

A FRIEDLÄNDER APPROACH TO POLYCONDENSED 1,8-NAPHTHYRIDINE DERIVATIVES

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Abstract- An efficient method is proposed for the preparation of a variety of polycondensed 1,8-naphthyridines from 2-amino-3-cyano-6-ethoxy-5-formyl-4-phenylpyridine (**1**) by Friedländer condensation with cyclic and heterocyclic ketones.

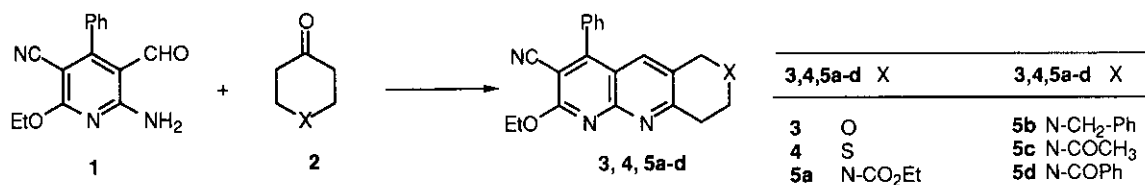
Naphthyridines are an important class of pharmaceutically active compounds and their chemistry was recently reviewed.¹ Their anti-allergy/anti-inflammatory properties have been reported² and many 1,8-naphthyridine compounds have demonstrated important antibacterial activity.³ Other 1,8-naphthyridines have shown antithrombic activity,⁴ and tranquilizer, muscle relaxant, and hypnotic properties, as well as anticonvulsant behaviour.⁵ Some other derivatives have antihypertensive effects,⁶ shown attracted interest as a platelet aggregation inhibitor drug,^{6b} or have the property of inhibiting secretion of acid stomach.⁷

The actual resurgence of interest in quinolones, naphthyridones and related compounds has resulted in an enormous account of research on new structural modifications to improve the overall spectrum of antibacterial activity, bioavailability and safety. Detailed structure-activity relationships have been reviewed.⁸ A series of naphthyridine derivatives which possessed excellent broad-spectrum activity against Gram-positive and Gram-negative bacteria as well as good pharmacokinetic properties have been recently prepared and are used clinically.⁹ Nevertheless a number of these compounds have quite often exhibited other properties which caused toxicity and preclude their clinical use.¹⁰ Prompted by the important medicinal application of these compounds and in continuation of our work on the study of nitrogen-containing heterocyclic compounds¹¹ we report in this paper the preparation of various polycondensed 1,8-naphthyridines with a potentially biological interest.

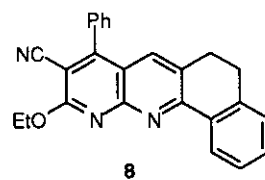
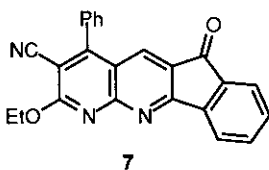
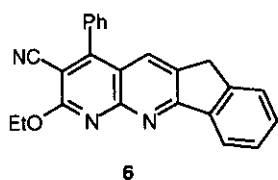
Aromatic *o*-amino aldehydes are valuable starting materials for a wide variety of *N*-heterocyclic compounds. Annulation reactions with heterocyclic amino aldehydes provide

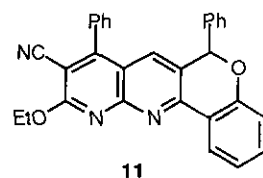
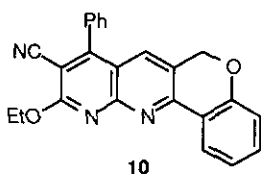
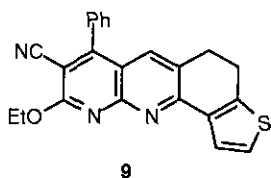
synthetic entry into heterocyclic systems fused to a pyridine or pyrimidine nucleus by condensation reactions involving activated methylene compounds.¹² Reactions of heterocyclic amino aldehydes with cyclic ketones are specially valuable for the construction of polycondensed heterocyclic systems. The direction of annelation and the position of the heteroatom(s) are in general uniquely defined by the participating functional groups. The availability and structural variety of cyclic ketones provide easy and direct access to a large number of fused heterocyclic systems for which in many cases alternate annelation methods are not readily available. Furthermore, the mild reaction conditions employed in the Friedländer condensation permit the unaltered transposition of functional groups from the starting ketone into the annelated heterocyclic ring.

Scheme 1

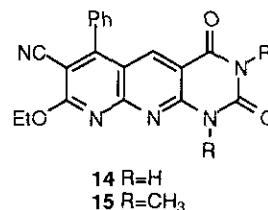
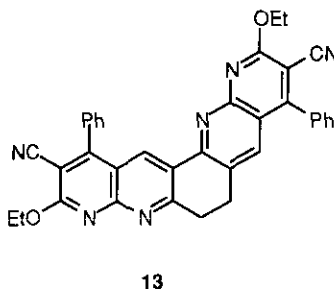
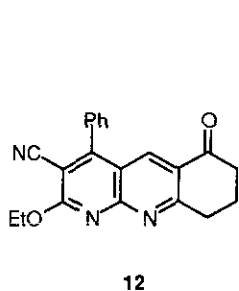


