Synthesis of Pyridines by Heterocyclization of New Dienamino Esters

Maria Teresa Cocco, Cenzo Congiu and Antonio Maccioni

Istituto di Chimica Farmaceutica Tossicologica e Applicata, Università, Via Ospedale 72, I-09124 Cagliari, Italy

Received September 5, 1989

The synthesis of pyridine derivatives is reported starting from the new dienamino esters **2**. Thermal cyclization of **2** afforded the ethyl 2-amino-3-pyridinecarboxylate derivatives **3**; from the reaction of **2** in sodium ethoxide the 2-aminopyridines **3** and **4**, and the 1,2-dihydro-2-oxopyridines **5** and **6** were obtained.

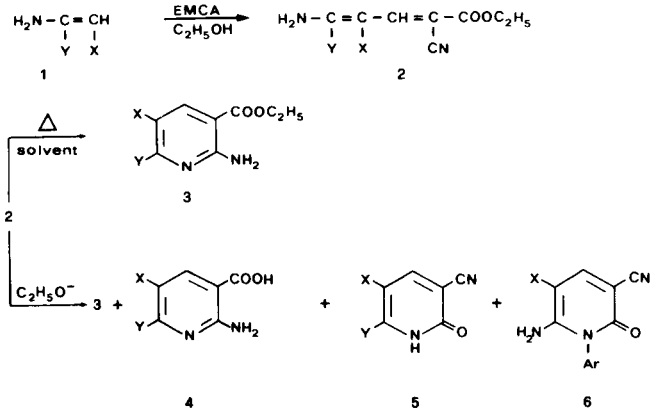
J. Heterocyclic Chem., **27**, 1143 (1990).

In recent years 4-oxoquinoline and 1,8-naphthyridine-3-carboxylic acid derivatives have acquired a great deal of importance for their strong antimicrobial activity. The common structure of all these compounds is the pyridin-4-one moiety, which is essential for their biological activity. Since specific substituents can not always be readily introduced directly on the pyridine nucleus, the 6-amino-2(1*H*)-pyridone and 2,6-diaminopyridine derivatives are a good substrate for the synthesis of condensed heterocyclic systems having the pyridin-4-one moiety.

In the present study we report an efficient method for the preparation of the 2,6-diaminopyridine derivatives starting from ethyl 3-ethoxy-3-iminopropionate (**1a**) or 3-ethoxy-3-iminopropanenitrile (**1b**) or their corresponding amidines **1c-n**, extremely versatile synthons previously utilized by us for the synthesis of 6-amino-2(1*H*)-pyridone [1] and 2-aminopyrrole derivatives [2].

By reacting compounds **1** with an equivalent of ethoxymethylenecyanoacetate (EMCA) in alcohol solution at room temperature, we obtained dienamino esters **2** in good yields (Scheme 1): five term polyfunctionalized compounds with an ethoxycarbonyl and an amino terminal group and an high degree of unsaturation, such that they can easily undergo intramolecular cyclization to pyridine derivatives.

Scheme 1



X	Y			
a, $COOC_2H_5$	OC_2H_5	**h**,	CN	2-C_3H_7NH
b, CN	OC_2H_5	**i**,	CN	4-morpholinyl
c, $COOC_2H_5$	NH_2	**j**,	CN	pyrrolidinyl
d, $COOC_2H_5$	*n*-C_4H_9NH	**k**,	CN	piperidinyl
e, $COOC_2H_5$	4-morpholinyl	**l**,	CN	C_6H_5NH
f, $COOC_2H_5$	pyrrolidinyl	**m**,	CN	4-$CH_3C_6H_4NH$
g, $COOC_2H_5$	piperidinyl	**n**,	CN	3-$CH_3OC_6H_4NH$

Ar = C_6H_5, 4-$CH_3C_6H_4$, 3-$CH_3OC_6H_4$

The structure and geometry of the dienamino esters **2** can be deduced from analytical (Table 1) and spectroscopic (Table 2) data.

The ^1H nmr spectra in DMSO-d_6 indicate that they exist as only one isomer: they present a sharp singlet for the olefinic proton in the range 7.60-8.18 ppm and a signal for the protons of the NH_2 group between 8.00 and 9.48 ppm. These downfield shifts suggest the presence of a hydrogen bond between the amino group and the adjacent carbethoxy or nitrile group. Moreover in compounds **2d-g** we indicate the non-equivalence of the NH_2 protons due to the presence, in the spectra, of two NH signals of equal intensity; the downfield signal can be assigned to the chelated form, and the other to the free NH, and the double bond between C-4 and C-5 can thus be assigned to the *E* configuration [3].

