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Heterocyclic β-Enamino Esters, 33[1]

Addition and Cyclization Reaction of 3-(2-Imidazolidinylidene)- and 3-(Hexahydro-2-pyrimidinylidene)-2(3*H*)-furanones with Hydrochloric Acid, Halogens, and Methyl Propiolate

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The 3-(2-imidazolidinylidene)- and 3-(hexahydro-2-pyrimidinylidene)-2(3*H*)-furanones **1a – e** react with methyl propiolate in benzene or dioxane solution to afford the adducts **2a – e** *via syn*-addition. In the presence of alcohols **2a – e** are cyclized to give the imidazo[1,2-*a*]pyridines and pyrido[1,2-*a*]pyrimidines **3a – j** with ring cleavage of the γ-lactone ring; in turn **3a – j** are directly formed from **1a – e** in alcoholic solution. Upon treatment with bromine or chlorine **1a – e** give the halogenated hydrohalides **4a – c**, **5a – c**, or **6** depending on the individual substituents; they are furthermore smoothly protonated with hydrochloric acid to form the immonium salts **7a – e**.

Heterocyclische β-Enaminoester, 33[1]

Additions- und Ringschlußreaktionen der 3-(2-Imidazolidinyliden)- und 3-(Hexahydro-2-pyrimidinyliden)-2(3*H*)-furanone mit Chlorwasserstoffsäure, Halogenen und Propiolsäure-methylester

Die 3-(2-Imidazolidinyliden)- und 3-(Hexahydro-2-pyrimidinyliden)-2(3*H*)-furanone **1a – e** reagieren unter *syn*-Addition mit Propiolsäure-methylester in Benzol oder Dioxan zu den Addukten **2a – e**. In Alkoholen findet Ringschluß zu den Imidazo[1,2-*a*]pyridinen und Pyrido-[1,2-*a*]pyrimidinen **3a – j** statt unter Öffnung des γ-Lactonringes. In alkoholischer Lösung entstehen **3a – j** direkt. In Abhängigkeit von der Substitution reagieren **1a – e** mit Brom oder Chlor zu den halogenierten Hydrohalogeniden **4a – c**, **5a – c** und **6**; sie werden ferner mit Chlorwasserstoffsäure glatt zu den Immoniumsalzen **7a – e** protoniert.

Recently, the reaction of ethyl 2-amino-4,5-dihydro-3-furancarboxylates with ethylenediamine and 1,3-diaminopropane has been reinvestigated, and the products have been characterized to be 3-(2-imidazolidinylidene)- and 3-(hexahydro-2-pyrimidinylidene)-4,5-dihydro-2(3*H*)-furanones (**1a – e**), respectively[1]. The constitutions of **1a – e** were confirmed with the aid of ^{13}C NMR gated decoupling technique. Thus, **1a – e** can be considered as ring-fixed as α-alkoxycarbonyl-ketene aminals, and for the double bond a high nucleophilicity can be predicted. We have investigated the reactivity of these title compounds. Due to the considerably downfield shifted ^{13}C NMR signal for C-3 (62.4 – 72.4 ppm) an electrophilic attack might be expected to occur preferably on this carbon atom.

I. Addition and Cyclization Reaction with Methyl Propiolate

It is well known that a variety of enamines afford cyclobutene derivatives[3,4] on the reaction with propiolates, but in fewer cases a Michael-type adduct is formed[4]. Furthermore, the reaction

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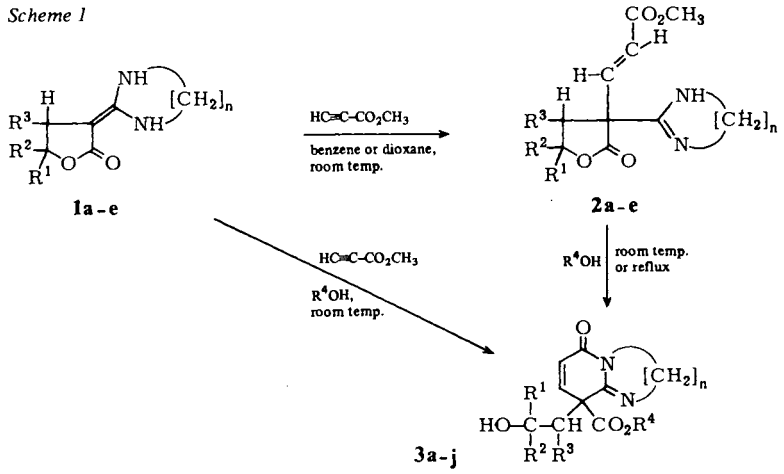
of heterocyclic β-enamino esters with acetylenic esters has been reported[5]. However, the reaction of "ring-fixed" α-alkoxycarbonyl-ketene aminales, like **1a–e**, with methyl propiolate has not been investigated so far, and from our results a Michael-type adduct was expected.