The starting material (**1**) for the preparation of the title polycondensed 1,8-naphthyridine derivatives was readily prepared by LiAlH₄ reduction¹³ of 2-amino-3,5-dicyano-6-ethoxy-4-phenylpyridine, which is easily accessible from malononitrile and benzaldehyde.¹⁴ Polycyclic systems containing a fused terminal 1,8-naphthyridine moiety are easily obtained by Friedländer condensation of the heterocyclic aminoaldehyde (**1**) with cyclic ketones (**2**) (Scheme 1). Thus, a base-catalyzed reaction of **1** with tetrahydro-4*H*-pyran-4-one or tetrahydro-4*H*-thiopyran-4-one gave the pyrano[3,2-*b*]- or thiopyrano[3,2-*b*]-1,8-naphthyridines (**3**) and (**4**), respectively. Besides, annelation reactions of **1** with piperidones provide entry into the reduced 1,7,10-anthyridine system.¹⁵ In effect, 6,7,8,9-tetrahydro-1,7,10-anthyridine derivatives (**5a-d**) result from the reaction of the aminonicotinaldehyde (**1**) with 4-substituted piperidones. When bicyclic ketones such as 1-indanone, 1,3-indanone, α -tetralone or keto-4,5,6,7-tetrahydrothianaphthene were employed in a similar sequence, fused polycondensed systems (**6**, **7**, **8**, and **9**) were obtained. Condensation reactions with other ketones, such as 4-chromanone or flavanone, respectively resulted in the formation of the angularly-fused naphthyridine derivatives (**10** and **11**).





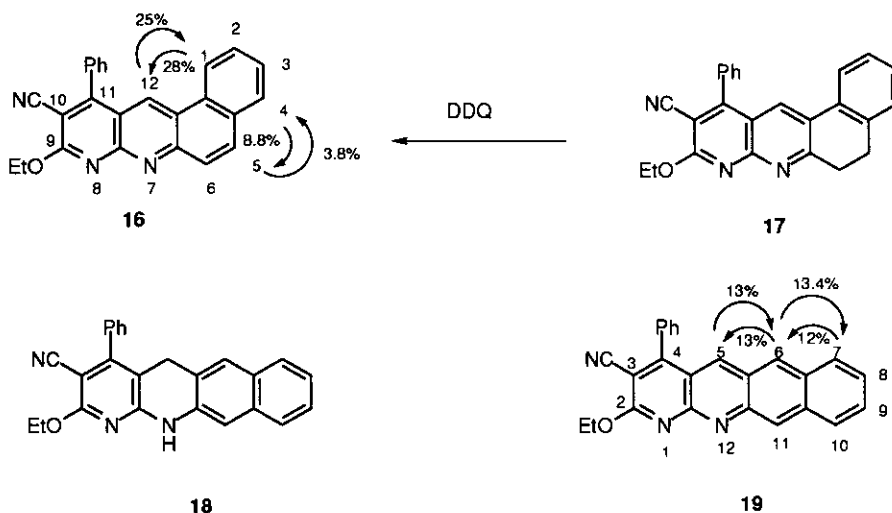
Base-catalyzed condensation of **1** with 1,3-cyclohexanedione gave tricyclic ketone (**12**) or pentacyclic derivative (**13**), depending on the molar ratio of the reactants. Treatment of the annelated ketone (**12**) with **1** likewise resulted in the formation of the bis-condensation product (**13**) in moderate yield. Similarly, aminoaldehyde (**1**) condenses with barbituric or 1,3-dimethylbarbituric acids to form substituted pyrimido[4,5-*b*]-1,8-naphthyridines (**14** and **15**), respectively.



In the closely related condensation of **1** with β -tetralone, on the other hand, ring closure with the benzyl carbon adjacent to the ketone becomes the predominant reaction pathway¹⁶ and the fully aromatic heterocyclic compound (**16**) or the reduced derivative (**17**), as the major products, are generated depending on the reaction conditions employed for the Friedländer synthesis. Thus, heating β -tetralone and **1** in refluxing ethanol for 24 hours in the presence of a small amount of 10% ethanolic sodium hydroxide, predominantly gives the angularly-fused derivative (**16**) and the polycondensed linearly compounds (**18** and **19**) as minor components. However, condensation reaction of **1** with β -tetralone (10% KOH as catalyst) in ethanol under reflux for 1 hour resulted in the formation of dihydro derivative (**17**) in 50% yield. The polycyclic linearly derivatives (**18** and **19**) were also isolated as minor products of the reaction mixture. Compound (**17**) could be oxidized to the fully aromatic derivative (**16**) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing THF.

The formation of a reduced annelation compound (**18**) can be interpreted in terms of an initial Claisen condensation with the formation of an α,β -unsaturated ketone. Double-bond transposition, ring closure with the amino group, and dehydration would lead to the tetracyclic derivative (**18**).

All analytical and spectral data are in accordance with the indicated structure. All ^1H and ^{13}C signals were attributed. The "angular" and "linear" nature of the compounds (**16** and **19**) were determined using ^1H nOe difference spectroscopy: irradiation of 5-H of **16** produced 3.8% nOe at H-4, conversely, irradiation of H-4 resulted in an enhancement of 8.8% at H-5; irradiation of H-12 of **16** give rises to a nOe of 25% at H-1, irradiation of which yielded an enhancement of 28% at H-5. On the other hand, irradiation of H-5 in **19** affords 13% nOe at H-6, irradiation of which gives rise to a nOe of 13% at H-5 and 13.4% at H-7; irradiation of H-7 resulted in an enhancement of 12% at H-6.



EXPERIMENTAL SECTION

All reagents used were commercial grade chemicals from freshly opened containers. Melting points were determined on a Büchi 510 apparatus and are reported uncorrected. Ir spectra were recorded on potassium bromide disks on a Perkin-Elmer 383 spectrophotometer. ^1H and ^{13}C nmr spectra were obtained on a Bruker AC200F instrument at room temperature. Mass spectra were obtained at 70 eV by using a VG4 spectrometer. The Silica gel 60 HF₂₅₄₊₃₆₆ used for analytical thin layer chromatography and the Silica gel 60 (230-400 mesh) employed 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 La Coruña.