In the spectrum of the adduct **2e**, for the morpholine protons two multiplets can be seen, one at 3.28-3.50 ppm corresponding to the two CHNCH protons, the other at 3.50-3.85 corresponding to six CHNCH and CH_2OCH_2

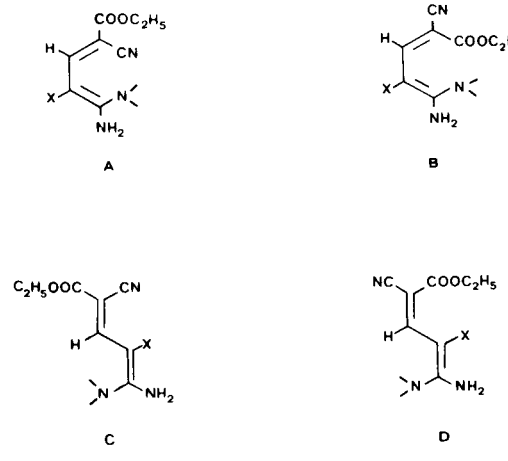
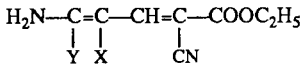


Figure 1

Table 1

Physical and Analytical Data of Compounds 2



Compound No.	X	Y	Yield (%)	Mp (°C)	Formula	Analysis % Calcd./Found C	H	N
2a	$COOC_2H_5$	OC_2H_5	72	142 [a]	$C_{13}H_{12}N_2O_5$	55.31 55.40	6.43 6.45	9.92 9.87
2b	CN	OC_2H_5	75	188 [b]	$C_{11}H_{13}N_3O_3$	56.16 56.23	5.57 5.54	17.86 17.91
2c	$COOC_2H_5$	NH_2	45	188 [c]	$C_{11}H_{15}N_3O_4$	52.55 52.47	5.18 5.21	16.56 16.59
2d	$COOC_2H_5$	*n*–C_4H_9NH	25	129 [d]	$C_{15}H_{23}N_3O_4$	58.23 58.17	7.49 7.45	14.69 14.72
2e	$COOC_2H_5$	4–morpholinyl	72	225 [d]	$C_{15}H_{21}N_3O_5$	55.72 55.65	6.55 6.51	13.00 13.09
2f	$COOC_2H_5$	pyrrolidinyl	74	257 [d]	$C_{15}H_{21}N_3O_4$	58.62 58.58	6.89 6.86	13.67 13.61
2g	$COOC_2H_5$	piperidinyl	57	249 [d]	$C_{16}H_{23}N_3O_4$	59.79 59.70	7.21 7.18	13.08 13.09
2h	CN	2–C_3H_7NH	52	180 [b]	$C_{12}H_{16}N_4O_2$	58.04 58.09	6.49 6.45	22.56 22.51
2i	CN	4–morpholinyl	83	195 [b]	$C_{13}H_{16}N_4O_3$	56.51 56.50	5.84 5.81	20.20 20.18
2j	CN	pyrrolidinyl	78	198 [b]	$C_{13}H_{16}N_4O_2$	59.98 59.90	6.20 6.17	21.53 21.49
2k	CN	piperidinyl	75	194 [b]	$C_{14}H_{18}N_4O_2$	61.29 61.26	6.61 6.59	20.43 20.38
2l	CN	C_6H_5NH	48	162 [d]	$C_{15}H_{14}N_4O_2$	63.82 63.75	5.00 5.03	19.85 19.80
2m	CN	4-$CH_3C_6H_4NH$	58	236 [d]	$C_{16}H_{16}N_4O_2$	64.85 64.90	5.44 5.40	18.91 18.87
2n	CN	3–$CH_3OC_6H_4NH$	67	158 [b]	$C_{16}H_{16}N_4O_3$	61.53 61.48	5.16 5.18	17.94 17.89

[a] From benzene. [b] From ethanol. [c] From 2-propanol. [d] From acetonitrile.

protons. The difference in the chemical shifts of the CH_2NCH_2 protons observed also in compounds **2f** and **2g**, suggests that the heterocyclic ring is on a plane almost perpendicular to the plane of the molecule, and for this reason the morpholine protons in positions 2 and 5 above the plane of the ring undergo the deshielding effect of the ethoxycarbonyl or cyano terminal groups. Consequently the dienamino compound will assume *s-cis* conformations (**A,B**), which are preferred to an *s-trans* conformations (**C,D**), in which there is a greater interaction between the substituents, as is shown by the molecular model. Moreover the fact that in compounds **2a** and **2c-g** the protons of the two different ethylic groups present an almost equal chemical shift and that the olefinic proton is downfield from the compounds **2h-n**, suggests that the two ethoxycarbonyl groups are on the same side of the olefinic proton and exert a greater deshielding effect on it; consequently of the two possible *s-cis* structures (**A** and **B**), the cisoid conformation *E,E* (**A**) can be attributed to the dienaminoesters **2** (Figure 1).