1a–e react smoothly with methyl propiolate at ambient temperature in benzene or dioxane solution to afford the adducts **2a–e**, *via syn*-addition. In the presence of alcohols at room temperature or on refluxing, **2a–e** are cyclized to give the imidazo-[1,2-*a*]pyridines and pyrido[1,2-*a*]pyrimidines **3a–j** while the γ-lactone ring is simultaneously cleaved. However, when **1a–e** are treated with methyl propiolate at ambient temperature in alcoholic solution, **2a–e** cannot be isolated, but instead direct conversion to **3a–j** takes place. The reactions are shown in Scheme 1.

Scheme 1



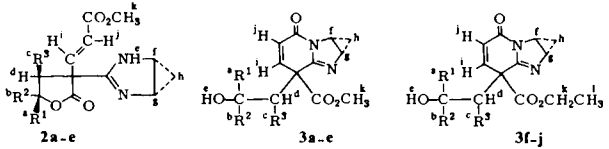
1, 2, 3	a	b	c	d	e	f	g	h	i	j
R^1	CH_3	CH_3	CH_3	CH_3	CH_3	CH_3	CH_3	CH_3	CH_3	CH_3
R^2	H	CH_3	H	CH_3	H	H	CH_3	H	CH_3	H
R^3	H	H	CH_3	H	CH_3	H	H	CH_3	H	CH_3
R^4	CH_3	CH_3	CH_3	CH_3	CH_3	C_2H_5	C_2H_5	C_2H_5	C_2H_5	C_2H_5
n	2	2	2	3	3	2	2	2	3	3

The constitutions of **2a–e** and **3a–j** are in best agreement with their spectral data and elemental analyses. The ^1H and ^{13}C NMR spectra are listed in Table 1 and 2.

Due to the conjugation of the lactone carbonyl with the enamine moiety in **1a–e** the lactone absorption is shifted bathochromically to the region of 1650–1690 cm^{-1}. When this conjugation is absent, as e.g. in the adducts **2a–e**, the lactone absorption moves back to the normal region (1758–1762 cm^{-1}).

The occurrence of two signals for olefinic protons in **2a–e** excludes a [2 + 2]-cycloaddition product, like **A**. ^1H and ^{13}C NMR spectra indicate that C-8 and C-9 and the protons at both these CH_2 groups are identical, which in turn excludes obviously an *N*-addition produkt **B**.

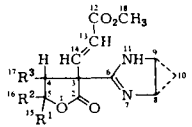
Table 1. ^{1}H NMR Spectra of **2a–e** and **3a–j** in $CDCl_3$ (δ in ppm; J in Hz)