Friedländer condensation of aminoaldehyde (**1**) with cyclic and heterocyclic ketones. General procedure:

A few drops of KOH (ethanolic 10%) were added to a solution of **1** (0.26 g, 1 mmol) and the appropriate ketone (1.2 mmol) in ethanol (10 ml) and the solution was refluxed until the starting material had disappeared as checked by tlc (0.5-3 h). The solvent was evaporated under reduced pressure and the residue was recrystallized or purified by mplc.

3-Cyano-2-ethoxy-4-phenyl-8,9-dihydro-6H-pyrano[4,3-b]-1,8-naphthyridine (3). Purified by medium-pressure chromatography using $\text{CH}_2\text{Cl}_2/\text{EtOH}$ (50:1 v/v) as eluent; yield 65%; mp 219-221°C. Ir (KBr): ν

2230 (CN) cm^{-1} . $^1\text{H-Nmr}$ (CDCl_3): δ 1.51 (t, 3H, $J = 7.1$ Hz, CH_3); 3.25 (t, 2H, $J = 5.8$ Hz, CH_2); 4.11 (t, 2H, $J = 5.8$ Hz, CH_2); 4.73 (q, 2H, $J = 7.1$ Hz, CH_2O); 4.78 (s, 2H, CH_2); 7.38-7.59 (m, 5H, C_6H_5), 7.52 (s, 1H, H-5). $^{13}\text{C-Nmr}$ (CDCl_3): 14.3 (CH_3); 32.8 (CH_2); 64.0 (CH_2O); 65.3, 67.1 (CH_2); 98.8 (C-3); 114.3 (CN); 116.2 (C-4a); 129.0, 129.1, 130.1, 131.5 (C_6H_5); 133.0 (C-5); 154.3; 158.1; 161.3; 162.1. Ms (DEI): m/z (%) 331 (M^+ , 49); 330 (100); 303 (67); 286 (18); 272 (9). *Anal.* Calcd for $\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}_2$: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.55; H, 5.12; N, 12.73.

3-Cyano-2-ethoxy-4-phenyl-8,9-dihydro-6H-thiopyrano[4,3-b]-1,8-naphthyridine (4). Recrystallized from ethanol; yield 60%; mp 130°C (decomp.). Ir (KBr): ν 2230 (CN) cm^{-1} . $^1\text{H-Nmr}$ (CDCl_3): δ 1.52 (t, 3H, $J = 7.1$ Hz, CH_3); 3.07 (t, 2H, $J = 6.4$ Hz, CH_2); 3.46 (t, 2H, $J = 6.4$ Hz, CH_2); 3.79 (s, 2H, CH_2); 4.75 (q, 2H, $J = 7.1$ Hz, CH_2O); 7.42-7.62 (m, 6H, H-5+ C_6H_5). $^{13}\text{C-Nmr}$ (CDCl_3): 14.4 (CH_3); 26.1, 29.5, 34.6 (CH_2); 64.2 (CH_2O); 98.9 (C-3); 114.4 (CN); 116.3 (C-4a); 129.1, 129.2, 130.2, 133.0 (C_6H_5); 134.0 (C-5); 154.3; 158.2; 162.3; 164.0. Ms (FAB): m/z (%) 347 (M^+ , 1); 346 (4); 318 (7); 314 (4); 286 (8); 272 (4). *Anal.* Calcd for $\text{C}_{20}\text{H}_{17}\text{N}_3\text{OS}$: C, 69.14; H, 4.93; N, 12.09. Found: C, 69.21; H, 5.00; N, 11.99.

3-Cyano-2-ethoxy-7-ethoxycarbonyl-4-phenyl-6,7,8,9-tetrahydro-1,7,10-anthryridine (5a). Recrystallized from ethanol; yield 45%; mp $298\text{-}300^\circ\text{C}$. Ir (KBr): ν 2220 (CN); 1700 (CO) cm^{-1} . $^1\text{H-Nmr}$ (CDCl_3): δ 1.27 (t, 3H, $J = 7.1$ Hz, CH_3); 1.52 (t, 3H, $J = 7.1$ Hz, CH_3); 3.28 (t, 2H, $J = 6.1$ Hz, CH_2); 3.85 (t, 2H, $J = 6.1$ Hz, CH_2); 4.18 (q, 2H, $J = 7.1$ Hz, CH_2O); 4.70 (s, 2H, CH_2); 4.76 (q, 2H, $J = 7.1$ Hz, CH_2O); 7.41-7.63 (m, 5H, C_6H_5); 7.66 (s, 1H, H-5). $^{13}\text{C-Nmr}$ (CDCl_3): 14.3 (CH_3); 14.6 (CH_3); 33.1, 41.1, 44.9 (CH_2); 61.8 (CH_2O); 64.2 (CH_2O); 99.0 (C-3); 114.3 (CN); 116.4 (C-4a); 127.0; 129.1, 129.2, 130.2, 133.0 (C_6H_5); 133.4 (C-5); 154.3; 155.4; 158.2; 162.3. Ms (FAB): m/z (%) 403 [(MH) $^+$, 31]; 376(26); 375 (100); 301 (16); 274 (21). *Anal.* Calcd for $\text{C}_{23}\text{H}_{22}\text{N}_4\text{O}_3$: C, 68.64; H, 5.11; N, 13.92. Found: C, 68.53; H, 5.19; N, 14.00.

