A NEW ENTRY TO THE 1,7,10-ANTHYRIDINE SYSTEM

Juan Vilar, Carlos Peinador, Mª. Carmen Veiga, Vicente Ojea, and José Mª Quintela*

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

Abstract- A synthesis for the 1,7,10-anthyridine system by condensation of ethyl 3-cyano-2-ethoxy-7-methyl-4-phenyl-1,8-naphthyridine-6-carboxylate **(1)** and DMFDMA, followed by ring closure with ammonium acetate is reported. The proposed procedure allows the easy preparation of 7-substituted 1,7,10-anthyridin-6-(7*H*)-ones **(5)** and 6-substituted 1,7,10-anthyridines **(6)** and **(7)**.

Prompted by the observation that many 1,8-naphthyridine derivatives possess a wide range of biological activity[1-7] and, in continuation of our research into nitrogen-containing heterocyclic compounds with potential pharmacological activity,[8-9] we focused attention on compounds consisting of an anthyridine skeleton, which has one more pyridine ring than the 1,8-naphthyridine system.

A literature scan revealed that very little has so far been reported on the anthyridine synthesis.[10] Unlike the linear carbocyclic series, introduction of the pyridine ring as building unit into linear carbocyclic polycondensed systems gives rise to an increased number of isomeric structures. Of the many possible structures for these heterocyclic compounds containing three linearly annelated pyridine rings, few have actually been synthesized. The 1,9,10-anthyridine derivatives are the most readily available on account of their affordability and promising biological properties.[11-13]

Recently,[14] we reported the first example of the formation of a series of 7-substituted 1,7,10-anthyridin-6-ones. In extension of our work on the synthesis of anthyridines and, in connection with our synthesis programme for biologically active compounds, we herein report the preparation of the 7-substituted 1,7,10-anthyridin-6-(7*H*)-ones **(5)** and 6-substituted 1,7,10-anthyridines **(6)** and **(7)**.

Ethyl 3-cyano-2-ethoxy-7-methyl-4-phenyl-1,8-naphthyridine-6-carboxylate **(1)**, readily obtained by condensation of a suitable substituted 2-aminonicotinaldehyde with ethyl acetoacetate in ethanol using piperidine as catalyst,[14] is a versatile building block for triazaanthracene derivatives

(**5**, **6** and **7**). The pyridine ring in these compounds can be synthesized by enamination of the activated methyl group in the starting compound (**1**), followed by ring closure with ammonium acetate.

Table 1. 1,7,10-Anthyridine derivatives (6a-j, and 7a-c)

No.	Reaction time (h)	Yield (%)	mp (°C)	Molecular formula	Analysis (%) Calcd/Found C	H	N
6a	4	88[a]	264-265	$C_{24}H_{21}N_5O_2$	70.06 70.16	5.14 5.02	17.02 17.09
6b	4	88[a]	280-282	$C_{25}H_{23}N_5O$	73.33 73.28	5.66 5.73	17.10 17.19
6c	4	72[b]	218-219	$C_{32}H_{29}N_5O$	76.93 76.86	5.85 5.93	14.02 14.09
6d	8	71[b]	249-250	$C_{27}H_{26}N_6O_3$	67.21 67.33	5.43 5.31	17.42 17.46
6e	3	77[a]	248-250	$C_{29}H_{29}N_7O_3$	66.53 66.65	5.58 5.49	18.73 18.79
6f	2	77[a]	254-55	$C_{29}H_{31}N_7O_2$	68.35 68.46	6.13 6.05	19.24 19.29
6g	24	72[b]	231-232	$C_{31}H_{28}N_6O$	74.38 74.44	5.64 5.57	16.79 16.71
6h	24	65[b]	239-240	$C_{31}H_{25}N_6OF_3$	67.14 67.08	4.54 4.67	15.15 15.21
6i	24	67[b]	245-246	$C_{29}H_{25}N_7O$	71.44 71.35	5.17 5.12	20.11 20.19
6j	1	75[c]	284-286	$C_{26}H_{28}N_6$	73.56 73.63	6.65 6.58	19.79 19.70
7a	24	75[d]	211-212	$C_{32}H_{27}N_6O_3Cl$	66.38 66.21	4.70 4.82	14.51 14.60
7b	20	71[d]	278-279	$C_{24}H_{20}N_5O_2Cl$	64.65 64.57	4.52 4.63	15.71 15.66
7c	15	74[d]	254-255	$C_{32}H_{28}N_5OCl$	71.97 71.86	5 28 5.37	13.11 13.19

[a] Recrystallized from ethanol/acetone.