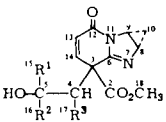
2a–e **3a–e** **3f–j**

	a	b	c	d	e	f	g	h	i	j	k	l
2a	1.47 d (6.0)	4.60 (J_{ab} = 6.0; J_{bc} = 4.6; J_{bd} = 7.6; J_{cd} = 14.0)	2.48	2.74		3.66 t (3.2)			6.98 d (16.0)	6.11 d (16.0)	3.77 s	
2b	1.46 s		2.37 d (13.4)	3.22 d (13.4)	5.18 broad	3.67 t (3.2)			7.03 d (16.0)	6.14 d (16.0)	3.76 s	
2c	1.36 d (6.6)	4.49 dq (6.6; 4.6)	1.04 d (7.2)	2.78 dq (7.2; 4.6)		3.66 t (4.2)			7.18 d (16.0)	5.99 d (16.0)	3.75 s	
2d	1.43 s		2.29 d (13.6)	3.27 d (13.6)		3.38 t (5.8)		1.75 quint (5.8)	7.06 d (16.0)	6.13 d (16.0)	3.76 s	
2e	1.34 d (6.4)	4.62 dq (6.4; 4.5)	1.07 d (7.2)	2.84 dq (7.2; 4.5)		3.38 t (5.8)		1.76 quint (5.8)	7.21 d (16.4)	5.96 d (16.4)	3.75 s	
3a	1.30 d (6.2)	4.62 (J_{ab} = 6.2; J_{bc} = 4.4; J_{bd} = 8.0; J_{cd} = 14.4)	2.36	2.70	5.61 s	3.77 (9.0)	4.23 (9.0)		7.02 d (9.0)	5.81 d (9.0)	3.80 s	
3b	1.51 s			2.61 s	5.53 s	3.68 (8.8)	4.25 (8.8)		7.04 d (9.0)	5.89 d (9.0)	3.71 s	
3c	1.18 d (6.2)	4.82 quint (6.2)	1.22 d (7.2)	2.70 quint (7.2)	5.04 s	3.73 (9.0)	4.23 (9.0)		7.13 d (9.2)	5.90 d (9.2)	3.78 s	
3d	1.50 s			2.64 s	5.81 s	3.40 dt (6.0; 2.0)	4.08 t (6.0)	2.03 quint (6.0)	6.97 d (8.8)	5.82 d (8.8)	3.72 s	
3e	1.19 d (6.2)	4.82 quint (6.2)	1.23 d (7.2)	2.76 dq (7.2; 6.6)	5.16 s	3.44 dt (6.0; 2.4)	4.10 dt (6.0; 4.0)	2.05 quint (6.0)	7.10 d (9.2)	5.88 d (9.2)	3.78 s	
3f	1.30 d (6.2)	4.64 (J_{ab} = 6.2; J_{bc} = 4.8; J_{bd} = 7.6; J_{cd} = 14.4)	2.42	2.71	6.02 s	3.80 (9.0)	4.25 (9.0)		7.07 d (8.8)	5.88 d (8.8)	4.19 q (7.0)	1.30 t (7.0)
3g	1.50 s			2.60 s	5.37 s	3.69 (9.0)	4.23 (9.0)		7.02 d (9.0)	5.85 d (9.0)	4.12 q (7.2)	1.28 t (7.2)
3h	1.19 d (6.0)	4.84 quint (6.0)	1.23 d (7.2)	2.78 dq (7.2; 5.8)	5.27 s	3.75 (9.0)	4.29 (9.0)		7.17 d (9.2)	5.92 d (9.2)	4.12 q (7.2)	1.30 t (7.2)
3i	1.51 s			2.64 s	5.82 s	3.39 dt (6.0; 2.8)	4.08 t (6.0)	2.03 quint (6.0)	6.98 d (8.8)	5.76 d (8.8)	4.14 q (7.2)	1.29 t (7.2)
3j	1.18 d (6.2)	4.82 quint (6.2)	1.23 d (7.2)	2.74 dq (7.2; 5.8)	5.12 s	3.42 dt (6.0; 2.6)	4.07 t (6.0)	2.04 quint (6.0)	7.09 d (9.2)	5.87 d (9.2)	4.19 q (7.2)	1.30 t (7.2)

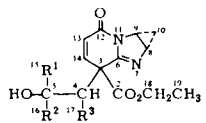
Table 2. ^{13}C Chemical Shifts of **2a–d** and **3a–d, f–h** in $CDCl_3$, and **4a, b** and **5a** in [D_6]DMSO (δ in ppm)