7-Benzyl-3-cyano-2-ethoxy-4-phenyl-6,7,8,9-tetrahydro-1,7,10-anthryridine (5b). Recrystallized from ethanol; yield 70%; mp $180\text{-}182^\circ\text{C}$. Ir (KBr): ν 2220 (CN) cm^{-1} . $^1\text{H-Nmr}$ (CDCl_3): δ 1.50 (t, 3H, $J = 7.1$ Hz, CH_3); 2.91 (t, 2H, $J = 6.0$ Hz, CH_2); 3.30 (t, 2H, $J = 6.0$ Hz, CH_2); 3.62 (s, 2H, CH_2); 3.69 (s, 2H, CH_2); 4.73 (q, 2H, $J = 7.1$ Hz, CH_2O); 7.25-7.57 (m, 5H, C_6H_5); 7.49 (s, 1H, H-5). $^{13}\text{C-Nmr}$ (CDCl_3): 14.4 (CH_3); 33.7, 50.4, 54.9 (CH_2); 62.6 ($\text{CH}_2\text{C}_6\text{H}_5$); 64.0 (CH_2O); 98.5 (C-3); 114.5 (CN); 116.0 (C-4a); 127.3, 128.4, 128.7, 129.0, 129.2, 130.0, 137.6 (C_6H_5); 133.2 (C-5); 154.3; 158.1; 162.0; 163.1. Ms (DEI): m/z (%) 420 (M^+ , 29); 419 (49); 329 (32); 301 (14); 272 (5). *Anal.* Calcd for $\text{C}_{27}\text{H}_{24}\text{N}_4\text{O}$: C, 77.12; H, 5.75; N, 13.32. Found: C, 77.05; H, 5.80; N, 13.43.

7-Acetyl-3-cyano-2-ethoxy-4-phenyl-6,7,8,9-tetrahydro-1,7,10-anthryridine (5c). Recrystallized from ethanol/acetone; yield 75%; mp $281\text{-}283^\circ\text{C}$. Ir (KBr): ν 2220 (CN); 1690 (CO) cm^{-1} . $^1\text{H-Nmr}$ (CDCl_3): δ 1.46 (t, 3H, $J = 7.1$ Hz, CH_3); 2.13 (s, 3H, CH_3); 3.24 (m, 2H, CH_2); 3.87 (m, 2H, CH_2); 4.68 (q, 2H, $J = 7.1$ Hz, CH_2O); 4.73 (s, 2H, CH_2); 7.35-7.61 (m, 5H, C_6H_5); 7.64 (s, 1H, H-5). $^{13}\text{C-Nmr}$ (CDCl_3): 14.1 (CH_3); 21.2 (CH_3); 33.3, 42.8, 43.3 (CH_2); 63.9 (CH_2O); 98.8 (C-3); 114.0 (CN); 116.3 (C-4a); 126.9; 128.8, 128.9, 130.1, 132.6 (C_6H_5); 133.6 (C-5); 154.0; 158.0; 161.4; 162.4; 169.3 (CO). Ms (DEI): m/z (%) 372 (M^+ , 100); 371 (84); 344 (17); 329 (58); 314 (30); 301 (82); 286 (78); 274 (20). *Anal.* Calcd for $\text{C}_{22}\text{H}_{20}\text{N}_4\text{O}_2$: C, 70.95; H, 5.41; N, 15.04. Found: C, 71.08; H, 5.30; N, 14.97.

7-Benzoyl-3-cyano-2-ethoxy-4-phenyl-6,7,8,9-tetrahydro-1,7,10-anthryridine (5d). Recrystallized from ethanol/acetone; yield 85%; mp $269\text{-}271^\circ\text{C}$. Ir (KBr): ν 2220 (CN); 1630 (CO) cm^{-1} . $^1\text{H-Nmr}$ (CDCl_3): δ 1.54 (t,

3H, $J = 7.1$ Hz, CH₃); 3.31 (br s, 2H, CH₂); 3.89 (br s, 2H, CH₂); 4.77 (q, 2H, $J = 7.1$ Hz, CH₂O); 4.91 (br s, 2H, CH₂); 7.45-7.60 (m, 10H, C₆H₅); 7.61 (s, 1H, H-5). ¹³C-Nmr (CDCl₃): 14.3 (CH₃); 33.6, 43.9, 44.7 (CH₂); 64.2 (CH₂O); 99.2 (C-3); 114.2 (CN); 116.4 (C-4a); 126.6; 126.9, 128.7, 129.1, 129.2, 130.2, 130.3, 132.8, 133.9, 135.2 (C₆H₅+C-5); 154.3; 158.2; 161.9; 162.4; 171.2 (CO). Ms (DEI): m/z (%) 434 (M⁺, 40); 433 (14); 301 (10); 286 (10). *Anal.* Calcd for C₂₇H₂₂N₄O₂: C, 74.64; H, 5.10; N, 12.89. Found: C, 74.73; H, 5.01; N, 12.99.

8-Cyano-9-ethoxy-7-phenyl-5H-indeno[1,2-*b*]-1,8-naphthyridine (6). Recrystallized from ethanol/acetone; yield 90%; mp 290-292°C. Ir (KBr): ν 2220 (CN) cm⁻¹. ¹H-Nmr (CDCl₃): δ 1.57 (t, 3H, $J = 7.1$ Hz, CH₃); 3.95 (s, 2H, CH₂); 4.84 (q, 2H, $J = 7.1$ Hz, CH₂O); 7.48-7.66 (m, 8H, C₆H₅); 7.97 (s, 1H, H-6); 8.44 (m, 1H, H-1). ¹³C-Nmr (CDCl₃): 14.4 (CH₃); 34.0 (CH₂); 64.0 (CH₂O); 97.6 (C-8); 114.7 (CN); 116.4 (C-6a); 123.5, 125.4, 127.8, 129.0, 129.3, 130.0, 131.0, 131.3, 134.5, 139.5, 146.1 (C_{arom}); 133.7 (C-6); 156.2; 158.2; 162.2; 166.8. Ms (DEI): m/z (%) 363 (M⁺, 72); 362 (99); 348 (33); 335 (100); 318 (31); 307 (33); 293 (14). *Anal.* Calcd for C₂₄H₁₇N₃O: C, 79.32; H, 4.72; N, 11.56. Found: C, 79.38; H, 4.80; N, 11.68.

