Synthesis of 6-Amino and 6-Ethoxy-2(1*H*)-pyridone Derivatives

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An efficient route allowing the synthesis of 6-amino and 6-ethoxy-2(1*H*)-pyridone derivatives by reaction of ethyl cyanoacetimidate, ethyl ethoxycarbonylacetimidate and related acetamidines with diethyl ethoxymethylenemalonate (EMME) is reported. The formation of dienamino derivatives as intermediates and their heterocyclization to the 2(1*H*)-pyridone derivatives is described.

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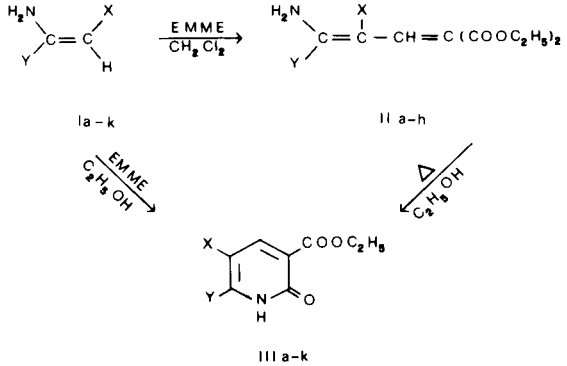
Ethyl 3-amino-3-ethoxypropenoate (**Ia**), 3-amino-3-ethoxypropenenitrile (**Ib**), the corresponding amidines **Ic-k** and their tautomeric forms are very versatile intermediates for the synthesis of heterocyclic compounds [1]. We have previously used these synthons for the preparation of 2-aminopyrrole derivatives [2], some of which have presented good inhibiting activity against different strains of blastomycetes and gram-positive microorganisms on microbiological screening. As a continuation of this research and with the aim of singling out new biologically active compounds, synthons **I** are now used as starting material to obtain some 6-amino and 6-ethoxy-2(1*H*)-pyridone derivatives **III**, which are very interesting compounds both as intermediates for the formation of the pyridine ring and as basic structural units for the synthesis of biologically active compounds.

The methods of synthesis of polysubstituted 2(1*H*)-pyridone derivatives reported in literature [3] are scarce because of the inavailability of adequately functionalized compounds that cyclize easily.

In this work 6-amino and 6-ethoxy-2(1*H*)-pyridone derivatives **III** (Table 1) are obtained in very good yields by reacting compounds **I** with an equivalent quantity of diethyl ethoxymethylenemalonate (EMME) in refluxing ethanol (Scheme 1). The formation of the pyridine skeleton in compounds **III** is clearly shown by ir and ^{1}H nmr spectra (Table 2).

Scheme 1



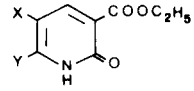
III a-k

	x	y		x	y
a	$COOC_2H_5$	OC_2H_5	g	CN	pyrrolidinyl
b	CN	OC_2H_5	h	CN	piperidinyl
c	$COOC_2H_5$	4-morpholinyl	i	CN	n-buthylamino
d	$COOC_2H_5$	pyrrolidinyl	j	CN	4-chlorophenylamino
e	$COOC_2H_5$	piperidinyl	k	CN	4-methylphenylamino
f	CN	4-morpholinyl			