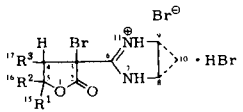
2a–d



3a–d



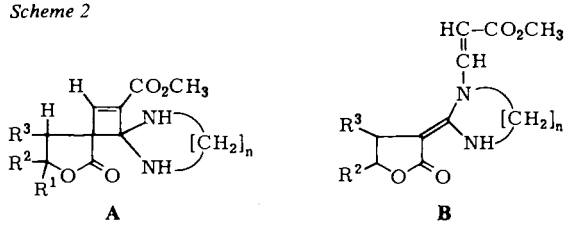
3f–h



4a, b, 5a

	C-2	C-3	C-4	C-5	C-6	C-8	C-9	C-10	C-12	C-13	C-14	C-15	C-16	C-17	C-18	C-19
2a	174.3 s	53.3 s	67.1 t	75.4 d	164.2 s	40.0 t			165.7 s	123.4 d	143.3 d	20.3 q			52.0 q	
2b	174.2 s	53.6 s	50.1 t	84.3 s	164.0 s	44.1 t			166.0 s	123.0 d	145.6 d	29.1 q	28.7 q		51.9 q	
2c	174.7 s	67.1 s	77.6 d	79.8 d	163.2 s	44.4 t			165.7 s	123.0 d	143.8 d	15.3 q		9.5 q	52.0 q	
2d	175.7 s	57.1 s	42.6 t	84.0 s	152.5 s	43.3 t		20.6 t	166.3 s	122.0 d	147.4 d	29.1 q	28.5 q		51.9 q	
3a	161.3 s	91.8 s	36.3 t	75.3 d	151.9 s	44.8 t	42.6 t		155.9 s	105.5 d	144.5 d	19.1 q			54.9 q	
3b	161.2 s	92.2 s	42.0 t	85.9 s	152.7 s	44.9 t	42.6 t		153.8 s	106.0 d	145.7 d	24.8 q			54.2 q	
3c	160.7 s	97.8 s	36.8 d	78.5 d	151.6 s	44.7 t	42.2 t		155.3 s	104.6 d	141.1 d	17.5 q		15.5 q	54.4 q	
3d	162.1 s	94.2 s	39.3 t	86.0 s	149.0 s	42.1 t	40.0 t	20.7 t	153.9 s	101.9 d	144.3 d	25.0 q			54.2 q	
3f	161.3 s	91.8 s	36.4 t	74.9 d	151.9 s	44.8 t	42.7 t		155.3 s	105.5 d	144.5 d	19.1 q			64.1 t	14.3 q
3g	161.3 s	92.5 s	41.9 t	85.6 s	152.9 s	45.0 t	42.3 t		153.4 s	105.9 d	145.8 d	25.0 q			63.4 t	14.3 q
3h	161.0 s	97.7 s	37.7 d	78.7 d	151.4 s	44.9 t	42.6 t		154.7 s	106.6 d	141.7 d	16.9 q		15.5 q	63.9 t	14.3 q
4a	168.8 s	42.7 s	44.5 t	76.1 d	164.6 s	44.7 t						18.6 q				
4b	169.6 s	46.4 s	45.6 t	84.4 s	159.4 s	39.3 t		17.0 t				28.7 q	26.2 q			
5a	168.8 s	43.2 s	45.6 t	84.8 s	165.5 s	44.6 t						28.6 q	26.4 q			

Scheme 2

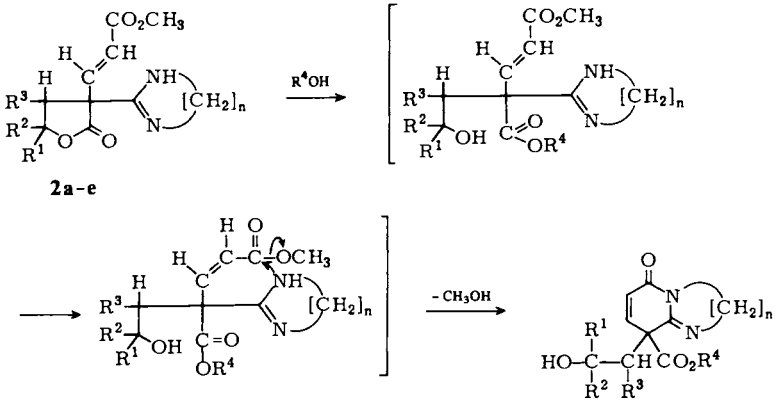


A **B**

As in **2a–e** the coupling constants of the olefinic protons H^i and H^j range between 16.0 and 16.4 Hz, these two protons are unambigously in *trans*-position caused by *syn*-addition. In contrast, in **3a–j** coupling constants of H^i and H^j range between 8.8 and 9.2 Hz, which shows now unequivocally the *cis*-position due to the cyclization step. Furthermore, in **3a–j** the ester carbonyl absorption between 1730 and 1742 cm^{-1}, instead of a typical γ-lactone absorption, and the appearance of only one ^{13}C signal for C-15 and C-16 in **3b,d,** and **g** instead of two signals for C-15 and C-16 in **2b** and **d** indicates that the γ-lactone ring is cleaved during the conversion of **2a–e** to **3a–j**.

For the conversion of **2a–e** to **3a–j** in alcohols we discuss the mechanism given in Scheme 3.

Scheme 3

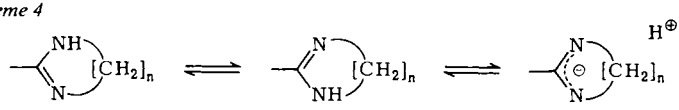


2a-e **3a-j**

At first the γ-lactone ring of **2a–e** is alcoholytically cleaved, and in the protic solvent with the aid of acidic or basic catalysts a *cis-trans*-isomerization smoothly takes place; in turn, this *cis*-intermediate is then cyclized to give **3a–j** by elimination of methanol. Consequently, when **1a–e** is reacted with methyl propiolate in alcoholic solution, the addition, ring cleavage, *cis-trans*-isomerization, and cyclization occur *in situ*, and therefore only **3a–j** are obtained.

