6a** shows characteristic signals at δ = 5.23 (s, H-5b), and δ = 3.26 and 3.35 (AB system, J = 16.2 Hz, H-7). If the amino moiety is the isoquinoline group, the thermal isomerization of **4b** could give rise to two isomers: isoquino[2,1-*a*]- and isoquino[2,3-*a*][1,8]naphthyridine. However, heating **4b** in ethanol (0.5 hours at refluxing temperature) or dimethyl sulfoxide (10 minutes at 140 °C) resulted in only one cyclized product (**6b**, Scheme 1) from reaction at the benzylic atom exclusively. This was confirmed by the ^1H NMR spectrum of the reaction product, which includes a characteristic singlet at δ = 4.94 that integrates for one proton and can only be assigned to H-6b in an isoquino[2,1-*a*][1,8]naphthyridine structure (Table 3). Heating the 2-alkylarylamino derivatives **5a** or **5b** (generated in situ from **3b** and malononitrile in the presence of butylamine and ammonium acetate) in methanol at refluxing temperature for 0.5 hours yielded a single cyclized product, the structure of which was assigned to **7a** or **7b** (Scheme 1), according to its NMR spectra. The ^1H NMR spectra of compounds **7a,b** include a characteristic AB system (δ = 3.42 and 4.79, J = 4.7 Hz for **7a** and δ = 3.32 and 4.54, J = 6.0 Hz for **7b**) for the $R_2HCCH(CN)_2$ absorptions. Correlation of these signals with the $R_2HCCH(CH)_2$ absorptions (at δ = 30.8 and 40.4 for **7a** and δ = 29.6 and 40.5 for **7b**) in the ^{13}C NMR spectra was checked by ^1H-^{13}C COSY experiments. Similarly, heating **5c** and **5d** (generated in situ from **3b** and malononitrile in the presence of butylamine and ammonium acetate) gave rise to the cyclic isomers **7c** and **7d**. While **7d** was obtained as a mixture of two diastereomers in a 2:1 ratio, that was calculated by integration of analogous signals in the ^1H NMR spectra, **7c** could only be isolated as one diastereomer in a total yield of 63 %. Methylation of the $RCH(CN)_2$ group of compound **7a** was found to be quite easy. Thus, heating **7a** in refluxing acetone for 0.5 hours with excess potassium carbonate and dimethyl sulfate resulted in the methyl derivative **8a**. The $R_2HCC(CN)_2CH_3$ absorption at δ = 4.75 and the $R_2HCC(CN)_2CH_3$ absorption at δ = 1.36 as singlets that integrate for one and three protons, respectively, in the ^1H NMR spectra are fully consistent with structure **8a**.

The thermal isomerization of compounds **4a,b** and **5a–d** can be assumed to occur in two steps (Scheme 2). The first step in the cyclization of **4a,b** involves a thermal suprafacial [1,5]-hydrogen shift of one α-methylene proton adjacent to the nitrogen of the amino group in order to yield the 1,5-dipolar intermediate **9a,b**. Subsequently, intramolecular addition of the negatively charged carbon to the iminium double bond gives rise to cyclized products **6a,b**.[9] The cyclization of compounds **5a–d**, which involves the formation of a new carbon–carbon bond between the α-position of the vinyl group and a β-methine group to the nitrogen of the amino moiety, must involve a 1,5-dipolar intermediate **10a–d**, the result of the electrocyclization of the 3-aza-1,3,5-hexatriene system included in one resonance canonical form of **5a–d**. Subsequently,