The adducts **2** undergo intramolecular condensation easily when refluxed in dimethyl sulfoxide or in toluene/di-

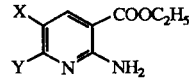
Table 2

Spectroscopic Data of Dienamino Esters **2**

Compound No.	IR cm^{-1}	^1H-NMR δ(ppm)
2a	3300, 3140, 2200, 1665, 1635	1.00-1.35 (m, 9H, $3CH_3$), 3.90-4.40 (m, 6H, $3CH_2$), 8.18 (s, 1H, =CH), 9.48 (br s, 2H, NH_2)
2b	3320, 3150, 2220, 2200, 1720, 1700, 1670, 1650	1.00-1.38 (m, 6H, $2CH_3$), 4.00-4.48 (m, 4H, $2CH_2$), 8.02 (s, 1H, =CH), 9.30 (s, 2H, NH_2)
2c	3330, 3170, 2195, 1675, 1625	1.20 (t, 6H, $2CH_3$), 4.10 (q, 4H, $2CH_2$), 7.93 (s, 1H, =CH), 8.10 (s, 4H, $2NH_2$)
2d	3250, 3100, 2200, 1695, 1630	0.75-0.95 (m, 3H, CH_3), 1.00-1.65 (m, 4H, $2CH_2$), 1.14 (t, 3H, CH_3), 1.20 (t, 3H, CH_3), 3.10 (m, 2H, $NHCH_2$), 3.85-4.30 (m, 4H, $2CH_2$), 7.00 (t, 1H, NH), 7.75 (s, 1H, =CH), 8.28 (s, 1H, NH), 8.80 (s, 1H, NH)
2e	3250, 3110, 2200, 1690, 1650, 1610	1.11 (t, 6H, $2CH_3$), 3.28-3.50 (m, 2H, CHNCH), 3.50-3.85 (m, 6H, CHNCH and CH_2OCH_2), 3.90-4.20 (m, 4H, $2CH_2$), 8.00 (s, 1H, =CH), 8.70 (s, 1H, NH), 8.95 (s, 1H, NH)
2f	3240, 3140, 2195, 1680, 1655, 1640, 1610	1.10 (t, 6H, $2CH_3$), 1.88 (m, 4H, $2CH_2$), 3.20 (m, 2H, CHNCH), 3.30 (m, 2H, CHNCH), 3.80-4.20 (2q, 4H, $2CH_2$), 7.85 (s, 1H, =CH), 8.16 (s, 1H, NH), 8.63 (s, 1H, NH)
2g	3260, 3160, 2195, 1690, 1660, 1610	1.10 (t, 6H, $2CH_3$), 1.54 (m, 6H, $3CH_2$), 3.30 (m, 2H, CHNCH), 3.50 (m, 2H, CHNCH), 3.80-4.18 (m, 4H, $2CH_2$), 7.95 (s, 1H, =CH), 8.45 (s, 1H, NH), 8.70 (s, 1H, NH)
2h	3330, 3220, 2200, 2190, 1690, 1645	1.00-1.30 (m, 6H, $2CH_3$), 3.75 (m, 1H, CH), 4.20 (q, 2H, CH_2), 7.70 (s, 1H, =CH), 8.00 (br s, 3H, NH_2 and NH)
2i	3420, 3330, 3230, 2210, 2200, 1675, 1650	1.14 (t, 3H, CH_3), 3.35-3.76 (m, 8H morphiline protons), 4.02 (q, 2H, CH_2), 7.65 (s, 1H, =CH), 8.35 (br s, 2H, NH_2)
2j	3350, 3210, 2200, 2180, 1685, 1640	1.13 (t, 3H, CH_3), 1.90 (m, 4H, $2CH_2$), 3.48 (m, 4H, CH_2NCH_2), 4.05 (q, 2H, CH_2), 7.75 (s, 1H, =CH), 8.00 (s, 2H, NH_2)
2k	3410, 3330, 3200, 2210, 2200, 1660	1.14 (t, 3H, CH_3), 1.60 (m, 6H, $3CH_2$), 3.40 (m, 4H, CH_2NCH_2), 4.02 (q, 2H, CH_2), 7.60 (s, 1H, =CH), 8.20 (br s, 2H, NH_2)
2l	3420, 3310, 3240, 2200, 2190, 1700, 1630	1.20 (t, 3H, CH_3), 4.10 (q, 2H, CH_2), 7.10-7.75 (m, 5H, Ar), 7.90 (s, 1H, =CH), 8.20 (br s, 2H, NH_2), 9.75 (br s, 1H, NH)
2m	3300, 3250, 2200, 2190, 1700, 1640	1.20 (t, 3H, CH_3), 2.30 (s, 3H, CH_3), 4.10 (q, 2H, CH_2), 6.9-7.27 (m, 4H, Ar), 7.86 (s, 1H, =CH), 8.05 (br s, 2H, NH_2), 9.80 (br s, 1H, NH)
2n	3320, 3250, 2210, 2200 1700, 1650	1.18 (t, 3H, CH_3), 3.72 (s, 3H, OCH_3), 4.10 (q, 2H, CH_2), 6.67-7.40 (m, 4H, Ar), 7.86 (s, 1H, =CH), 8.15 (br s, 2H, NH_2), 9.93 (br s, 1H, NH)