8-Cyano-9-ethoxy-7-phenyl-5-oxo-indeno[3,2-*b*]-1,8-naphthyridine (7). Recrystallized from ethanol/CH₂Cl₂; yield 52%; mp 281-283°C. Ir (KBr): ν 2220 (CN); 1740 (CO) cm⁻¹. ¹H-Nmr (CDCl₃): δ 1.57 (t, 3H, $J = 7.1$ Hz, CH₃); 4.83 (q, 2H, $J = 7.1$ Hz, CH₂O); 7.43-7.84 (m, 8H, C₆H₅); 8.15 (s, 1H, H-6); 8.24 (d, 1H, $J = 7.4$ Hz, H-1). ¹³C-Nmr (CDCl₃): 14.3 (CH₃); 64.8 (CH₂O); 99.3 (C-8); 113.8 (CN); 117.4 (C-6a); 123.1; 124.3; 126.5; 129.1; 129.3; 130.5; 132.1; 132.6; 132.9; 135.9; 137.3; 142.5; 159.4; 160.0; 163.8; 168.2; 189.5 (CO). Ms (DEI): m/z (%) 377 (M⁺, 55); 376 (100); 362 (13); 349 (80); 332 (18); 321 (33). *Anal.* Calcd for C₂₄H₁₅N₃O₂: C, 76.38; H, 4.01; N, 11.13. Found: C, 76.46; H, 4.10; N, 11.00.

9-Cyano-10-ethoxy-5,6-dihydro-8-phenylaphto[1,2-*b*]-1,8-naphthyridine (8). Recrystallized from ethanol/CH₂Cl₂; yield 94%; mp 261-263°C. Ir (KBr): ν 2220 (CN) cm⁻¹. ¹H-Nmr (CDCl₃): δ 1.56 (t, 3H, $J = 7.1$ Hz, CH₃); 2.99 (s, 4H, CH₂CH₂); 4.80 (q, 2H, $J = 7.1$ Hz, CH₂O); 7.24-7.63 (m, 8H, C₆H₅); 7.70 (s, 1H, H-6); 8.66 (m, 1H, H-1). ¹³C-Nmr (CDCl₃): 14.4 (CH₃); 28.0, 28.2 (CH₂); 63.9 (CH₂O); 98.1 (C-9); 114.7 (CN); 117.0 (C-7a); 127.3; 127.4; 127.9; 128.9; 129.3; 130.0; 130.4; 131.0; 133.4 (C-7); 134.1; 139.8; 155.2; 157.6; 158.4; 162.2. Ms (DEI): m/z (%) 377 (M⁺, 82); 376 (100); 362 (60); 349 (97); 332 (52); 320 (39); 307 (19); 303 (14); 292 (14). *Anal.* Calcd for C₂₅H₁₉N₃O: C, 79.55; H, 5.07; N, 11.13. Found: C, 79.40; H, 5.15; N, 11.24.

8-Cyano-9-ethoxy-4,5-dihydro-7-phenylbenzothiopheno[4,5-*b*]-1,8-naphthyridine (9). Recrystallized from ethanol/acetone; yield 60%; mp 273-275°C. Ir (KBr): ν 2220 (CN) cm⁻¹. ¹H-Nmr (CDCl₃): δ 1.54 (t, 3H, $J = 7.1$ Hz, CH₃); 3.04 (s, 4H, CH₂CH₂); 4.78 (q, 2H, $J = 7.1$ Hz, CH₂O); 7.24 (d, 1H, $J = 5.3$ Hz, CH); 7.44-7.62 (m, 5H, C₆H₅); 7.65 (s, 1H, H-6); 7.96 (d, 1H, $J = 5.3$ Hz, H-1). ¹³C-Nmr (CDCl₃): 14.4 (CH₃); 23.3, 29.0 (CH₂); 63.9 (CH₂O); 97.6 (C-8); 114.8 (CN); 116.4 (C-6a); 123.3, 125.8 (C-1, C-2); 128.3; 128.9, 129.3, 130.0 (C₆H₅); 133.5; 133.7; 136.4; 146.1; 155.5; 156.2; 157.4; 162.3. Ms (DEI): m/z (%) 383 (M⁺, 100); 382 (93); 368 (30); 355 (91); 338 (17); 326 (23); 322 (20); 249 (9). *Anal.* Calcd for C₂₃H₁₇N₃OS: C, 72.04; H, 4.47; N, 10.96. Found: C, 72.18; H, 4.67; N, 10.87.