H^b, H^c, and H^d of **2a**, **3a**, and **3f** form an ABX-pattern, H^b being further splitted by the adjacent methyl group. In **3a–c** and **3f–h**, H^f and H^g form an A_2B_2-pattern. ^1H and ^{13}C NMR spectra indicate further, that H^f and H^g as well as C-8 and C-9 of **2a–d** are identical; this implies the imidazoline- and tetrahydropyrimidine rings existing in the tautomeric forms given in Scheme 4.

Scheme 4

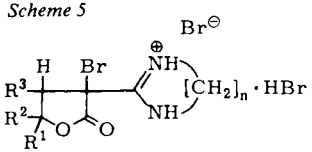


II. Addition of Bromine and Chlorine and Protonation with Hydrochloric Acid

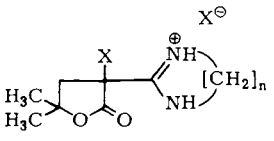
The addition of halogen[6] to and protonation[7] of enamines have been reviewed, and in this respect **1a–e** turned out to behave similarly to enamines.

Thus, **1a–e** react smoothly with bromine in methylene chloride solution. When the bromine solution is added dropwise, the reaction mixture fades immediately. As we have found, the constitutions of the individual reaction products depend strongly on the nature of the substituents involved. Thus, from **1a,d,e** yellow or orange-yellow crystals are obtained; from the analytical data follows that they are hydrobromide salts of the addition products **4a–c**. However, from **1b** colourless crystals are obtained, which were identified to be the bromine addition product **5a**. The addition product stemming from **1c** was somewhat different, being not a bromine addition product, but instead a HBr-addition product **6**; the constitution of this latter product was confirmed by elemental analysis and its ^{1}H NMR spectrum. Most probably, due to the 4-methyl group the proton is more favourable to addition and might be stemming from small amounts of moisture in the reaction mixture.

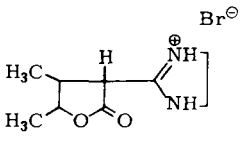
Scheme 5



4	R^1	R^2	R^3	n
a	CH_3	H	H	2
b	CH_3	CH_3	H	3
c	CH_3	H	CH_3	3



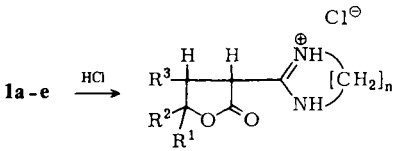
5	X	n
a	Br	2
b	Cl	2
c	Cl	3



6

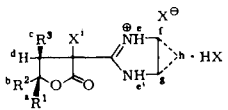
1b and **d** react with chlorine to give the addition products **5b,c**. **1b** can be also reacted with *N*-bromo- or *N*-chlorosuccinimide to afford the halogen addition products **5a,b**, respectively. In methanolic hydrochloric acid **1a–e** are easily protonated to form the immonium salts **7a–e**, the proton being added to C-3, as it is confirmed by ^{1}H NMR analysis.

Scheme 6



7	R^1	R^2	R^3	n
a	CH_3	H	H	2
b	CH_3	CH_3	H	2
c	CH_3	H	CH_3	2
d	CH_3	CH_3	H	3
e	CH_3	H	CH_3	3

Table 3. ^{1}H NMR Spectra of **4a – c**, **5a – c**, **6**, and **7a – e** in [D$_6$]DMSO (δ in ppm; *J* in Hz)