The formation of 2(1*H*)-pyridone derivatives **III** presumably proceeds through open-chain structure intermediates **II**, which are susceptible of a subsequent intramolecular cyclization. In the above mentioned conditions, however, it has not been possible to isolate adducts **II**, but the final products of cyclization have always been reached. On the contrary the formation of adducts **II** was proved by carrying out the reaction in aprotic apolar solvents (dichloromethane, benzene) at relatively low temperatures (−10-0°). In these conditions, intermediates **II** were isolated together with variable quantities of compounds **III** (Table 3). By increasing the reaction times, the latter are transformed into cyclic derivatives; this transformation was observed by ^{1}H nmr spectroscopy for compound **IIa**. As soon as this chromatographically pure substance is dissolved in deuteriochloroform, its spectrum presents two multiplets centered at 1.25 and 4.10 ppm due to the protons of the ethoxycarbonyl groups, a singlet at 7.90 ppm of the olefinic proton and another broadened singlet at 8.10 ppm of the amino protons, that disappears after deuteration. On repeating the spectrum at room temperature after two hours, a decrease in the intensity of the olefinic proton is observed together with the appearance of a new singlet relating to the γ-proton of the cyclic compound **IIIa** and of a new quartet at 3.62 ppm due to the methylene protons of the ethanol which is being released, whose intensities increase in time. The transformation of **IIa** into **IIIa** is completed within 24 hours. The ir and ^{1}H nmr spectra (Table 4) show that adducts **II** exist in only one isomeric form; the values of the chemical shifts at low fields of the amino protons and the values in the ir of the frequencies at 1650 and 1670 cm^{-1} (CO) and 3360, 3180 cm^{-1} (NH_2) in compounds **IIa** and **IIc-e** suggest the presence of an intramolecular hydrogen bond between the aminic group and the adjacent ester function; therefore an *E* configuration. No other information on the geometry of adducts **II** can be obtained from the spectroscopic data. One can hy-

Table 1

Physical and Analytical Data of Compounds **IIIa-k**



Compound No.	X	Y	Yield (%)	Mp (°C)	Molecular Formula	Analyses % Calcd./Found C	H	N
IIIa	$COOC_2H_5$	OC_2H_5	86	83 [a]	$C_{13}H_{17}NO_6$	55.12 55.06	6.05 6.06	4.95 4.88
IIIb	CN	OC_2H_5	88	148 [b]	$C_{11}H_{12}N_2O_4$	55.93 55.89	5.12 5.10	11.86 11.80
IIIc	$COOC_2H_5$	4-morpholinyl	82	90 [c]	$C_{15}H_{20}N_2O_6$	55.55 55.49	6.22 6.20	8.64 8.66
IIId	$COOC_2H_5$	pyrrolidinyl	92	102 [c]	$C_{15}H_{20}N_2O_5$	58.43 58.39	6.54 6.52	9.09 9.07
IIIe	$COOC_2H_5$	piperidinyl	88	89 [a]	$C_{16}H_{22}N_2O_5$	59.61 59.62	6.88 6.85	8.69 8.65
IIIf	CN	4-morpholinyl	95	145 [b]	$C_{13}H_{15}N_3O_4$	56.31 56.29	5.45 5.46	15.16 15.10
IIIg	CN	pyrrolidinyl	86	170 [d]	$C_{13}H_{15}N_3O_3$	59.76 59.70	5.79 5.73	16.08 16.02
IIIh	CN	piperidinyl	90	120 [d]	$C_{14}H_{17}N_3O_3$	61.08 61.02	6.22 6.24	15.26 15.21
IIIi	CN	*n*-buthylamino	68	193 [b]	$C_{13}H_{17}N_3O_3$	59.30 59.20	6.51 6.49	15.96 16.00
IIIj	CN	4-chlorophenylamino	60	228 [e]	$C_{15}H_{12}ClN_3O_3$	56.69 56.65	3.76 3.75	13.21 13.18
IIIk	CN	4-methylphenylamino	62	225 [e]	$C_{16}H_{15}N_3O_3$	64.63 64.71	5.09 5.07	14.14 14.21

[a] From *n*-hexane. [b] From ethanol. [c] From ligroin. [d] From 2-propanol. [e] From ethoxyethanol.