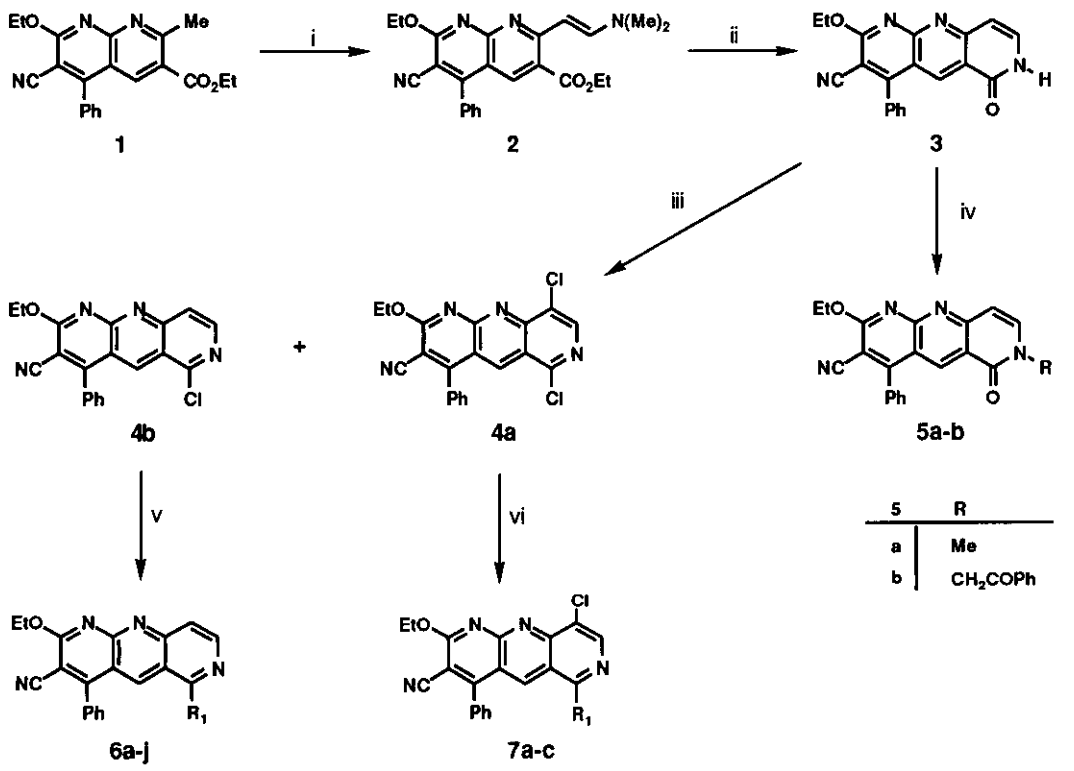
[b] Purified by column chromatography on silica gel with 0.5 % ethanol in dichloromethane.

[c] Purified by column chromatography on silica gel with ethyl acetate/hexane 1:1.

[d] Purified by column chromatography on silica gel with 2.0 % ethanol in dichloromethane and recrystallized from ethanol.

Thus, as shown in Scheme 1, the naphthyridinecarboxylate **(1)** can be reacted with dimethylformamide dimethyl acetal (DMFDMA) to give the enamino ester **(2)**, which has an E configuration according to its coupling constant, J_{AB}= 12.4 Hz.[15] In contrast to the reported one-step synthesis of ethyl 2-methyl-5-oxo-5,6-dihydro-1,6-naphthyridine-3-carboxylate[16] or ethyl 4-substituted 2-methyl-5-oxo-5,6-dihydro-1,6-naphtyridine-3-carboxylates[15] by use of 1,3,5-triazine as the ring closure agent, attempts at aminomethinylation of naphthyridine **(1)** with *s*-triazine resulted in an