9-Cyano-10-ethoxy-8-phenyl-1-benzopirano[4,3-*b*]-1,8-naphthyridine (10). Purified by medium-pressure chromatography using hexane/CH₂Cl₂ (1:2 v/v) as eluent; yield 58%; mp 242-244°C Ir (KBr): ν 2220 (CN)

cm⁻¹. ¹H-Nmr (CDCl₃): δ 1.57 (t, 3H, *J* = 7.1 Hz, CH₃); 4.81 (q, 2H, *J* = 7.1 Hz, CH₂O); 5.24 (s, 2H, CH₂); 7.02-7.65 (m, 8H, C₆H₅); 8.58 (m, 1H, H-1). ¹³C-Nmr (CDCl₃): 14.3 (CH₃); 64.1 (CH₂O); 67.7 (CH₂); 98.4 (C-9); 114.4 (CN); 117.0 (C-7a); 117.3; 122.0; 122.6; 124.7; 126.8; 129.0; 129.2; 130.1; 131.5; 133.1; 133.4 (C-7); 154.2; 156.0; 157.9; 162.6. Ms (DEI): *m/z* (%) 379 (M⁺, 86); 378 (78); 350 (100); 334 (11); 322 (14); 294 (7). *Anal.* Calcd for C₂₄H₁₇N₃O₂: C, 75.97; H, 4.52; N, 11.07. Found: C, 76.03; H, 4.60; N, 11.13.

9-Cyano-10-ethoxy-6,8-diphenyl-1-benzopyrano[4,3-*b*]-1,8-naphthyridine (11). Recrystallized from ethanol/acetone; yield 40%; mp 183-185°C. Ir (KBr): ν 2220 (CN) cm⁻¹. ¹H-Nmr (CDCl₃): δ 1.57 (t, 3H, *J* = 7.1 Hz, CH₃); 4.82 (q, 2H, *J* = 7.1 Hz, CH₂O); 6.30 (s, 1H, H-6); 7.00-7.54 (m, 13H, C₆H₅); 8.58 (m, 1H, H-1). ¹³C-Nmr (CDCl₃): 14.4 (CH₃); 64.2 (CH₂O); 79.3 (C-6); 98.1 (C-9); 114.4 (CN); 116.9 (C-7a); 117.8, 122.0, 122.6, 126.8, 127.7, 128.4, 128.7, 128.9, 129.3, 130.1, 132.7 (C₆H₅); 133.4, 133.6, 133.7 (C-7+C₆H₅); 138.1; 154.0; 155.9; 156.7; 158.0; 162.9. Ms (DEI): *m/z* (%) 455 (M⁺, 94); 454 (54); 426 (34); 378 (71); 367 (13); 350 (100); 338 (10); 321 (12). *Anal.* Calcd for C₃₀H₂₁N₃O₂: C, 79.10; H, 4.65; N, 9.23. Found: C, 79.21; H, 4.56; N, 9.30.

3-Cyano-2-ethoxy-4-phenyl-6-oxo-6,7,8,9-tetrahydrobenzo[*b*]-1,8-naphthyridine (12). Recrystallized from ethanol/acetone; yield 66%; mp 282-284°C. Ir (KBr): ν 2230 (CN); 1680 (CO) cm⁻¹. ¹H-Nmr (CDCl₃): δ 1.56 (t, 3H, *J* = 7.1 Hz, CH₃); 2.26 (m, 2H, H-8); 2.76 (t, 2H, *J* = 6.2 Hz, CH₂); 3.38 (t, 2H, *J* = 6.2 Hz, CH₂); 4.81 (q, 2H, *J* = 7.1 Hz, CH₂O); 7.42-7.64 (m, 5H, C₆H₅); 8.61 (s, 1H, H-5). ¹³C-Nmr (CDCl₃): 14.3 (CH₃); 21.3 (C-8); 33.5, 38.7 (CH₂); 64.8 (CH₂O); 79.3; 99.8 (C-3); 113.9 (CN); 116.7 (C-4a); 126.1; 129.2, 130.7, 132.4 (C₆H₅); 137.5 (C-5); 157.0; 160.2; 163.8; 168.7; 196.5 (CO). *Anal.* Calcd for C₂₁H₁₇N₃O₂: C, 73.45; H, 4.99; N, 12.23. Found: C, 73.55; H, 4.59; N, 11.17.

7-Cyano-8-ethoxy-6-phenyl-2,4-dioxo-1,2,3,4-tetrahydropyrimido[4,5-*b*]-1,8-naphthyridine (14). Recrystallized from ethanol/CH₂Cl₂; yield 97%; mp >300°C. Ir (KBr): ν 3180 (NH); 2230 (CN); 1700 (CO) cm⁻¹. ¹H-Nmr (DMSO-*d*₆): δ 1.42 (t, 3H, *J* = 7.1 Hz, CH₃); 4.59 (q, 2H, *J* = 7.1 Hz, CH₂O); 7.56-7.70 (m, 5H, C₆H₅); 8.19 (s, 1H, H-5); 11.82 (br s, 2H, NH). ¹³C-Nmr (DMSO-*d*₆): 14.1 (CH₃); 64.1 (CH₂O); 96.8 (C-7); 110.3; 114.1 (CN); 114.3; 129.1, 129.3, 130.4, 132.7 (C₆H₅); 138.1 (C-5); 150.4; 154.8; 157.4; 159.3; 161.5; 163.5. Ms (DEI): *m/z* (%) 359 (M⁺, 30); 358 (77); 331 (70); 287 (16). *Anal.* Calcd for C₁₉H₁₃N₅O₃: C, 63.51; H, 3.65; N, 19.49. Found: C, 63.63; H, 3.77; N, 19.38.