Table 2

Spectroscopic Data of Compounds **IIIa-k**

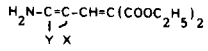
Compound No.	IR cm^{-1}	^{1}H-NMR δ (ppm)
IIIa	3100, 1710, 1675	1.05-1.55 (m, 9H $(CH_3)_3$), 4.00-4.65 (m, 6H, $(OCH_2)_3$), 8.65 (s, 1H, H-4), 11.95 (s, 1H, NH exchangeable) [a]
IIIb	3080, 2240, 1670	1.15-1.45 (m, 6H, $(CH_3)_2$), 4.10-4.60 (m, 4H, $(OCH_2)_2$), 8.45 (s, 1H, H-4), 9.5-11 (br, 1H, NH exchangeable) [b]
IIIc	3080, 1720, 1670	1.20 (t, 6H, $(CH_3)_2$), 3.45 (m, 4H, CH_2NCH_2), 3.65 (m, 4H, CH_2O CH_2), 4.05-4.45 (m, 4H, $(OCH_2)_2$), 8.38 (s, 1H, H-4), 11.58 (br, 1H, NH exchangeable) [b]
IIId	3160, 1730, 1700	1.23 (t, 6H, $(CH_3)_2$), 1.82 (m, 4H, $(CH_2)_2$), 3.33 (m, 4H, CH_2-N-CH_2), 4.19 (q, 4H, $(OCH_2)_2$), 8.27 (s, 1H, H-4), 11.23 (s, 1H, NH exchangeable) [b]
IIIe	3130, 1710, 1680	1.25 (t, 6H, $(CH_3)_2$), 1.55 (m, 6H, $(CH_2)_3$), 3.35 (m, 4H, CH_2-N-CH_2), 4.05-4.40 (m, 4H, $(OCH_2)_2$), 8.32 (s, 1H, H-4), 11.45 (br, 1H, NH exchangeable) [b]
IIIf	3080, 2210, 1660	1.32 (t, 3H, CH_3), 3.60-4.05 (m, 8H, morpholine protons), 4.33 (q, 2H, OCH_2), 8.20 (s, 1H, H-4), 9.12 (br, 1H, NH exchangeable) [a]
IIIg	3140, 2210, 1690	1.21 (t, 3H, CH_3), 1.86 (m, 4H, $(CH_2)_2$), 3.63 (m, 4H, CH_2-N-CH_2), 4.13 (q, 2H, OCH_2), 8.05 (s, 1H, H-4), 11.63 (br, 1H, NH exchangeable) [b]
IIIh	3120, 2210, 1685	1.31 (t, 3H, CH_3), 1.62 (m, 6H, $(CH_2)_3$), 3.81 (m, 4H, CH_2-N-CH_2), 4.28 (q, 2H, OCH_2), 8.13 (s, 1H, H-4), 11.25 (br, 1H, NH exchangeable) [a]

IIIi	3300, 3100, 2220, 1730	0.95 (t, 3H, CH_3), 1.10-1.70 (m, 4H, $(CH_2)_2$), 1.33 (t, 3H, CH_3), 3.50 (m, 2H, CH_2NH), 4.32 (q, 2H, OCH_2), 5.55 (br, 1H, NH exchangeable), 8.23 (s, 1H, H-4) [a]
IIIj	3320, 2220, 1680	1.23 (t, 3H, CH_3), 4.23 (q, 2H, OCH_2), 7.40 (d, 2H, Ar), 7.61 (d, 2H, Ar), 8.30 (s, 1H, H-4), 9.5-10.5 (br, 1H, NH) [b]
IIIk	3200, 2220, 1675	1.25 (t, 3H, CH_3), 2.23 (s, 3H, CH_3), 4.20 (q, 2H, OCH_2), 7.15 (d, 2H, Ar), 7.45 (d, 2H, Ar), 8.26 (s, 1H, H-4) [b]

[a] Deuteriochloroform solution. [b] Deuteriodimethyl sulfoxide solution.

Table 3

Physical and Analytical Data of Compounds **IIa-h**



Compound No.	X	Y	Yield (%)	Mp (°C)	Molecular Formula	Analyses % Calcd./Found C	H	N
IIa	$COOC_2H_5$	OC_2H_5	68	95 [a]	$C_{15}H_{23}NO_7$	54.70 54.76	7.04 7.02	4.25 4.26
IIb	CN	OC_2H_5	45	180 [b]	$C_{13}H_{18}N_2O_5$	55.31 55.27	6.43 6.40	9.92 9.89
IIc	$COOC_2H_5$	4-morpholinyl	72	168 [c]	$C_{17}H_{26}N_2O_7$	55.12 55.22	7.08 7.05	7.56 7.59
IId	$COOC_2H_5$	pyrrolidinyl	75	173 [d]	$C_{17}H_{26}N_2O_6$	57.61 57.67	7.40 7.38	7.91 7.94
IIe	$COOC_2H_5$	piperidinyl	66	138 [e]	$C_{18}H_{28}N_2O_6$	58.68 58.57	7.66 7.70	7.60 7.65
IIf	CN	4-morpholinyl	75	200 [f]	$C_{15}H_{21}N_3O_5$	55.72 55.68	6.55 6.51	13.00 12.95
IIg	CN	pyrrolidinyl	70	164 [f]	$C_{15}H_{21}N_3O_4$	58.62 58.58	6.89 6.85	13.67 13.64
IIh	CN	piperidinyl	70	167 [e]	$C_{16}H_{23}N_3O_4$	59.79 59.70	7.21 7.23	13.08 13.02

[a] From diisopropyl ether. [b] From acetonitrile. [c] From acetone. [d] From ligroin. [e] From 2-propanol. [f] From ethanol.