Scheme 1



5	R
a	Me
b	CH_2COPh

6	R_1
a	morpholino
b	piperidino
c	4-benzylpiperidino
d	ethyl 1-piperazinocarboxylate
e	1-(morpholinocarbonylmethyl)piperazino
f	*N*-isopropyl-1-piperazinacetamide
g	4-benzylpiperazino
h	1-(α, α, α-trifluoro-*m*-tolyl)piperazino
i	1-(2-pyridyl)-piperazino
j*	nBuNH

7	R_1
a	1-piperonylpiperazino
b	morpholino
c	4-benzylpiperidino

Reagents:

i: DMFDMA, DMF, reflux
ii: $CH_3CO_2NH_4$ (anhydrous), EtOH, reflux
iii: PCl_5, $POCl_3$, reflux
iv: RX, NaOEt, EtOH, reflux
v: R_2NH, EtOH, reflux
vi: R_2NH, EtOH, reflux

(*): The EtO- group was substituted by nBuNH-

unresolvable multi-component mixture. In an alternative approach, the treatment of naphthyridinecarboxylate **(1)** with ammonium acetate in ethanol affords the 1,7,10-anthyridin-6-

Table 2. 1,7,10-Anthyridines derivatives (6a-j, and 7a-c)

No.	Ir (KBr) ν (cm^{-1})	Ms (70eV) m/z (%)	^{1}H-Nmr ($CDCl_3$/TMS) δ, J (Hz)	^{13}C-Nmr ($CDCl_3$/TMS) δ
6a	2225 (CN)	411 (M^+, 26); 410 (100); 409 (46); 381 (13); 379 (26)	1.58 (3H, t, J=7.1); 3.39-3.44 (4H, m); 3.71-3.75 (4H, m); 4.85 (2H, q, J=7.1); 7.50-7.60 (6H, m); 8.35 (1H, d, J=6.3); 8.66 (1H, s)	14.3; 51.8; 64.8; 66.5; 97.7; 114.0; 114.6; 115.9; 116.6; 129.1; 129.3; 130.7; 132.7; 137.9; 147.1; 155.6; 159.6; 162.0; 163.4
6b	2225 (CN)	409 (M^+, 14); 408 (51); 379 (42); 353 (15); 352 (23)	1.54-1.60 (9H, m); 3.39 (4H, br s; 4.84 (2H, q, J=7.1); 7.45-7.67 (6H, m); 8.30 (1H, d, J=6.1); 8.65 (1H, s)	14.3; 24.6; 25.8; 52.7; 64.7; 99.3; 114.2; 114.7; 115.0; 116.3; 129.1; 129.3; 130.5; 132.9; 138.3; 147.4; 155.8; 159.8; 162.9; 163.3
6c	*2225 (CN)*	499 (M^+, 100); 498 (31); 483 (15); 408 (43)	*1.22-1.24 (2H, m); 1.58 (3H, t, J=7.1);* 1.67-1.73 (3H, m); 2.57 (2H, d, J=6.8); 2.93 (2H, t, J=11.8); 3.85-3.91 (2H, m); 4.85 (2H, q, J=7.1); 7.14-7.74 (11H, m); 8.30 (1H, d, J=6.1); 8.62 (1H, s)	*14.3; 32.0; 38.2; 43 1; 51.8; 64.7; 99.3;* 114.2; 114.6; 114.8; 116.3; 126.1; 128.2; 129.1; 129.2; 129.3; 130.4; 132.9; 138.6; 140.0; 147.4; 155.8; 159.7; 162.5; 163.3
6d	2225 (CN) 1690 (CO)	482 (M^+, 22); 368 (7); 366 (11); 355 (24); 354 (100)	1.30 (3H, t, J=7.1); 1.58 (3H, t, J=7.1); 3.36-3.40 (4H, m); 3.49-3.54 (4H, m); 4.18 (2H, q, J=7.1); 4.85 (2H, q, J=7.1); 7.51-7.72 (6H, m); 8.35 (1H, d, J=6.1); 8.67 (1H, s)	14.3; 14.7; 43.4; 61.7; 64.9; 99.9; 114.0; 114.8; 116.1; 116.7; 129.2; 129.3; 130.8; 132.7; 137.7; 147.0; 155.5; 155.6; 155.9; 159.7; 162.0; 163.4
6e	2225 (CN)	523 (M^+, 1); 502 (1); 458 (1);	1.57 (3H, t, J=7.1); 2.54-2.59 (4H, m); 3.42-3.47 (4H, m); 3.62-3.66 (8H, m); 4.85 (2H, q, J=7.1); 7.50-7.70 (6H, m); 8.33 (1H, d, J=6.2); 8.68 (1H, s)	14.3; 42.2; 46.2; 51.2; 52.7; 61.0; 64.8; 66.9; 99.8; 114.0; 114.8; 115.7; 116.5; 129.1; 129.3; 130.7; 132.6, 138.0; 147.1, 155.5; 156.0; 159.7; 162.0; 163.4; 167.7