Table 3

Physical and Analytical Data of Compound **3**



3

Compound No.	X	Y	mp (°C)	Formula	Analysis Calcd./Found C	H	N
3a	$COOC_2H_5$	OC_2H_5	78 [a]	$C_{13}H_{18}N_2O_5$	55.31 55.28	6.43 6.40	9.92 9.87
3b	CN	OC_2H_5	168 [b]	$C_{11}H_{13}N_3O_3$	56.16 56.10	5.57 5.55	17.86 17.81

3c	$COOC_2H_5$	NH_2	166 [b]	$C_{11}H_{15}N_3O_4$	52.17 52.23	5.97 5.98	16.59 16.53
3e	$COOC_2H_5$	4-morpholinyl	104 [c]	$C_{15}H_{21}N_3O_5$	55.72 55.68	6.55 6.51	13.00 13.06
3f	$COOC_2H_5$	pyrrolidinyl	96 [d]	$C_{15}H_{21}N_3O_4$	58.62 58.65	6.89 6.86	13.67 13.64
3g	$COOC_2H_5$	piperidinyl	68 [a]	$C_{16}H_{23}N_3O_4$	59.79 59.74	7.21 7.19	13.08 13.04
3h	CN	$2\text{-}C_3H_7NH$	168 [b]	$C_{12}H_{16}N_4O_2$	58.05 58.09	6.50 6.51	22.57 22.53
3i	CN	4-morpholinyl	161 [b]	$C_{13}H_{16}N_4O_3$	56.51 56.48	5.84 5.81	20.28 20.24
3j	CN	pyrrolidinyl	135 [b]	$C_{13}H_{16}N_4O_2$	59.98 59.93	6.20 6.18	21.53 21.50
3k	CN	piperidinyl	108 [b]	$C_{14}H_{18}N_4O_2$	61.29 61.25	6.61 6.59	20.43 20.40
3l	CN	C_6H_5NH	164 [b]	$C_{15}H_{14}N_4O_2$	63.82 63.79	5.00 5,03	19.85 19.81
3m	CN	$4\text{-}CH_3C_6H_4NH$	233 [b]	$C_{16}H_{16}N_4O_2$	64.85 64.80	5.44 5.41	18.91 18.87
3n	CN	$3\text{-}CH_3OC_6H_4NH$	172 [b]	$C_{16}H_{16}N_4O_3$	61.53 61.50	5.16 5.13	17.94 17.91

[a] From *n*–hexane. [b] From ethanol. [c] From isopropyl ether. [d] From *n*–hexane-chloroform (5:1).

Table 4

Spectroscopic Data of Compounds **3**

Compound No.	IR cm^{-1}	^1H NMR δ (ppm)
3a	3440, 3330, 1700, 1680	1.12-1.40 (m, 9H, $3CH_3$), 4.00-4.45 (m, 6H, $3CH_2$), 7.75 (s, 2H, NH_2), 8.50 (s, 1H, H-4)
3b	3430, 3320, 2210, 1700	1.15-1.40 (m, 6H, $2CH_3$), 4.10-4.52 (m, 4H, $2CH_2$), 8.01 (s, 2H, NH_2), 8.25 (s, 1H, H-4)
3c	3385, 3265, 1680	1.20 (t, 6H, $2CH_3$), 4.15 (q, 4H, $2CH_2$), 7.30 (s, 2H, 2NH), 7.65 (s, 2H, 2NH), 8.39 (s, 1H, H-4)
3e	3340, 3320, 1715, 1690	1.24 (t, 6H, $2CH_3$), 3.40 (m, 4H, $CH_2\text{-}N\text{-}CH_2$), 3.60 (m, 4H, $CH_2\text{-}O\text{-}CH_2$), 4.20 (q, 4H, $2CH_2$), 7.40 (br s, 2H, NH_2), 8.35 (s, 1H, H-4)
3f	3440, 3340, 1690, 1670	1.21 (t, 6H, $2CH_3$), 1.78 (m, 4H, $2CH_2$), 3.30 (m, 4H, $CH_2\text{-}N\text{-}CH_2$), 4.18 (q, 4H, $2CH_2$), 7.25(br s, 2H, NH_2), 8.2 (s, 1H, H-4)
3g	3450, 3350, 1710, 1680	1.22 (t, 6H, $2CH_3$), 1.51 (m, 6H, $3CH_2$), 3.32 (m, 4H, $CH_2\text{-}N\text{-}CH_2$), 4.19 (q, 4H, $2CH_2$), 7.33 (br s, 2H, NH_2), 8.27(s, 1H, H-4)
3h	3480, 3330, 2220, 1685	1.13 (d, 6H, $2CH_3$), 1.22 (t, 3H $CH_2\text{-}CH_3$), 4.15 (q, 2H $CH_2\text{-}CH_3$), 4.38 (m, 1H, CH), 6.9 (d, 1H, NH), 7.45 (br s, 1H, NH), 7.75 (br s, 1H, NH), 8.01 (s, 1H, H-4)
3i	3430, 3320, 2220, 1675	1.22 (t, 3H, CH_3), 3.66 (s, 8H, morpholine protons), 4.16 (q, 2H, CH_2), 7.59 (br s, 2H, NH_2), 8.10 (s, 1H, H-4)
3j	3450, 3420, 3320, 3270, 2200, 1680	1.22 (t, 3H, CH_3), 1.84 (m, 4H, $2CH_2$), 3.60 (m, 4H, $CH_2\text{-}N\text{-}CH_2$), 4.15 (q, 2H, CH_2), 7.33 (br s, 1H, NH), 7.60 (br s, 1H, NH), 7.97 (s, 1H, H-4)
3k	3450, 3340, 2200, 1685	1.23 (t, 3H, CH_3), 1.56 (m, 6H, $3CH_2$), 3.69 (m, 4H, $CH_2\text{-}N\text{-}CH_2$), 4.16 (q, 2H, CH_2), 7.56 (br s, 2H, NH_2), 8.05 (s, 1H, H-4)
3l	3410, 3290, 2220, 1690	1.23 (t, 3H, CH_3), 4.18 (q, 2H, CH_2), 6.92-7.90 (m, 5H, Ar), 7.20 (br s, 2H, NH_2), 8.16 (s, 1H, H-4), 9.02 (br s, 1H, NH)