7-Cyano-8-ethoxy-1,3-dimethyl-6-phenyl-2,4-dioxo-1,2,3,4-tetrahydropyrimido[4,5-*b*]-1,8-naphthyridine (15). Recrystallized from ethanol/acetone; yield 62 %; mp >300°C. Ir (KBr): ν 2220 (CN); 1725 (CO); 1675 (CO) cm⁻¹. ¹H-Nmr (CDCl₃): δ 1.57 (t, 3H, *J* = 7.1 Hz, CH₃); 3.49 (s, 3H, NMe); 3.86 (s, 3H, NMe); 4.80 (q, 2H, *J* = 7.1 Hz, CH₂O); 7.44-7.65 (m, 5H, C₆H₅); 8.76 (s, 1H, H-5). ¹³C-Nmr (CDCl₃): 14.3 (CH₃); 28.6 (NMe); 30.3 (NMe); 64.8 (CH₂O); 98.7 (C-7); 110.1; 114.2 (CN); 114.5; 129.3, 130.8, 132.4 (C₆H₅); 140.7 (C-5); 151.7; 153.0; 158.0; 159.6; 160.4; 164.2. Ms (DEI): *m/z* (%) 387 (M⁺, 59); 386 (100); 372 (19); 359 (71); 331 (20). *Anal.* Calcd for C₂₁H₁₇N₅O₃: C, 65.11; H, 4.42; N, 18.08. Found: C, 65.01; H, 4.49; N, 18.17.

3,11-Dicyano-2,10-diethoxy-4,12-diphenyl-6,7-dihydrobenzo[1,2-*b*:3,4-*b'*]-1,8-dinaphthyridine (13):

Method A:

A few drops of KOH (ethanolic 10%) were added to a solution of **1** (0.53 g, 2 mmol) and α-tetralone (0.17 g, 1.2 mmol) in ethanol (10 ml) and the solution was refluxed for 3 h. The solid was filtered off and recrystallized from

ethanol/acetone to obtain **13** (0.38 g, 50 %); mp >300°C. Ir (KBr): ν 2220 (CN) cm^{-1} . $^1\text{H-Nmr}$ (CDCl_3): δ 1.52 (t, 3H, $J = 7.1$ Hz, CH_3); 1.54 (t, 3H, $J = 7.1$ Hz, CH_3); 3.14 (t, 2H, $J = 6.9$ Hz, CH_2); 3.43 (t, 2H, $J = 6.9$ Hz, CH_2); 4.69 (q, 2H, $J = 7.1$ Hz, CH_2O); 4.78 (q, 2H, $J = 7.1$ Hz, CH_2O); 7.44-7.68 (m, 10H, C_6H_5); 7.78 (s, 1H, H-4); 9.11 (s, 1H, H-13). $^{13}\text{C-Nmr}$ (CDCl_3): 14.3, 14.4 (CH_3); 27.1, 31.8 (CH_2); 64.1, 64.4 (CH_2O); 99.2, 99.5 (C-2, C-11); 114.2, 114.3 (CN); 117.1, 117.5 (C-4a, C-12a); 127.1; 129.1, 129.2, 129.6, 129.7, 130.2, 130.5, 132.9 (C_6H_5); 135.1 (C-13); 155.0; 155.8; 156.2; 157.8; 159.5; 162.4; 163.1; 165.8. *Anal.* Calcd for $\text{C}_{36}\text{H}_{26}\text{N}_6\text{O}_6$: C, 75.25; H, 4.56; N, 14.62. Found: C, 75.38; H, 4.67; N, 14.78.

Method B:

Compound (**13**) was also prepared from **1** and **12** following the General Procedure of Friedländer condensation of aminoaldehyde **1** with ketones in 53 % yield.

Reaction of aminoaldehyde (**1**) with β -tetralone:

A few drops of KOH (ethanolic 10%) were added to a solution of **1** (0.56 g, 2 mmol) and β -tetralone (0.32 g, 2.2 mmol) and the solution was refluxed 1 h. The solid formed was filtered off and recrystallized from EtOH/acetone to yield **17** (0.30 g, 50%). The filtrate was evaporated under reduced pressure and the residue was purified by medium-pressure chromatography using CH_2Cl_2 as eluent to obtain **19** (0.03 g, 8%) and $\text{CH}_2\text{Cl}_2/\text{EtOH}$ (50:1 v/v) to obtain **18** (0.07 g, 17%).

When the reaction time was 24 h the solid formed was filtered off and recrystallized from EtOH/acetone to yield **16** (0.37 g, 60%). The filtrate was evaporated under reduced pressure and the residue was purified by medium-pressure chromatography using CH_2Cl_2 as eluent to obtain **19** (0.03 g, 7%) and $\text{CH}_2\text{Cl}_2/\text{EtOH}$ (50:1 v/v) to obtain **18** (0.07 g, 16%).

10-Cyano-9-ethoxy-11-phenylanthra[2,1-b]-1,8-naphthyridine (16). The solid was recrystallized from ethanol/acetone; mp >300°C. Ir (KBr): ν 2220 (CN) cm^{-1} . $^1\text{H-Nmr}$ (CDCl_3): δ 1.58 (t, 3H, $J = 7.1$ Hz, CH_3); 4.85 (q, 2H, $J = 7.1$ Hz, CH_2O); 7.55-7.75 (m, 7H, H-2, H-3, C_6H_5); 8.05, 8.12 (AB system, 2H, $J = 9.4$ Hz, H-5, H-6); 8.27-8.35 (m, 1H, H-1); 9.21 (s, 1H, H-12). $^{13}\text{C-Nmr}$ (CDCl_3): 14.4 (CH_3); 64.4 (CH_2O); 99.5 (C-10); 114.5 (CN); 116.5 (C-11a); 122.6; 123.6; 127.9; 128.0; 129.2; 129.4; 129.6; 130.5; 131.1; 132.0; 133.2; 135.3 (C-12); 152.5; 154.0; 159.2; 162.3. Ms (DEI): m/z (%) 375 (M^+ , 80); 374 (100); 347 (93); 330 (34); 319 (51). *Anal.* Calcd for $\text{C}_{25}\text{H}_{17}\text{N}_3\text{O}$: C, 79.98; H, 4.56; N, 11.19. Found: C, 80.08; H, 4.67; N, 11.31.