6f	*3360 (NH)* 2225 (CN) 1685 (CO)	509 (M^+, 8); 423 (4); 422 (15); 354 (25); 353 (57)	*1.15 (3H, s); 1.18 (3H, s); 1.58 (3H,* t, J=7.1); 2.54-2.59 (4H, m); 3.02 (2H, s); 3.41-3.46 (4H, m); 4.05-4.16 (1H, m), 4.85 (2H, q, J=7.1); 6.89 (1H, d, J=8.4), 7.50-7.71 (6H, m); 8.35 (1H, d, J=6.1); 8.67 (1H, s)	*14.3; 22.8; 40.7, 51.4; 53.0; 61.4, 64.8; 99.8;* 114.0; 114.6; 116.6, 129.1; 129.3; 130.8; 132.6; 137.9; 147.0; 155.5; 159.7; 162.1; 163.4; 168.6
6g	2225 (CN)	500 (M^+, 3); 366 (3); 355 (7); 354 (25)	1.58 (3H, t, J=7.1); 2.46-2.51 (4H, m); 3.45-3.50 (4H, m); 3.56 (2H, s); 4.85 (2H, q, J=7.1); 7.30-7.72 (11H, m); 8.32 (1H, d, J=6.2); 8.66 (1H, s)	114 3; 51.3; 52.7; 63.0; 64.8; 99.5; 114.2; 114.7; 115.1; 116.4; 127.3; 128.3; 129.1; 129.2; 129.3; 130.5; 132.8; 137.5; 138.2; 147.4; 155.8; 159.7; 162.0; 163.4
6h	2225 (CN)	554 (M^+, 11); 355 (22); 354 (100)	1.58 (3H, t, J=7.0); 3.22-3.27 (4H, m); 3.57-3.61 (4H, m); 4.85 (2H, q, J=7.0); 7.01-7.17 (3H, m); 7.53-7.70 (7H, m); 8.35 (1H, d, J=6.1); 8.71 (1H, s)	114.3; 48.5; 51.0; 64.8; 99.7; 112.1; 114.0; 114.7; 115.8; 116.5; 116.6; 119.1; 126.9; 129.1; 129.3; 129.6; 130.7; 131.2; 131.8; 132.7; 137.8; 147.1; 151.0; 155.5; 155 9; 159.6; 161.7; 163.4
6i	2225 (CN)	487 (M^+, 5); 368 (9); 354 (27); 326 (16)	1.59 (3H, t, J=7.1); 3.53-3.62 (8H, m); 4.86 (2H, q, J=7.1); 6.65-6.72 (2H, m); 7.50-7.70 (7H, m); 8.21-8.25 (1H, m); 8.37 (1H, d, J=6.1); 8.76 (1H, s)	14.3; 44.8; 51.1; 64.8; 99.7; 106.9; 113.8; 114.8; 115.7; 116.5; 129.2; 129.5; 130.8; 132.6; 137.6; 137.9; 147.1; 148.0; 155.6; 155.9; 159.1; 159.7; 162.1; 163.4
6j	3400-3240 (NH); 2220 (CN)	424 (M^+, 8); 408 (26); 395 (19); 380 (24); 324 (20)	0.89-1.01 (6H, m); 1.25-1.76 (8H, m); 3.49-3.59 (2H, m); 3.72-3.82 (2H, m); 5.41 (1H, m); 5.75 (1H, m); 7.14 (1H, d, J=6.4); 7.27-7.63 (5H, m); 8.16 (1H, d, J=6.3); 8.24 (1H, s)	13.8; 18.2; 20.1; 20.2; 31.2; 31.3; 97.4; 110.9; 111.8; 114.6; 115.5; 129.0; 129.2; 130.2; 133.0; 133.4; 148.8; 155.6; 156.4; 157.4; 157.8
7a	2240 (CN)	579 (M^++2, 1); 578 (M^+, 1); 543 (1); 402 (1); 390 (1); 388 (3)	1.57 (3H, t, J=7.1); 2.51-2.75 (4H, m); 3.45 (6H, br s); 4.88 (2H, q, J=7.1); 5.98 (2H, s); 6.71-6.84 (3H, m); 7.50-7.73 (5H, m); 8.38 (1H, s); 8.63 (1H, s)	14.3; 51.3; 52.4; 62.6; 65.1; 100.1; 101.0; 108.0; 109.5; 114.0; 115.1; 116.7; 120.5; 122.3; 129.2; 129.3; 130.6; 131.2; 132.6; 138.8; 145.6; 146.8; 147.7; 151.4; 155.9; 159.5; 160.8; 163.7
7b	2235(CN)	447 (M^++3, 37), 446 (M^++2, 40); 445 (M^+, 100); 444 (44); 402 (27); 400 (47); 388 (88)	1.58 (3H, t, J=7.1); 3.38-3.42 (4H, m); 3.70-3.75 (4H, m); 4.89 (2H, q, J=7.1); 7.52-7.71 (5H, m); 8.41 (1H, s); 8.65 (1H, s)	14.3; 51.9; 65.2; 66.4; 100.5; 113.8; 115.1; 117.0; 121.6; 129.2; 129.3; 130.9; 132.5; 138.6; 145.3; 151.3; 156.0; 159.4; 160.8; 163.8
7c	2235 (CN)	535 (M^++3, 21); 534 (M^++2, 23); 533 (M^+, 55); 499 (9); 498 (24)	1.08-1.16 (2H, m); 1.57 (3H, m, J=7.1); 1.66-1.78 (3H, m); 2.56 (2H, d, J=6.9); 2.92 (2H, t, J=12.0); 3.84 (2H, d, J=13.0); 4.87 (2H, q, J=7.1); 7.14-7.78 (10H, m); 8.34 (1H, s); 8.59 (1H, s)	14.3; 32.0; 38.1; 43.0; 51.9; 65.0; 100.0; 114.0; 115.2; 116.6; 119.9; 126.1; 128.3; 129.1; 129.2; 129.4; 130.5; 132.7; 138.9; 139.9; 145.6; 151.4; 155.9; 159.5; 161.1; 163.7