Table 1. 2-Amino-3-formylpyridines **2** and **3** Prepared

Product	Yield (%)[a]	mp (°C) (solvent)	Molecular Formula[b]	IR (KBr) ν (cm^{-1})	MS (70 eV) m/z (M^+, %)	^1H NMR ($CDCl_3$/TMS)[c] δ, J (Hz)	^{13}C NMR ($CDCl_3$/TMS)[d,e] δ, J (Hz)
2a	97	180–183 (EtOH)	$C_{23}H_{19}N_3O_2$ (369.4)	2980, 2860, 2220, 1655, 1565, 1515	369 (15.6)	4.93 (br s, 4H, NCH_2), 7.29 (s, $4H_{arom}$), 9.45 (s, 1H, CHO)	56.2 (NCH_2), 122.3, 127.6, 135.9 (C_{arom}), 187.1 (CHO)
2b	94	110–112 (EtOH/ hexane)	$C_{24}H_{21}N_3O_2$ (383.4)	2990, 2940, 2220, 1670, 1580, 1565	383 (100)	3.08 (t, 2H, J= 5.8, NCH_2CH_2), 4.02 (t, 2H, J= 5.8, NCH_2), 4.65 (s, 2H, NCH_2Ph), 7.05–7.25 (m, $4H_{arom}$), 9.30 (s, 1H, CHO)	28.6 (NCH_2CH_2), 46.7 (NCH_2), 52.7 (NCH_2Ph), 126.2, 126.5, 126.9, 128.5, 133.6, 134.7 (C_{arom}), 186.2 (CHO)
3a	95	144–147 (EtOH)	$C_{23}H_{19}N_3O_2$ (369.4)	2980, 2875, 2220, 1665, 1565, 1555	369 (100)	3.18 (t, 2H, J= 7.7, NCH_2CH_2), 4.02 (t, 2H, J= 7.7, NCH_2), 7.04–7.10 (m, $1H_{arom}$), 7.18–7.31 (m, $2H_{arom}$), 7.61–7.64 (m, $1H_{arom}$), 9.44 (s, 1H, CHO)	28.9 (NCH_2CH_2), 54.7 (NCH_2), 117.3, 124.2, 125.1, 126.5, 133.4, 143.0 (C_{arom}), 186.3 (CHO)
3b	70	174–176 (EtOH/ hexane)	$C_{24}H_{21}N_3O_2$ (383.4)	3020, 2950, 2930, 2220, 1670, 1555, 1520, 1490	383 (100)	2.02–2.12 (m ~ tt, 2H, J= ~6.6, 6.4, NCH_2CH_2), 2.89 (t, 2H, J= 6.6, CH_2Ph), 3.93 (t, 2H, J= 6.4, NCH_2), 6.97–7.22 (m, $4H_{arom}$), 9.23 (s, 1H, CHO)	23.9 (NCH_2CH_2), 26.6 (CH_2Ph), 48.8 (NCH_2), 119.3, 124.3, 126.1, 129.2, 131.2, 141.8 (C_{arom}), 185.8 (CHO)
3c	85	110–113 (CH_2Cl_2/ hexane)	$C_{24}H_{21}N_3O_2$ (383.4)	3040, 2985, 2220, 1675, 1555, 1490	383 (100)	1.47 (d, 3H, J= 6.2, $NCHCH_3$), 2.80 (dd, 1H, J= 4.7, 15.3, CH_2Ph), 3.44 (dd, 1H, J= 8.4, 15.3, CH_2Ph), 4.99–5.10 (m, 1H, NCH), 6.95–7.25 (m, $4H_{arom}$), 9.40 (s, 1H, CHO)	19.8 ($NCHCH_3$), 36.5 ($PhCH_2$), 60.8 (NCH), 113.0, 123.3, 125.4, 126.3, 132.1, 142.8 (C_{arom}), 185.5 (CHO)
3d	50	183–186 (EtOH)	$C_{25}H_{22}FN_3O_2$ (415.5)	3050, 2970, 2930, 2840, 2220, 1670, 1560, 1530, 1490	415 (100)	1.31 (d, 3H, J= 6.0, $NCHCH_3$), 1.57–1.70 (m, 1H), 2.35–2.49 (m, 1H), 2.70–2.94 (m, 2H), 4.81–4.94 (m, 1H, NCH), 6.71–6.75 (m, $1H_{arom}$), 6.91–6.99 (m, $2H_{arom}$), 9.09 (s, 1H, CHO)	19.1 ($NCHCH_3$), 24.7 (CH_2CH_2Ph), 30.6 (CH_2Ph), 52.6 (NCH), 113.2 (d, J= 22.8, ArC-1), 115.2 (d, J= 22.2, ArC-1), 120.1 (d, J= 8.3, ArC-2), 134.7 (d, J= 7.2, ArC-2), 136.5 (ArC-3), 159.5 (d, J= 244.2 Hz, ArC-F), 185.6 (CHO)