Table 4

Spectroscopic Data of Compounds **IIa-h**

Compound No.	IR cm^{-1}	^{1}H-NMR δ (ppm)
IIa	3350, 3200, 1750, 1665	1.05-1.50 (m, 12H, $(CH_3)_4$), 3.85-4.35 (m, 8H, $(OCH_2)_4$), 7.90 (s, 1H, =CH), 8.10 (br, 2H, NH_2 exchangeable) [a]
IIb	3340, 3220, 2220, 1700, 1665	1.10-1.45 (m, 9H, $(CH_3)_3$), 3.95-4.60 (m, 6H, $(OCH_2)_3$), 7.00 (br, 2H, NH_2 exchangeable), 8.45 (s, 1H, =CH) [b]
IIc	3290, 3130, 1710, 1670	1.20 (t, 9H, $(CH_3)_3$), 3.50 (m, 4H, CH_2-N-CH_2), 3.70 (m, 4H, CH_2-O-CH_2), 4.05 (q, 6H, $(OCH_2)_3$), 7.45 (s, 2H, NH_2 exchangeable), 8.25 (s, 1H, =CH) [a]
IId	3360, 3200, 1690, 1660	1.20 (t, 9H, $(CH_3)_3$), 1.90 (m, 4H, $(CH_2)_2$), 3.35 (m, 4H, CH_2-N-CH_2), 4.05 (q, 6H, $(OCH_2)_3$), 6.70 (s, 2H, NH_2 exchangeable), 8.30 (s, 1H, =CH) [a]
IIe	3340, 3180, 1680, 1660	1.00-1.12 (m, 9H, $(CH_3)_3$), 1.54 (m, 6H, $(CH_2)_3$), 3.32 (m, 4H, CH_2-N-CH_2), 3.75-4.10 (m, 6H, $(OCH_2)_3$), 7.85 (br, 2H, NH_2 exchangeable), 8.05 (s, 1H, =CH) [b]
IIf	3340, 3200, 2190, 1700, 1670	0.90-1.35 (m, 6H, $(CH_3)_2$), 3.30-3.70 (m, 8H morpholine protons), 3.80-4.30 (m, 4H, $(OCH_2)_2$), 7.35 (s, 1H, =CH), 7.80 (s, 2H, NH_2 exchangeable) [b]
IIg	3350, 3210, 2195, 1700, 1670	1.00-1.45 (m, 6H, $(CH_3)_2$, 1.95 (m, 4H, $(CH_2)_2$), 3.55 (m, 4H, CH_2-N-CH_2), 3.95-4.40 (m, 4H, $(OCH_2)_2$), 6.40 (s, 2H, NH_2 exchangeable), 7.55 (s, 1H, =CH) [a]
IIh	3360, 3240, 2200, 1700, 1670	1.00-1.50 (m, 6H, $(CH_3)_2$), 1.70 (m, 6H, $(CH_2)_3$), 3.50 (m, 4H, CH_2-N-CH_2), 3.95-4.45 (m, 4H, $(OCH_2)_2$), 6.45 (s, 2H, NH_2 exchangeable), 7.45 (s, 1H, =CH) [a]

[a] Deuteriochloroform solution. [b] Deuteriodimethyl sulfoxide solution.

pothesize that the cyclization of dienamino compounds **II** occurs, after cleavage of the hydrogen bond, with the formation of an extremely reactive iminic species **IV**, which cyclizes rapidly in protic solvents under relatively mild conditions, with elimination of an ethanol molecule.