(7*H*)-one **(3)** in a satisfactory yield. The structure of this compound **(3)** was determined by microanalyses and spectral data. The mass spectra showed the expected molecular ion peak and the ir spectra exhibited the absorption band at υ= 1665 cm^{-1} due to the carbonyl group. The ^{1}H nmr and ^{13}C nmr spectra were also consistent with the assigned structure, which was further confirmed by conversion to the 7-substituted derivatives **(5a-b)** on treatment with electrophilic reagents such as methyl iodide and 2-bromoacetophenone, respectively.

Refluxing **3** with phosphorus oxychloride gave rise to a mixture of the 3-cyano-6,9-dichloro-2-ethoxy-4-phenyl-1,7,10-anthyridine **(4a)** and 6-chloro-3-cyano-2-ethoxy-4-phenyl-1,7,10-anthyridine **4b** in 20% and 80% yields, respectively. Compounds **(4a)** and **(4b)** in turn, exhibited the remarkable reactivity of its 6-chloro substituent towards nucleophilic agents affording the derivatives **(6)** and **(7)**.

The structural proof for all the newly synthesized anthyridine derivatives **(6)** and **(7)** was provided by correct elemental analyses and spectroscopic data. Table 1 lists the yields, as well as physical and analytical data for all of the compounds prepared. Their most salient spectroscopic features are also summarized in Table 2.

In conclusion, the results clearly show the usefulness of suitable *ortho*-substituted naphthyridines for the annelation of a pyridine moiety to the 1,8-naphthyridine system. Because the starting materials are quite affordable and the experimental procedure is simple, the proposed synthetic approach provides a new, general entry to a variety of 6- and 7-substituted derivatives of the 1,7,10-anthyridine system.