3m	3390, 3290, 2220, 1670	1.21 (t, 3H, CH_2CH_3), 2.35 (s, 3H, CH_3), 4.15 (q, 2H, CH_2CH_3), 5.50-7.50 (br s, 2H, NH_2), 7.10-7.45 (m, 4H, Ar), 7.92 (s, 1H, H-4), 8.80 (br s, 1H, NH)
3n	3450, 3390, 3330, 2200, 1685	1.21 (t, 3H, CH_3), 3.73 (s, 3H, OCH_3), 4.13 (q, 2H, CH_2), 6.60 (br s, 2H, NH_2), 6.80–7.60 (m, 4H, Ar), 7.91 (s, 1H, H-4), 8.83 (br s, 1H, NH)

Table 5

Thermal Cyclization of Dienamino Esters **2**

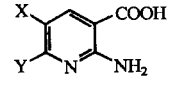
Dienamino ester	% 3 Method A (minutes)	% 3 Method B (hours)
2a	91 (5)	86 (6)
2b	94 (15)	84 (2)
2e	37 (15)	85 (10)
2f	62 (15)	
2g	60 (10)	
2h	93 (15)	

Table 5 (Continued)

2i	72 (15)	68 (10)
2j	80 (15)	76 (2)
2k	56 (10)	56 (10)
2l	76 (10)	84 (24)
2m	80 (10)	60 (6)
2n	52 (10)	80 (6)

Table 6

Physical and Analytical Data of Compounds **4**



4

Compound No.	X	Y	mp (°C)	Formula	Analysis % Calcd./Found C	H	N
4a	$COOC_2H_5$	OC_2H_5	161 [a]	$C_{11}H_{14}N_2O_5$	51.96 51.90	5.55 5.53	11.02 11.00
4b	CN	OC_2H_5	180 [b]	$C_9H_9N_3O_3$	52.17 52.14	4.38 4.35	20.28 20.24
4e	$COOC_2H_5$	4-morpholinyl	173 [c]	$C_{13}H_{17}N_3O_5$	52.87 52.81	5.80 5.83	14.23 14.19
4f	$COOC_2H_5$	pyrrolidinyl	189 [c]	$C_{13}H_{17}N_3O_4$	55.90 55.85	6.14 6.11	15.05 15.00
4g	$COOC_2H_5$	piperidinyl	171 [c]	$C_{14}H_{19}N_3O_4$	57.32 57.35	6.53 6.50	14.33 14.29
4i	CN	4-morpholinyl	222 [c]	$C_{11}H_{12}N_4O_3$	53.22 53.18	4.87 4.85	22.57 22.53
4j	CN	pyrrodinyl	225 [c]	$C_{11}H_{12}N_4O_2$	56.89 56.82	5.21 5.17	24.13 24.10
4k	CN	piperidinyl	215 [d]	$C_{12}H_{14}N_4O_2$	62.59 62.54	6.13 6.00	24.33 24.35

[a] From benzene. [b] From isopropyl ether. [c] From ethanol. [d] From acetonitrile.