[a] After column chromatography.
[b] Satisfactory microanalyses obtained: C ±0.19, H ±0.22, N ±0.24.
[c] The ^1H NMR spectra of compounds **2a,b** and **3a–d** exhibit typical absorption signals for C_6H_5 [7.26–7.56 (m, 5H)], and OCH_2CH_3 [1.44–1.49 (t, 3H, J= ~7.1 Hz, OCH_2CH_3), and 4.49–4.55 (q, 2H, J= ~7.1 Hz, OCH_2)].
[d] ^{13}C NMR spectra recorded with broad band decoupling.
[e] The ^{13}C NMR spectra of compounds **2a,b** and **3a–d** exhibit typical signals for the pyridine nucleus [109.4–112.3, 114.9–115.3, 153.8–158.9, and 163.3–165.1 (1 or 2 absorptions)] and its substituents: C_6H_5 [128.6–128.8, 129.1–129.7, 129.8–130.2, 133.7–134.1], CN [85.9–88.8], and OCH_2CH_3 [14.2–14.3 (OCH_2CH_3), 63.6–63.9 (OCH_2)].

loss of a proton by intermediate **10a–d** in an aromatization process makes the cyclization irreversible.

As concluded from the NMR spectral data, the ring closure of **4b** takes place exclusively at the benzylic atom. This regiospecific character can be accounted for on the basis of a better stabilization of the positive end of the dipolar intermediate **9b** compared to a dipolar intermediate obtained by a hydrogen shift from the other carbon atom adjacent to the nitrogen. As a rule, cyclization of **4a,b** takes place more rapidly than that of analogues in which the dialkylamino group is a pyrrolidinyl or piperidino function,[2] as a result of greater stabilization of the dipolar intermediate by the adjacent aromatic system. The involvement of a dipolar intermediate **10a–d** in the cyclization of 2-alkylarylamino derivatives **5a–d** results in the isomerization temperature being dependent on the solvent polarity. Thus, no reaction was observed when **5a,c** was refluxed in dichloromethane, acetone or chloroform for 15 hours, whereas heating the same compounds in methanol at 40 °C for 6 hours resulted in their quantitative conversion into the cyclized product **7a,c**.

All reagents used were commercial grade chemicals from freshly opened containers. The amines were purchased from Aldrich Chemical Co., except for 1,3-dihydro-2*H*-isoindole, which was synthesized by following the literature procedure.[10] Silica gel $HF_{254+366}$ for TLC and silica gel 60 (230–400 mesh) for medium-pressure chromatography (MPLC) were purchased from Merck. Microanalyses for C, H, and N were performed by the Elemental Analyses General Service of the University of Santiago. Melting points were measured using a Büchi 510 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 383 IR spectrophotometer, ^1H and ^{13}C NMR on a Bruker WM 250 spectrometer and MS on a Kratos MS-50 spectrometer.