EXPERIMENTAL SECTION

All melting points were measured by using a Büchi 510 instrument and are given uncorrected. Ir spectra (potassium bromide) were recorded on a Perkin-Elmer 383 spectrophotometer. ^{1}H Nmr and ^{13}C nmr spectra were recorded on a Bruker AC200F espectrometer. Chemical shifts are given on the scale δ and using tetramethylsilane as internal standard. Electron impact mass spectra (ms) were obtained at 70 ev, on a VG4 spectrometer. Microanalyses for C, H and N were performed by the Elemental Analyses General Service of the University of La Coruña. Silica gel HF $_{254+366}$ for thin layer chromatography and silica gel 60 (230-400 mesh) for medium-pressure chromatography (mplc) were purchased from Merck. All reagents used were commercial grade chemicals from freshly opened containers.

3-Cyano-2-ethoxy-6-oxo-4-phenyl-6,7-dihydro-1,7,10-anthyridine (3)

To an ethanol suspension (10 ml) of **2**[14] (0.2 g, 0.48 mmol) was added an excess (0.3 g, 4.8 mmol) of anhydrous ammonium acetate. The mixture was refluxed for 14 h. After cooling, the solid was collected by filtration and washed with water. The solid was subjected to column chromatography (49:1 dichloromethane-ethanol) to obtain 0.15 g (92%), mp >300 °C (ethanol). ^{1}H-Nmr (DMSO-d_6) δ: 1.47 (3H, t, J=7.1 Hz); 4.67 (2H, q, J=7.1 Hz); 6.69 (1H, d, J=7.4 Hz); 7.59-7.71 (6H, m); 8.58 (1H, s); 11.65 (1H, s). Ms (70ev) m/z(%): 342 (M^+, 30); 341 (30); 328 (71); 327 (100); 314 (32); 297 (23). Ir

(KBr): 3800, 3050, 2940 (NH); 2230 (CN); 1685 (CO). Anal. Calcd for $C_{20}H_{19}N_4O_2$: C, 70.17; H, 4.12; N, 16.36. Found: C, 70.10; H, 4.21; N, 16.22.

6-Chloro- and 6,9-dichloro-1,7,10-anthyridine derivatives (4a, 4b)

A solution of **3** (0.15 g, 0.44 mmol) and phosphorus pentachloride (0.11 g, 0.53 mmol) in phosphorus oxychloride (10 ml, 0.11 mol) was refluxed for 3.5 h. Then, the reaction mixture was cooled and evaporated in vacuum, and water (20 ml) was added. The crude was extracted with dichloromethane (2 x 20 ml) and subjected to column chromatography to obtain 3-cyano-6,9-dichloro-2-ethoxy-4-phenyl-1,7,10-anthyridine **(4a)** (2:1 dichloromethane-hexane) 0.04 g (20%), mp 288-289 °C (ethanol). ^{1}H Nmr ($CDCl_3$/TMS) δ: 1.60 (3H, t, J=7.1 Hz); 4.92 (2H, q, J=7.1 Hz); 7.55-7.74 (5H, m); 8.63 (1H, s); 9.03 (1H, s).^{13}C Nmr ($CDCl_3$/TMS) δ: 14.2; 65.6; 102.3; 113.4; 119.2; 121.0; 128.8; 129.4; 131.2, 131.9; 140.1; 144.9; 150.0; 151.0; 156.9; 159.9; 164.3. Ms (70ev) m/z (%): 398 (M^++4, 6); 397 (M^++3, 16); 396 (M^++2, 32); 395 (M^+, 65); 394 (50); 370 (12); 369 (16); 368 (65); 366 (29). Ir (KBr): 3060; 2225 (CN); 1580; 1425; 1240; 1155; 810; 605. Anal. Calcd for $C_{20}H_{12}N_4OCl_2$: C, 60.78; H, 3.06; N, 14.17. Found: C, 60.86; H, 3.12; N, 14.02. And 6-chloro-3-cyano-2-ethoxy-4-phenyl-1,7,10-anthyridine **(4b)** (dichloromethane) 0.15 g (80%), mp 269-271 °C (ethanol). ^{1}H Nmr ($CDCl_3$/TMS) δ: 1.53 (3H, t, J=7.1 Hz); 4.79 (2H, q, J=7.1 Hz); 7.56-7.67 (5H, m); 7.87 (1H, d, J=6.1 Hz); 8.42 (1H, d, J=6.1 Hz); 8.92 (1H, s).^{13}C Nmr ($CDCl_3$/TMS) δ: 14.1; 65.1; 101.4; 113.4; 118.4; 120.3; 121.3; 129.2; 130.9; 131.9; 139.0; 146.4; 152.6; 153.5; 156.4; 163.6. Ms (70ev) m/z (%): 362 (M^++3, 6); 361 (M^++2, 17); 360(M^+, 49); 359 (43); 358 (100); 3346 (7); 3345 (8); 344 (16). Ir (KBr): 3060; 2225 (CN); 1580; 1415; 1335; 1150; 850. Anal. Calcd for $C_{20}H_{13}N_4OCl$: C, 66.58; H, 3.63; N, 15.53. Found: C, 66.67; H, 3.50; N, 15.59.