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 ^{1}H nmr spectra were recorded 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 F_{254} (Merck). The ethyl 3-ethoxy-3-iminopropionate (**Ia**) [4] and 3-ethoxy-3-iminopropanenitrile (**Ib**) [5] were prepared by literature procedures. The amidines **Ic-k** [2] are obtained at an almost pure state and are utilized for subsequent reactions without purification.

Triethyl 4-Amino-4-ethoxy-1,3-butadiene-1,1,3-tricarboxylate (**IIa**).

A mixture of diethyl ethoxymethylenemalonate (2.16 g, 10 mmoles) and ethyl 3-ethoxy-3-iminopropionate in dichloromethane (or benzene) (20 ml) was kept at −10° for 24 hours. After removal of the solvent, the resulting solid was triturated with diisopropyl ether and collected by filtration and recrystallized from diisopropyl ether to give **IIa**, mp 95°, in 68% yield. By concentration of the washing liquor, compound **IIIa** in 15% yield was obtained.

Diethyl (3-Amino-2-cyano-3-ethoxy-2-propenylidene)propanedioate (**IIb**).

This compound was synthesized from diethyl ethoxymethylenemalonate (2.16 g, 10 mmoles) and 3-ethoxy-3-iminopropanenitrile (1.1 g, 10 mmoles) in a manner similar to that described for the preparation of **IIa**. Fractional crystallization (acetonitrile) of residues give 45% of **IIb** (mp 181°) and 25% of **IIIb** (mp 148°).

Dienamino Derivatives **IIc-h**.

General Method.

The solution of the imidate (11 mmoles) and the appropriate amine (10 mmoles) in anhydrous ethanol (20 ml) was stirred at room temperature until the starting material disappeared by tlc (24-48 hours). The ethanol was totally removed under reduced pressure and the amidine so obtained was dissolved in dichloromethane (or benzene) and the diethyl ethoxymethylenemalonate (10 mmoles) was added under stirring at 0°. The reaction mixture was kept at 0° for 24 hours. After removal of the solvent under reduced pressure, the residue was collected and crystallized from the appropriate solvent to give **IIc-h** in 62-75% yield.

By concentration of the mother liquor, compounds **IIIc-h** in 10-20% yield was obtained.

Diethyl 1,2-Dihydro-6-ethoxy-2-oxo-3,5-pyridinedicarboxylate (**IIIa**).

Ethyl 3-ethoxy-3-iminopropionate (1.59 g, 10 mmoles) in anhydrous ethanol (20 ml) was added to diethyl ethoxymethylenemalonate (2.16 g, 10 mmoles) in anhydrous ethanol (10 ml) and the reaction mixture was stirred at room temperature for 24 hours. The solvent was then evaporated to dryness under reduced pressure. The solid residue was collected and crystallized from *n*-hexane to give **IIIa**, mp 83°, in 86% yield.

Ethyl 5-Cyano-1,2-dihydro-6-ethoxy-2-oxo-3-pyridinecarboxylate (**IIIb**).

A solution of 3-ethoxy-3-iminopropanenitrile (1.1 g, 10 mmoles) and diethyl ethoxymethylenemalonate (2.16 g, 10 mmoles) in anhydrous ethanol (20 ml) was stirred at room temperature for 24 hours. The formed precipitate was collected by filtration and recrystallized from ethanol to give **IIIb**, mp 148°, in 88% yield.

Ethyl 6-Substituted Amino-1,2-dihydro-2-oxo-3-pyridinecarboxylate Derivatives **IIIc-k**.

Method A.

The appropriate amine (10 mmoles) was added to a solution of imidate (11 mmoles) in anhydrous ethanol (20 ml). The reaction mixture was stirred at room temperature until the starting material disappeared by tlc (benzene), the diethyl ethoxymethylenemalonate (10 mmoles) in anhydrous ethanol (20 ml) was then added and the mixture was refluxed with stirring for 2 hours. After evaporation of the ethanol under reduced pressure, the residue was crystallized from the appropriate solvent to give **IIIc-k** in 60-93% yield.

Method B.

A solution of **IIc-h** (10 mmoles) in ethanol (20 ml) was refluxed for 1 hour. The solvent was evaporated under reduced pressure and the residue was recrystallized from the appropriate solvent to give **IIIc-h** in quantitative yield.

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