Table 2. 2-Amino-3-(2,2-dicyanovinyl)pyridines **4a,b** and **5a,c** Prepared

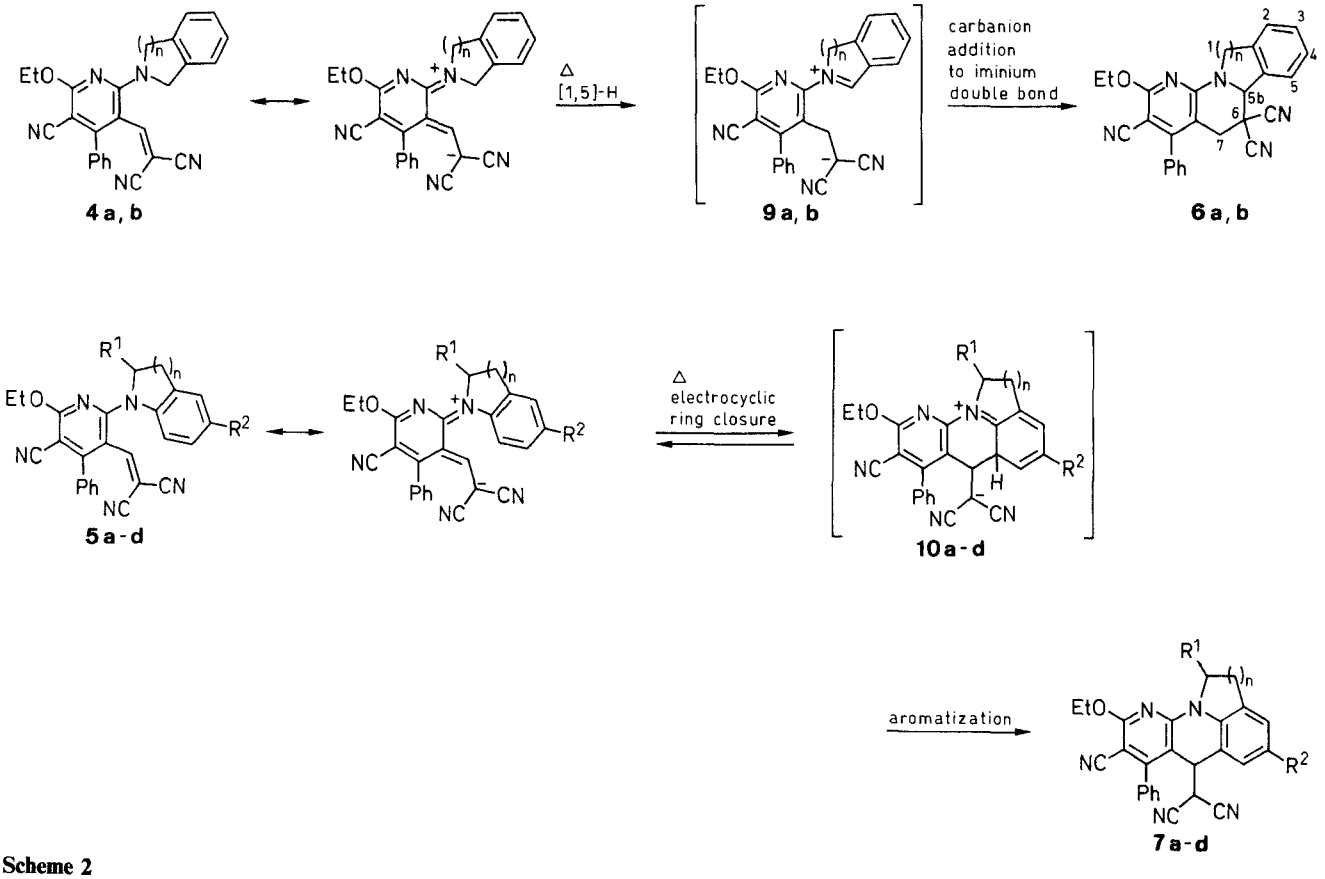
Product	Yield (%)[a]	mp (°C) (solvent)	Molecular Formula[b]	IR (KBr) ν (cm^{-1})	MS (70 eV) m/z (M^+, %)	^1H NMR ($CDCl_3$/TMS)[c] δ, J (Hz)	^{13}C NMR ($CDCl_3$/TMS)[d] δ
4a	90	217–219 (EtOH)	$C_{26}H_{19}N_5O$ (417.5)	3040, 2980, 2920, 2220, 1600, 1570	417 (76.1)	4.80 (br s, 4H, NCH_2), 7.35 (s, $4H_{arom}$), 7.64 (s, 1H, =CH)	56.0 (NCH_2), 79.4 [$\underline{C}(CN)_2$], 114.2, 114.6 (CN), 122.6, 128.2, 135.2 (C_{arom}), 156.3 (=CH)
4b	85	105–110 (CH_2Cl_2/hexane)	$C_{27}H_{21}N_5O$ (431.5)	3010, 2910, 2860, 2220, 1560, 1510, 1490	431 (100)	3.04–3.08 (m, 2H, $NCH_2C\underline{H}_2$), 3.95–4.01 (m, 2H, NCH_2), 4.36 (s, 2H, NCH_2Ph), 7.07–7.13 (m, $1H_{arom}$), 7.20–7.27 (m, $3H_{arom}$), 7.59 (s, 1H, =CH)	28.7 ($NCH_2\underline{C}H_2$), 45.9 (NCH_2), 51.8 (NCH_2Ph), 78.1 [$\underline{C}(CN)_2$], 114.4 (CN), 126.1, 126.9, 127.6, 128.4, 132.2 (C_{arom}), 156.5 (=CH)