3-Cyano-2-ethoxy-7-methyl-6-oxo-4-phenyl-6,7-dihydro-1,7,10-anthyridine (5a)

A stirred suspension of **4** (0.10 g, 0.29 mmol), methyl iodide (0.08 g, 0.56 mmol) and a catalytic amount of sodium ethoxide in ethanol (7 ml) was refluxed for 48 h. After cooling, the solid was collected by filtration and washed with ethanol-water. The solid was subjected to column chromatography (dichloromethane) to obtain 0.10 g (96%) of **5a**, mp 287-289 °C (ethanol). ^{1}H-Nmr ($CDCl_3$/TMS) δ: 1.56 (3H, t, J=7.1 Hz); 3.58 (3H, s); 4.82 (2H, q, J=7.1 Hz); 6.89 (1H, d, J=7.8 Hz); 7.40-7.65 (6H, m); 9.01 (1H, s). ^{13}C Nmr ($CDCl_3$/TMS)δ: 14.3; 36.8; 64.7; 99.6; 107.4; 114.1; 116.8; 120.1; 129.2; 129.3; 130.6; 132.6; 139.5; 139.8; 156.9; 157.3; 160.0; 162.1; 163.7. Ms (70ev) m/z(%): 356 (M^+, 89); 355 (100); 329 (24); 328 (97). Ir (KBr): 2220 (CN); 1665 (CO). Anal. Calcd for $C_{21}H_{16}N_4O_2$: C, 70.77; H, 4.52; N, 15.72. Found: C, 70.84; H, 4.46; N, 15.65.

7-Acetophenyl-3-cyano-2-ethoxy-6-oxo-4-phenyl-6,7-dihydro-1,7,10-anthyridine (5b)

A stirred suspension of **4** (0.10 g, 0.29 mmol), 2-bromoacetophenone (0.23 g, 1.16 mmol) and a catalytic amount of sodium ethoxide in ethanol (10 ml) was refluxed for 24 h. After cooling, the precipitate was collected by filtration and washed with ethanol-water. The solid was subjected to column chromatography (100:2 dichloromethane-ethanol) to obtain 0.07 g (74%) of **5b**, mp 299-300 °C (ethanol). ^{1}H-Nmr (DMSO-d_6)δ: 1.47 (3H, t, J=7.1 Hz); 3.58 (3H, s); 4.69 (2H, q, J=7.1 Hz); 5.59 (2H, s); 6.85 (1H, d, J=7.7 Hz); 7.55-8.07 (11H, m); 8.60 (1H, s). ^{13}C Nmr (DMSO-d_6)δ: 14.2; 54.8; 64.1; 98.6; 106.0; 114.4; 116.5; 119.1; 128.0; 129.0; 129.5; 130.4; 132.8; 134.2; 134.4; 138.6; 141.2; 156.6; 156.7; 159.8; 161.0; 162.9; 192.9. Ms (70ev) m/z(%): 460 (M^+, 12); 446 (2); 356 (3); 355 (11); 297 (12). Ir (KBr): 2220 (CN); 1685 (CO); 1660 (CO). Anal. Calcd for $C_{28}H_{20}N_4O_3$: C, 73.03; H, 4.38; N, 10.42. Found: C, 73.15; H, 4.22; N, 10.35.