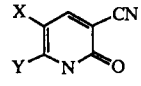
Table 7

Spectroscopic Data of Compounds **4**

Compound No.	IR cm^{-1}	^1H-NMR δ(ppm)
4a	3470, 3360, 1680, 1620	1.26 (t, 6H, $2CH_3$), 4.08-4.41 (m, 4H, $2CH_2$), 7.68 (br s, 2H, NH_2), 8.47 (s, 1H, H-4), 12.24 (s, 1H, OH)
4b	3460, 3330, 2220, 1675, 1605	1.21 (t, 3H, CH_3), 4.41 (q, 2H, CH_2), 7.98 (br s, 2H, NH_2), 8.20 (s, 1H, H-4), 11.90 (br s, 1H, OH)
4e	3420, 3280, 1670, 1640, 1610	1.20 (t, 3H, CH_3), 3.39 (m, 4H, CH_2NCH_2), 3.54 (m, 4H, CH_2OCH_2), 4.14 (q, 2H, CH_2), 7.42 (s, 2H, NH_2), 8.32 (s, 1H, H-4), 12.30 (br s ,1H, OH)
4f	3470, 3350, 1695, 1640, 1600	1.20 (t, 3H, CH_3), 1.77 (m, 4H, $2CH_2$), 3.29 (m, 4H, CH_2NCH_2), 4.14 (q, 2H, CH_2), 7.27 (s, 2H, NH_2), 8.25 (s, 1H, H-4), 12.26(br s, 1H, OH)
4g	3485, 3355, 1690, 1650, 1605	1.17 (t, 3H, CH_3), 1.47 (s, 6H, $3CH_2$), 3.29 (m, 4H, CH_2NCH_2), 4.10 (q, 2H, CH_2), 7.33 (s, 2H, NH_2), 8.25 (s, 1H, H-4), 12.23 (br s, 1H, OH)
4i	3420, 3320, 2200, 1680, 1640, 1600	3.67 (br s, 8H morphiline protons), 7.64 (s, 2H, NH_2), 8.34 (s, 1H, H-4), 12.26 (br s, 1H, OH)
4j	3460, 3340, 2220, 1660, 1615, 1590	1.84 (m, 4H, $2CH_2$), 3.61 (m, 4H, CH_2NCH_2), 7.48 (br s, 2H, NH_2), 7.98 (s, 1H, H-4), 12.00 (br s, 1H, OH)
4k	3450, 3320, 2220, 1710, 1655, 1620	1.57 (m, 6H, $3CH_2$), 3.65 (m, 4H, CH_2NCH_2), 7.56 (s, 2H, NH_2), 8.18 (s, 1H, H-4), 12.23 (br s, 1H, OH)

Table 8

Physical and Analytical Data of Compounds **5**



5

Compound No.	X	Y	mp (°C)	Formula	Analysis % Calcd./Found C	H	N
5a	$COOC_2H_5$	OC_2H_5	188 [a]	$C_{11}H_{12}N_2O_4$	55.93 55.95	5.12 5.15	11.86 11.80
5e	$COOC_2H_5$	4-morpholinyl	252 [b]	$C_{13}H_{15}N_3O_4$	56.31 56.28	5.45 5.43	15.16 15.13
5f	$COOC_2H_5$	pyrrolidinyl	278 [b]	$C_{13}H_{15}N_3O_3$	59.76 59.70	5.79 5.76	16.08 16.02
5g	$COOC_2H_5$	piperidinyl	256 [c]	$C_{14}H_{17}N_3O_3$	61.08 61.00	6.22 6.19	15.26 15.24

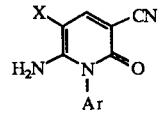
[a] From benzene. [b] From ethanol. [c] From acetonitrile.

methylsulfoxide 2:1 solution, or when treated with sodium ethoxide in ethanol at room temperature, to yield the ethyl 2-aminopyridine-3-carboxylate derivatives **3** as principal compound (Tables 3, 4).

With brief heating (15 minutes) in dimethyl sulfoxide, compounds **3** were obtained in good yields; an increase in the heating time leads to decomposition of the products. At lower heating temperature by dilution of dimethyl-

Table 9

Physical and Analytical Data of Compounds **6**



6

Compound No.	Ar	X	mp (°C)	Formula	Analysis % Calcd./Found C	H	N
6a	C_6H_5	CN	314 [a]	$C_{13}H_8N_4O$	66.09 66.00	3.41 3.39	23.72 23.69
6b	4-$CH_3C_6H_4$	CN	353 [a]	$C_{14}H_{10}N_4O$	67.19 67.15	4.03 4.05	22.39 22.33
6c	3-$CH_3OC_6H_4$	CN	298 [a]	$C_{14}H_{10}N_4O_2$	63.15 63.10	3.79 3.75	21.04 20.97

[a] From acetonitrile.