5a	95	205–208 (CH_2Cl_2/hexane)	$C_{26}H_{19}N_5O$ (417.5)	3050, 2975, 2920, 2220, 1550, 1520, 1485	417 (100)	3.25 (t, 2H, J = 7.7, $NCH_2C\underline{H}_2$), 4.20 (t, 2H, J = 7.7, NCH_2), 6.70–6.74 (m, $1H_{arom}$), 7.03–7.12 (m, $2H_{arom}$), 7.25–7.28 (m, $1H_{arom}$), 7.45 s, 1H, =CH)	28.6 ($NCH_2\underline{C}H_2$), 53.7 (NCH_2), 81.1 [$\underline{C}(CN)_2$]; 113.7, 114.4 (CN), 114.2, 124.4, 125.7, 126.3, 133.4, 140.1 (C_{arom}); 155.5 (=CH)
5c	91	110–115 (CH_2Cl_2/hexane)	$C_{27}H_{21}N_5O$ (431.5)	3040, 2980, 2930, 2220, 1570, 1490, 1420	431 (100)	1.53 (d, 3H, J = 5.9, $NCHC\underline{H}_3$), 2.70 (dd, 1H, J = 1.9, 15.3, CH_2Ph), 3.63 (dd, 1H, J = 7.9, 15.3, CH_2Ph), 5.04 (m ~ dqd, 1H, J = ~1.9, 5.9, 15.3, NCH), 6.35–6.39 (m, $1H_{arom}$), 6.95–7.06 (m, $2H_{arom}$), 7.20–7.25 (m, $1H_{arom}$), 7.54 (s, 1H, =CH)	19.9 ($NCH\underline{C}H_3$), 37.4 ($PhCH_2$), 62.8 (NCH), 81.9 [$\underline{C}(CN)_2$], 113.4, 114.4 (CN), 113.9, 124.6, 125.9, 126.2, 134.7, 138.7 (C_{arom}), 155.8 (=CH)