3-Cyano-2-ethoxy-4-phenyl-6-substituted 1,7,10-anthyridines (6a-j); General Procedure:

A stirred suspension of **4b** (0.10 g, 0.28 mmol) and a suitable heterocyclic or aliphatic amine (0.56 mmol) in ethanol (10 ml) was refluxed until all starting material had disappeared as checked by tlc. After cooling, the precipitate was collected by filtration and recrystallized from a suitable solvent or purified by medium-pressure chromatography. For the reaction conditions, analytical, physical and spectroscopic data, see Tables **1** and **2**.

9-Chloro-3-cyano-2-ethoxy-6-substituted 1,7,10-anthyridines (7a-c); General Procedure:

A stirred suspension of **4a** (0.10 g, 0.25 mmol) and a suitable heterocyclic amine (0.56 mmol) in ethanol (7 ml) was refluxed until all starting material had disappeared as checked by tlc. After cooling, the precipitate was collected by filtration, purified by medium-pressure chromatography (100:2.5 dichloromethane-ethanol) and recrystallized from ethanol. For the reaction conditions, analytical, physical and spectroscopic data, see Tables **1** and **2**.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the Xunta de Galicia for financial support. They are also indebted to the General Services of the Universidad de La Coruña for recording the nmr and mass spectra.

REFERENCES

1. W. Kreutner, J. Sherwood, S. Sehring, C. Rizzo, R. W. Chapman, M. I. Siegel, and R. W. Egan, J. Pharmacol. Exp. Ther., 1989, **247**, 947.
2. E. Israel, M. A. Rosenberg, M. R. Danzing, J. Fourre, and J. M. Drazer, Am. Rev. Respir. Dis., 1989, **139**, A 65.
3. M. W. Abraham, J. S. Stevenson, and R. Garrido, J. Pharmacol. Exp. Ther., 1989 , **247**, 1004.
4. K. Shimabori, H. Egawa, T. Miyamoto, Y. Nishimura, A. Itokawa, J. Nakano, and J. Matsumoto, Chem. Pharm. Bull., 1990, **38**, 2390.
5. D. Bouzard, P. Di Cesare, M. Essiz, J. P. Jacquet, P. Remuzon, R. E. Kessler, and J. Fung-Tomé, J. Med. Chem., 1992, **35**, 518.
6. P. Remuzon, M. Massouli, D. Bouzard, and J. P. Jacquet, Heterocycles, 1992, **34**, 679.
7. L. A. Mitscher, P. V. Devasthale, and R. M. Zavod: The Quinolones, ed. G. G. Crumpin, Springer Verlag, London 1990, pp. 115-146.
8. C. Peinador, M. C. Veiga, J. Vilar, and J. M. Quintela, Heterocycles, 1994, **38**, 1299.
9. C. Peinador, M. J. Moreira, and J. M. Quintela, Tetrahedron, 1994, **50**, 6705.
10. P. A. Lowe, Comprehensive Heterocyclic Chemistry, Vol. **2**, A, eds. by J. Boulton and A. McKillop, Pergamon Press Ltd., Oxford OX3 OBW, England, 1984, pp. 581-627 and references therein.
11. S. Carboni, A. Da Settimo, D. Bertini, P. L. Ferrarini, O. Livi, and I.Tonetti, Il Farmaco, 1974, **29**, 366.
12. K. R. Reddy, K. Mogilaiah, and B. Sreenivasulu, J. Indian Chem. Soc., 1987, **54**, 709.
13. S. Carboni, A. Da Settimo, D. Bertini, O. Livi, and I. Tonetti, J. Med. Chem., 1972, **9**, 801.
14. J. Vilar, J. Mª. Quintela, C. Peinador, C. Veiga, and V. Ojea, Heterocycles, 1993, **36**, 2697.
15. M. Balogh, I. Hermecz, K. Simon, and L. Pusztay, J. Heterocycl. Chem., 1989, **26**, 1755.
16. M. Balogh, I. Hermecz, G. Náray-Szabó, K. Simon, and Z. Mészáros, J. Chem. Soc. Perkin Trans. 1, **1986**, 753.

Received, 16th August, 1994