10-Cyano-9-ethoxy-11-phenyl-5,6-dihydroanthra[2,1-b]-1,8-naphthyridine (17). The solid was recrystallized from ethanol/acetone; mp >300°C. Ir (KBr): ν 2220 (CN) cm^{-1} . $^1\text{H-Nmr}$ (CDCl_3): δ 1.53 (t, 3H, $J = 7.1$ Hz, CH_3); 3.05 (m, 2H, CH_2); 3.31 (m, 2H, CH_2); 4.76 (q, 2H, $J = 7.1$ Hz, CH_2O); 7.17-7.28 (m, 4H, H-1, H-2, H-3, H-4); 7.41-7.60 (m, 5H, C_6H_5); 8.14 (s, 1H, H-12). $^{13}\text{C-Nmr}$ (CDCl_3): 14.4 (CH_3); 28.1, 32.9 (C-5, C-6); 64.1 (CH_2O); 98.5 (C-10); 114.5 (CN); 117.1 (C-11a); 124.1; 127.3; 128.5; 128.8; 129.0; 129.3; 130.2; 133.2; 131.7; 132.0; 135.3; 137.1 (C-12); 154.6; 158.3; 162.3; 165.7. Ms (DEI): m/z (%) 377 (M^+ , 100); 375 (48); 349 (46); 315 (40); 287 (85); 216 (49). *Anal.* Calcd for $\text{C}_{25}\text{H}_{19}\text{N}_3\text{O}$: C, 79.55; H, 5.07; N, 11.13. Found: C, 79.47; H, 4.95; N, 11.25.

3-Cyano-2-ethoxy-4-phenyl-5,12-dihydroanthra[2,3-b]-1,8-naphthyridine (18). Purified by medium-pressure chromatography using $\text{CH}_2\text{Cl}_2/\text{EtOH}$ (50:1 v/v) as eluent; mp 220-222°C. Ir (KBr): ν 3300 (NH);

2220 (CN) cm^{-1} . $^1\text{H-Nmr}$ (CDCl_3): δ 1.44 (t, 3H, $J = 7.1$ Hz, CH_3); 3.95 (s, 2H, H-5); 4.45 (q, 2H, $J = 7.1$ Hz, CH_2O); 7.06-7.65 (m, 11H, H_{arom}). $^{13}\text{C-Nmr}$ (CDCl_3): 14.5 (CH_3); 28.6 (C-5); 62.9 (CH_2O); 104.6; 109.2 (C-11); 116.2 (CN); 121.4; 124.2, 126.2, 126.4, 127.3, 127.6, (C-6, C-7, C-8, C-9, C-10); 128.1, 128.9, 129.1, 133.1 (C_6H_5); 130.2; 135.3; 135.6; 152.5; 155.1; 163.7. Ms (DEI): m/z (%) 377 (M^+ , 91); 376 (59); 375 (55); 348 (100); 319 (34); 174 (54). *Anal.* Calcd for $\text{C}_{25}\text{H}_{19}\text{N}_3\text{O}$: C, 79.55; H, 5.07; N, 11.13. Found: C, 79.68; H, 5.13; N, 10.98.

3-Cyano-2-ethoxy-4-phenylanthra[2,3-b]-1,8-naphthyridine (19). Purified by medium-pressure chromatography using CH_2Cl_2 as eluent; mp $>300^\circ\text{C}$. Ir (KBr): ν 2225 (CN) cm^{-1} . $^1\text{H-Nmr}$ (CDCl_3): δ 1.60 (t, 3H, $J = 7.1$ Hz, CH_3); 4.87 (q, 2H, $J = 7.1$ Hz, CH_2O); 7.45-7.70 (m, 7H, H_{arom}); 7.98 (d, 1H, $J = 6.5$ Hz, H-7); 8.10 (d, 1H, $J = 8.4$ Hz, H-10); 8.53 (s, 1H, H-6); 8.78 (s, 1H, H-5); 8.89 (s, 1H, H-11). $^{13}\text{C-Nmr}$ (CDCl_3): 14.4 (CH_3); 64.5 (CH_2O); 100.5 (C-3); 114.4 (CN); 117.8 (C-4a) 124.4 (C-5a); 126.2, 126.6, 127.7, 128.4, 128.5, 128.6 (C-6, C-7, C-8, C-9, C-10, C-11); 129.2, 129.4, 130.5, 133.1 (C_6H_5); 131.6, 136.3 (C-6a, C-10a); 140.7 (C-5); 146.5; 153.3; 160.2; 162.1. Ms (DEI): m/z (%) 375 (M^+ , 100); 374 (54); 347 (67); 319 (59); 288(22). *Anal.* Calcd for $\text{C}_{25}\text{H}_{17}\text{N}_3\text{O}$: C, 79.98; H, 4.56; N, 11.19. Found: C, 79.87; H, 4.63; N, 11.03.

Oxidation of naphthyridine (17) with DDQ.

A solution of **17** (0.133 g, 0.35 mmol) and DDQ (0.09 g, 0.39 mmol) in THF (20 ml) was refluxed for 4 h. The solid formed was filtered off and recrystallized from EtOH/acetone to obtain **16** (0.065 g, 65%).

ACKNOWLEDGEMENTS

Financial support (Project 10303B93) from the Xunta de Galicia are gratefully acknowledged. The nmr, mass spectra and elemental analyses facilities were kindly provided by Servicios Generales de Apoyo a la Investigacion of the University of La Coruña.

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Received, 20th June, 1995