[a] After column chromatography.

[b] Satisfactory microanalyses obtained: C ± 0.24, H ± 0.24, N ± 0.22.

[c] The ^1H NMR spectra of compounds **4a,b** and **5a,c** exhibit typical absorption signals for C_6H_5 [7.25–7.35 (m, 2H), 7.50–7.59 (m, 3H)], and OCH_2CH_3 [1.48–1.51 (t, 3H, J = ~7.1 Hz, $OCH_2C\underline{H}_3$), 4.55–4.62 (q, 2H, J = ~7.1 Hz, OCH_2)].

[d] The ^{13}C NMR spectra of compounds **4a,b** and **5a,c** exhibit typical signals for the pyridine nucleus [103.5–105.2, 111.1–111.9, 152.1–156.7, 160.9–161.9 and 163.6–164.1] and its substituents: C_6H_5 [128.4–129.3 (1 or 2 absorptions), 130.3–130.4, 133.5–134.7], CN [88.7–90.2], and OCH_2CH_3 [14.1–14.3 ($OCH_2\underline{C}H_3$), 64.1–64.4 (OCH_2)].



Scheme 2

Table 3. 1,8-Naphthyridine Containing Heterotetracyclic Compounds **6** and **7** Prepared

Product	Yield (%)[a]	mp (°C) (EtOH)	Molecular Formula[d]	IR (KBr) ν (cm^{-1})	MS (70 eV) m/z (%)	^1H NMR ($CDCl_3$/TMS)[e] δ, J (Hz)	^{13}C NMR ($CDCl_3$/TMS)[h] δ, J (Hz)
6a	75	245–248	$C_{26}H_{19}N_5O$ (417.5)	3060, 2990, 2885, 2220, 1595, 1585, 1575, 1550	417 (M^+, 74.9)	3.26, 3.35 (AB system, 2H, J = 16.2, H-7), 5.00 (d, 2H, J = 15.3, H_{ax}-1), 5.14 (dd, 1H, J = 15.3, 2.5, H_{eq}-1), 5.23 (s, 1H, H-5b), 7.44–7.56 (m, 3H_{arom}), 7.84–7.87 (m, 1H_{arom})	33.9 (C-6), 36.1 (C-7), 54.1 (C-1), 66.5 (C-5b), 114.2, 115.7 (CN), 123.3, 127.9, 129.0, 129.5, 133.3, 137.3 (C_{arom})
6b	98	258–260	$C_{24}H_{21}N_3O$ (431.5)	3050, 2905, 2875, 2220, 1585, 1570, 1550	431 (M^+, 96)	2.85 (dt, 1H, J = 15.5, 2.3, H_{eq}-2), 3.11 (td, 1H, J = 12.5, 2.3, H_{ax}-1), 3.33 (ddd, 1H, J = 15.5, 12.5, 4.4 H_{ax}-2), 3.21, 3.36 (AB system, 2H, J = 16.6, H-8), 4.94 (s, 1H, H-6b), 5.19 (ddd, 1H, J = 12.5, 4.4, 2.3, H_{eq}-1), 7.22–7.59 (m, 4H_{arom})	29.1 (C-2), 36.5 (C-8), 38.5 (C-7), 41.3 (C-1), 62.0 (C-6b), 114.4, 115.0 (CN), 126.9, 127.7, 128.2, 129.0, 129.5, 137.6 (C_{arom})
7a	82	200[b]	$C_{26}H_{19}N_5O$ (417.5)	3060, 2980, 2900, 2220, 1635, 1610, 1580, 1570, 1545, 1505	415 (M^+-2, 10.7)	3.33–3.42 (m, 2H, H-2), 3.42[f] [d, 1H, J = 4.7, $HC(CN)_2$], 4.21–4.31 (m, 2H, H-1), 4.79 (d, 1H, J = 4.7, H-6), 7.04–7.10 (m, 1H_{arom}), 7.19–7.29 (m, 1H_{arom}), 7.50–7.67 (m, 1H_{arom})	28.1 (C-2), 30.8 [$\underline{C}(CN)_2$], 40.4 (C-6), 47.2 (C-1), 110.9, 111.3 (CN), 112.3, 124.2, 125.8, 126.3, 127.3, 141.8 (C_{arom})
7b	80	200[b]	$C_{27}H_{21}N_5O$ (431.5)	3080, 2995, 2975, 2900, 2220, 1610, 1580, 1570, 1550	429 (M^+-2, 19.9)	1.98–2.22 (m, 2H, H-3), 2.78–3.02 (m, 2H, H-2), 3.32[f] [d, 1H, J = 6.0, $HC(CN)_2$], 3.99 (ddd, 1H, J = 13.2, 11.2, 3.9, H_{ax}-1), 4.20 (dtd, 1H, J = 13.2, 4.2, 1.5, H_{eq}-1), 4.54 (d, 1H, J = 6.0, H-7), 6.95–7.01 (m, 1H_{arom}), 7.10–7.18 (m, 1H_{arom}), 7.41–7.56 (m, 3H_{arom})	20.9 (C-2), 27.3 (C-3), 29.6 [$\underline{C}(CN)_2$], 40.5 (C-7), 44.3 (C-1), 111.2 (CN); 116.9, 122.8, 126.1, 127.1, 127.6, 129.7, 135.7 (C_{arom})
7c	63	200[b]	$C_{27}H_{21}N_5O$ (431.5)	3080, 2960, 2900, 2220, 1665, 1605, 1565, 1540, 1505	429 (M^+-2, 20.6)	1.66 (d, 3H, J = 6.3, $NCHC\underline{H}_3$), 3.00 (dd, 1H, J = 5.3, 16.6, H_{ax}-2), 3.39[f] [d, 1H, J = 4.7, $HC(CN)_2$], 3.58 (dd, 1H, J = 9.7, 16.6, H_{eq}-2), 4.74 [d, 1H, J = 4.7, H-6], 7.04–7.10 (m, 1H_{arom}), 7.19–7.26 (s, 1H_{arom}), 7.50–7.65 (s, 1H_{arom})	20.5 ($NCH\underline{C}H_3$), 30.6 [$\underline{C}(CN)_2$], 37.0 (C-2), 40.4 (C-6), 56.1 (C-1), 111.0, 111.3 (CN), 112.1, 124.3, 125.9, 126.3, 127.3, 141.3 (C_{arom})
7d	72	200[b,c]	$C_{28}H_{22}FN_5O$ (463.5)	2980, 2965, 2220, 1605, 1615, 1580, 1570, 1500	461 (M^+-2, 19.7)	1.39 (d, 3H, J = 6.7, $NCHC\underline{H}_3$), 1.95–2.08 (m, 2H, H-3), 2.76–2.85 (m, 1H, H_{ax}-2), 3.00–3.13 (m, 1H, H_{eq}-2), 3.37[f] [d, 1H, J = 5.85, $HC(CN)_2$], 4.61 (d, 1H, J = 5.85, H-7), 5.53–5.65 (m, 1H, H-1), 6.91–6.99 (m, 1H_{arom}), 7.15–7.25 (m, 1H_{arom}), 7.51–7.64 (m, 1H_{arom})[g]	17.6 ($NCH\underline{C}H_3$), 23.3 (C-2), 26.6 (C-3), 31.2 [$\underline{C}(CN)_2$], 40.6 (C-7), 46.0 (C-1), 110.9, 111.0 (CN), 113.9 (d, J = 23.2, C-4 or C-6), 117.0 (d, J = 21.9, C-4 or C-6), 158.2 (d, J = 240.5, C-5)[g]