Table 10

Spectroscopic Data of Compounds **5** and **6**

Compound No.	IR cm^{-1}	^1H MNR δ (ppm)
5a	2230, 1725, 1640	1.14-1.38 (m, 6H, $2CH_3$), 4.10-4.40 (m, 4H, $2CH_2$), 8.33 (s, 1H, H-4), 11.50 (br s, 1H, NH)
5e	3100, 2220, 1715, 1640	1.21 (t, 3H, CH_3), 3.56-3.62 (m, 4H, $2CH_2$), 4.01-4.10 (m, 4H, $2CH_2$), 4.23 (q, 2H, CH_2), 8.02 (s, 1H, H-4)
5f	3120, 2220, 1710, 1640	1.21 (t, 3H, CH_3), 1.82 (m, 4H, $2CH_2$), 3.32 (m, 4H, CH_2NCH_2), 4.15 (q, 2H, CH_2), 8.02 (s, 1H, H-4)
5g	3120, 2220, 1710, 1645	1.20 (t, 3H, CH_3), 1.56 (m, 6H, $3CH_2$), 3.26 (m, 4H, CH_2NCH_2), 8.07 (s, 1H, H-4), 11.79 (br s, 1H, NH)
6a	3330, 3220, 2200	7.22-7.55 (m, 5H, Ar), 7.73 (s, 2H, NH_2), 8.23 (s, 1H, H-4)
6b	3280, 3170, 2220, 1680, 1630	2.31 (s, 3H, CH_3), 7.05-7.16 (d, 2H arom), 7.26-7.35 (d, 2H arom), 7.69 (s, 2H, NH_2), 8.19 (s, 1H, H-4)
6c	3300, 3200, 2220, 1690, 1640	3.71 (s, 3H, CH_3), 6.70-7.50 (m, 4H, arom), 7.74 (s, 2H, NH_2), 8.21 (s, 1H, H-4)

Table 11

Yield (%) of Cyclization Products of Dienamino Esters **2** in Sodium Ethoxide

Dienamino ester No.	Reaction time (hours)	% **3**	% **4**	% **5**	% **6**
2a	1	46	–	12	–
2b	1	36	8	–	–
2c	1.5	65	–	–	–
2e	24	25	16	12	–
2f	24	53	38	7	–
2g	24	48	36	6	–
2h	0.5	80	–	–	–
2i	0.5	74	20	–	–
2j	0.5	96	–	–	–
2k	0.5	78	10	–	–
2l	1	64	–	–	25
2m	1	70	–	–	20
2n	1	55	–	–	20

sulfoxide with toluene, the yields were generally still satisfactory, but the reaction time was remarkably increased (Table 5).

In sodium ethoxide solution, besides compounds **3**, small quantities of their partial hydrolysis products **4** (Tables 6 and 7) were formed, which increase on increas-

ing the reaction time, and become the main product of the reaction by reflux for about at hour.

In the case of adducts **2a** and **2c-e**, about 10% of the 6-amino-2(1*H*)-pyridone derivatives **5** (Table 8) were also formed, while during condensation of the adducts **2l-n**, the 1-substituted 2-oxopyridine-3-carbonitriles **6** (Table 9) were formed. The yields of the cyclization products are reported in Table 11. 1,5-Dipolar cyclization occurs prevalently by nucleophilic attack of the NH_2 group on cyano on the 2 position, while in sodium ethoxide, even though to a lesser degree, there was a concomitant attack on the ethoxycarbonyl group.

The structures of the compounds **3**, **4**, **5** and **6** were deduced on the basis of the analytical and spectroscopic data. On the ir spectra the compounds **3** present two intense bands at 3450-3385 and 3340-3265 cm^{-1} typical of a primary amino group and the absorption bands of the carbonyl functions at 1710-1670 cm^{-1}. In the nmr spectra a broad singlet is observed at 8.50-7.91 ppm due to the NH_2 protons, which disappears by deuteration, and another sharp singlet at 7.90-8.00 ppm due to the H-4 of the pyridinic ring. For the 2-aminopyridine-3-carboxylic acids **4** the chemical shifts of the NH_2 group appear at 7.98-7.72 ppm, while COOH resonates at very low fields 12.30-11.90 ppm, suggesting a strong intramolecular hydrogen bond with the adjacent amino group. This indicates that, in reaction conditions, the ethoxycarbonyl group undergoing hydrolysis is invariably in position 3.

The ir spectra of the 2(1*H*)-pyridone derivatives **5** exhibit two strong bands at 1640-1630 and 1725-1710 cm^{-1}, corresponding respectively to the amido and ester CO groups. In the pyridones **6**, besides absorption of the amido CO group, typical bands of the NH_2 group are also present.

EXPERIMENTAL

The melting points were determined on Köfler hot stage and are uncorrected. The ir spectra were obtained in nujol with a Perkin-Elmer 325 spectrophotometer. The ^1H nmr spectra were recorded for hexadeuteriodimethyl sulfoxide solution with a Varian FT80 spectrometer; chemical shifts are reported in ppm from HMS as an internal standard and are given in δ units. The elemental analyses (C,H,N) were carried out with a Carlo Erba model 1106 Elemental Analyzer. Reaction mixtures were monitored by tlc on DC-Alufolien Kieselgel 60-F254 (Merck). The ethyl 3-ethoxy-3-iminopropionate (**1a**) [4] and 3-ethoxy-3-iminopropanenitrile (**1b**) [5] were performed by literature procedures. The amidines **1c-n** were obtained at an almost pure state and are utilized for subsequent reaction without purification.