[a] After column chromatography.
[b] Decomposition.
[c] Mixture of diastereomers.
[d] Satisfactory microanalyses obtained: C ± 0.23, H ± 0.21, N ± 0.24.
[e] The ^1H NMR spectra of compounds **6a,b** and **7a–d** exhibit typical absorption signals for C_6H_5 [6.91–7.64 (m, 5H)] and OCH_2CH_3 [1.48–1.50 (t, 3H, J = ~7.1 Hz, $OCH_2C\underline{H}_3$), 4.53–4.56 (q, 2H, J = ~7.1 Hz, OCH_2)].
[f] Exchangeable with D_2O.
[g] Majority diastereomer data.
[h] The ^{13}C NMR spectra of compounds **6a,b** and **7a–d** exhibit typical signals for the pyridine nucleus [99.1–102.0, 111.5–115.3, 152.6–154.1, 156.0–156.8 and 163.7–164.6] and its substituents: C_6H_5 [128.5–130.5 (4 or 5 absorptions), 133.6–134.6], CN [86.1–88.8], and OCH_2CH_3 [14.3–14.5 (OCH_2CH_3), 63.1–63.5 (OCH_2)].

2-Amino-5-cyano-6-ethoxy-3-formyl-4-phenylpyridines 2a,b, 3a–d; General Procedure:

Method A (for 2,3-dihydroindole, 2,3-dihydro-2-methylindole, 1,3-dihydro-2H-isoindole and 1,2,3,4-tetrahydroisoquinoline derivatives **2a,b** and **3a,c**): A solution of **1** (0.5 g, 1.75 mmol), an appropriate bicyclic amine (1.75 mmol) and Et_3N (0.24 mL, 1.75 mmol) in THF (10 mL) was refluxed for 10 min. Upon cooling, precipitated Et_3NHCl was filtered, washed with THF (2 mL), and discarded. The solvent was removed at low pressure and the residue purified by MPLC on a silica gel column (22 × 1.5 cm) using the

following eluents: CH_2Cl_2/hexane (3:2) for **2a** and **3d**, CH_2Cl_2/hexane (2:1) for **3a,c** and CH_2Cl_2/hexane (3:1) for **2b** and **3b** (Table 1).

Method B (for 1,2,3,4-tetrahydroquinoline and 6-fluoro-1,2,3,4-tetrahydro-2-methylquinoline derivatives **3b,d**): A solution of **1** (0.5 g, 1.75 mmol), an appropriate bicyclic amine (1.75 mmol) and Et_3N (0.24 mL, 1.75 mmol) in DMF (5 mL) was refluxed for 2 h. The mixture was cooled, poured into H_2O (50 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The resulting solid was purified by MPLC on a silica gel column (22 × 1.5 cm) using the following eluents: CH_2Cl_2/hexane (2:1) for **3b** and CH_2Cl_2/hexane (1:1) for **3d** (Table 1).

2-Amino-5-cyano-3-(2,2-dicyanovinyl)-6-ethoxy-4-phenylpyridines 4a,b, and 5a,c; General Procedure:

A solution of **2a,b** or **3a,c** (1.4 mmol), malononitrile (0.185 g, 2.8 mmol), $BuNH_2$ (0.14 mL, 1.4 mmol) and NH_4OAc (0.11 g, 1.4 mmol) in CH_2Cl_2 was refluxed for 2 h. Upon cooling, the solvent was removed under reduced pressure and the resulting solid was purified by MPLC on a silica gel column (15 × 1.5 cm) using the following eluents: CH_2Cl_2/hexane (2:1) for **4a,b** and CH_2Cl_2/hexane (3:2) for **5a,c** (Table 2).