Ethyl 5-Amino-2-cyano-5-ethoxy-4-ethoxycarbonyl-2,4-pentadienoate (**2a**).

A mixture of ethyl 3-ethoxy-3-iminopropionate (20 mmoles) and ethyl ethoxymethylenecyanoacetate (20 mmoles) in anhydrous ethanol (30 ml) was stirred at room temperature for 24 hours. After removal of the solvent, the residue was collected and crystallized from benzene to give **2a**, mp 142°, in 72% yield.

Ethyl 5-Amino-2,4-dicyano-5-ethoxy-2,4-pentadienoate (**2b**).

A mixture of 3-ethoxy-3-iminopropanenitrile (20 mmoles) and ethyl ethoxymethylenecyanoacetate (20 mmoles) in anhydrous ethanol (30 ml) was stirred at room temperature for 1 hour. The formed precipitate was collected by filtration and crystallized from ethanol to give **2b**, mp 188°, in 75% yield.

Ethyl 2-Cyano-5,5-diamino-4-ethoxycarbonyl-2,4-pentadienoate (**2c**).

A solution of the ethoxycarbonylacetamidine hydrochloride (**1c**) (20 mmoles), ethyl ethoxymethylenecyanoacetate (20 mmoles) and triethylamine (20 mmoles) in anhydrous ethanol (30 ml) was stirred at room temperature for 24 hours. The solvent was removed under reduced pressure and the residue was washed with water and crystallized from 2-propanol to give **2c**, mp 185°, in 45% yield.

General Method for Dienamino Esters **2d-n**.

A solution of imidate (20 mmoles) and the appropriate amine (20 mmoles) in anhydrous ethanol (30 ml) was stirred at room temperature until the starting material disappeared by tlc (24-48 hours). The ethyl ethoxymethylenecyanoacetate (20 mmoles) was added and the reaction mixture was stirred for 1 hour. The resulting solid was collected by suction and crystallized from an appropriate solvent to give the dienamino esters **2d-n**.

For **2h** the reaction mixture was evaporated to dryness and the residue crystallized.

Thermal Cyclization of Dienaminoester **2**.

Method A.

A solution of **2** (5 mmoles) in dimethyl sulfoxide (5 ml) was refluxed for 15 minutes. After cooling, crushed ice was added and the resulting mixture was extracted with diethyl ether; the organic layer was washed with water, dried (sodium sulfate) and evaporated. The residue was collected and crystallized to give the ethyl 2-aminopyridine-3-carboxylate derivatives **3**.

Method B.

A solution of **2** (5 mmoles) in toluene/dimethyl sulfoxide 2:1 (v/v) (5 ml) was refluxed for the time reported in Table 5. The toluene was evaporated at reduced pressure and the residue treated as in method A.

Cyclization of Dienaminoester **2** in Sodium Ethoxide Solution.

The appropriate dienaminoester **2** was added under stirring to a solution of sodium ethoxide (5 mmoles) obtained from metal sodium (0.112 g) in anhydrous ethanol (15 ml) and the mixture was stirred at room temperature for the time reported in Table 11. Ice-water was then added and the solid collected by suction and crystallized from a suitable solvent to give the 2-aminopyridine derivatives **3a-c** and **3f-n**. Acetic acid was added to the mother liquor until *p*H 7.5 was reached and the 2(1*H*)-pyridone derivatives **5** and **6** were obtained and separated by filtration. By further adding of acetic acid up to *p*H 5.5, the 2-aminopyridine-3-carboxylic acid derivatives **4** were obtained.

Acknowledgements.

This work was supported by a grant from the Ministero della Pubblica Istruzione.

REFERENCES AND NOTES

[1] M. T. Cocco, C. Congiu, A. Maccioni and A. Plumitallo, *J. Heterocyclic Chem.*, in press, 1989.

[2] M. T. Cocco, C. Congiu, A. Maccioni and A. Plumitallo, M. L. Schivo and G. Palmieri, *Farmaco Ed. Sci.*, **43**, 103 (1988).

[3] T. Hayashi, I. Hari, H. Baba and H. Midorikawa, *Bull. Chem. Soc. Japan*, **40**, 2160 (1967); A. Gomez Sanchez, M. Tena Aldave and U. Scheidegger, *J. Chem. Soc. (C)*, 2570 (1968).

[4] S. A. Glickman and A. C. Cope, *J. Am. Chem. Soc.*, **67**, 1017 (1945).

[5] S. M. McElvain and J. P. Schroeder, *J. Am. Chem. Soc.*, **71**, 40 (1949).