1,8-Naphthyridine-Containing Heterotetracyclic Compounds 6a,b, 7a–d:

Method A [for 10-ethoxy-1,5b,6,7-tetrahydro-8-phenylisoindolo[2.1-*a*][1,8]naphthyridine-6,6,9-tricarbonitrile **(6a)** and 11-ethoxy-2,6b,7,8-tetrahydro-9-phenyl-1*H*-isoquino[2,1-*a*][1,8]naphthyridine-7,7,10-tricarbonitrile **(6b)**]: A solution of **4a** or **4b** (0.25 mmol) in DMSO (5 mL) was heated at 140 °C until all starting material had disappeared as checked by TLC (~ 12 h for **6a** and ~ 0.2 h for **6b**). Upon cooling, the reaction crude was poured into H_2O (50 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The resulting solid was purified by MPLC on a silica gel column (12 × 1 cm) using CH_2Cl_2/hexane (2:1) as eluent to obtain **6a** or **6b** (Table 3).

Method B (for 2,6-dihydro-1*H*-indolo[1,8,7-*a*,*b*][1,8]naphthyridine derivatives **7a,c**): A solution of **5a** or **5c** (0.25 mmol) in MeOH (5 mL) was refluxed for 2 h. The solvent was removed under reduced pressure and the resulting solid was purified by MPLC on a silica gel (12 × 1 cm) using CH_2Cl_2/hexane (3:1) as eluent to obtain **7a,c** (Table 3).

Method C (for 1,2,3,7-tetrahydroquino[1,9,8-*a*,*b*][1,8]naphthyridine derivatives **7b, d**): A solution of **3b** or **3d** (1.4 mmol), malononitrile (0.185 g, 2.8 mmol), $BuNH_2$ (0.14 mL, 1.4 mmol) and NH_4OAc (0.11 g, 1.4 mmol) in MeOH was refluxed for 2 h. The solvent was removed under reduced pressure and the resulting solid was purified by MPLC on a silica gel column (15 × 1.5 cm) using the following mixtures as eluents: CH_2Cl_2/hexane (1:1) for **7d**; CH_2Cl_2/hexane (3:2) for **7b**.

8-Cyano-6-(1,1-dicyanoethyl)-9-ethoxy-2,6-dihydro-7-phenyl-1*H*-indolo[1,8,7-*a*,*b*][1,8]naphthyridine (8a):

A solution of **7a** (0.1 g, 0.24 mmol), K_2CO_3 (0.07 g, 0.48 mmol) and Me_2SO_4 (0.04 mL, 0.48 mmol) in acetone (10 mL) was refluxed for 0.5 h. Upon cooling the reaction crude was poured into brine (50 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and the solvent removed under reduced pressure. The resulting solid was recrystallized from EtOH to obtain **8a** as a colorless solid; yield: 0.077 g (75%); mp 200 °C (dec).

$C_{27}H_{21}N_5O$	calc.	C 75.16	H 4.90	N 16.23
(431.5)	found	75.36	4.76	16.27

IR (KBr): ν = 3055, 2980, 2925, 2900 (CH); 2220 (CN); 1630, 1600, 1580, 1560, 1390 cm^{-1} (CC).

^1H NMR ($CDCl_3$/TMS): δ = 1.36 [s, 3 H, $C(CN)_2CH_3$], 1.49 (t, 3 H, J = 7.1 Hz, OCH_2CH_3), 3.36–3.46 (m, 2 H, H-2), 4.27–4.33 (m, 2 H, H-1), 4.58 (q, 2 H, J = 7.1 Hz, OCH_2), 4.75 (s, 1 H, H-6), 7.06–7.15 (m, 2 H_{arom}), 7.22–7.32 (m, 2 H_{arom}), 7.47–7.64 (m, 3 H_{arom}), 7.70–7.73 (m, 1 H_{arom}).

^{13}C NMR ($CDCl_3$/TMS): δ = 14.4 (OCH_2CH_3), 22.2 [$C(CN)_2CH_3$], 28.3 (C-2), 39.4 [$C(CN)_2$], 45.2 (C-6), 47.0 (C-1), 63.4 (OCH_2), 88.2 (PyCN), 99.8, 112.4, 153.5, 157.5, 164.6, ($C_{pyridyl}$), 115.0, 115.8 [$C(CN)_2$], 115.4, 124.0, 125.6, 126.5, 128.2, 129.0, 129.1, 129.7, 129.8, 131.7, 134,6, 142.5 (C_{arom}).

MS (DEI): m/z (%) = 352 [$M^+ - CCH_3(CN)_2$, 81], 338 (11), 325 (23), 324 (100), 294 (30), 241 (8).

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