Compd.	a	b	c	d	e	e'	f g	h	i
4a	1.44 d (6.0)	4.86 (J_{ab} = 6.0; J_{bc} = 6.0; J_{bd} = 10.0; J_{cd} = 14.2)	2.67	2.97		10.36 s	3.91 s		
4b	1.49 s	1.67 s	2.90 d (15.2)	3.05 d (15.2)		9.60 s	3.49 t (5.6)	1.87 quint (5.6)	
4c	1.38 d (6.4)	5.08 dq (6.4; 4.4)	0.91 d (7.4)	3.13 dq (7.4; 4.6)		9.85 s	3.50 t (5.2)	1.89 quint (5.2)	
5a	1.48 s	1.65 s	2.84 d (15.4)	3.06 d (15.4)		10.26 s	3.90 s		
5b	1.55 s	1.61 s	2.90 d (15.4)	3.17 d (15.4)		10.92 s	3.92 s		
5c	1.55 s	1.62 s	2.96 d (15.4)	3.11 d (15.4)		10.15 s	3.44 t (5.4)	1.86 quint (5.4)	
6	1.24 d (6.6)	4.88 dq (6.6; 7.6)	1.07 d (7.0)	3.05 ddq (7.0; 7.0; 12.4)	10.31 s	10.14 s	3.92 s		4.22 d (12.4)
7a	1.41 d (6.2)	4.75 (J_{ab} = 6.2; J_{bc} = 6.0; J_{bd} = 10.2; J_{cd} = 14.0)	2.29	2.76		10.70 s	3.88 s		4.44 dd (9.0; 13.0)
7b	1.39 s	1.50 s	2.52 d (10.6)			10.64 s	3.87 s		4.68 t (10.6)
7c	1.23 d (6.6)	4.91 dq (6.6; 7.6)	1.06 d (7.0)	3.17 ddq (7.0; 7.0; 12.8)	10.78 s	10.52 s	3.91 s		4.30 d (12.8)
7d	1.37 s	1.51 s		2.47 d (10.8)		10.28 s	3.38 t (5.6)	1.84 quint (5.6)	4.60 t (10.8)
7e	1.20 d (6.6)	4.87 quint (6.6)	1.05 d (7.0)	3.17 ddq (7.0; 7.0; 13.0)	10.40 s	9.96 s	3.40 t (5.6)	1.86 quint (5.6)	4.27 d (13.0)

In the presence of bases **7a–e** are smoothly converted back to **1a–e**, but due to different substituents different bases have to be employed. Thus, **7b,c** are retransformed into **1b,c** by aqueous ammonia, while for **7a,d,e** much stronger bases, such as 1,5-diazabicyclo[3.4.0]non-5-ene (DBN) or methanolic potassium hydroxide, are to be employed.

The lactone IR absorption bands of all addition products **4a–c**, **5a–c**, **6**, and **7a–c** occur in the usual region (1744–1768 cm^{-1}). The ^1H NMR data are listed in Table 3. The signal between δ = 4.22 and 4.68 of **6** and **7a–c** splitted by the vicinal 4-H indicates that the protonation occurs at C-3; in D_2O a smooth deuterium exchange takes place. In all products derived from **1a** H^b, H^c, and H^d form an ABX-pattern as expected. The ^{13}C NMR data of some bromine addition compounds are listed in Table 2.

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Experimental Part

IR-spectra: Perkin-Elmer 157-G. – ^1H and ^{13}C NMR spectra: Bruker WH-90 and WM-250. – MS: MS-30 of the AEI. – Melting points: not corrected. – Elemental analyses: Analytical Laboratory of the Institute.

Methyl 3-[Tetrahydro-3-(2-imidazolin-2-yl)-5-methyl-2-oxo-3-furanyl]-(E)-propenoate (**2a**): A solution of 0.085 g (1.0 mmol) of methyl propiolate in 5 ml of benzene was dropped into the solution of 0.17 g (1.0 mmol) of **1a** in 20 ml of benzene; then the mixture was stirred at room temp. for 2 days. After removal of the solvent the product was obtained as a viscous oil (with dioxane as solvent the same results were obtained); no further purification was possible. – IR (film): 3380 (NH), 1760 (lactone C=O), 1720 (ester C=O), 1685, 1645, 1610 cm^{-1} (C=C, C=N). – MS: M^+ *m/e* = 252.

$C_{12}H_{16}N_2O_4$ (252.3) Calcd. C 57.13 H 6.39 N 11.11 Found C 56.83 H 6.53 N 10.70

Methyl 3-[Tetrahydro-3-(2-imidazolin-2-yl)-5,5-dimethyl-2-oxo-3-furanyl]-(E)-propenoate (**2b**): According to the procedure for **2a**, 0.50 g (94%) of **2b** is obtained from 0.36 g (2.0 mmol) of **1b** and 0.17 g (2.0 mmol) of methyl propiolate in benzene or dioxane solution; m.p. 120–124°C. – IR (KBr): 3150 (NH), 1762 (lactone C=O), 1725 (ester C=O), 1680, 1655, 1600 cm^{-1} (C=C, C=N). – MS: *m/e* = 266.

$C_{13}H_{18}N_2O_4$ (266.3) Calcd. C 58.63 H 6.81 N 10.52 **2b**: Found C 58.96 H 6.85 N 10.24
2c: Found C 58.30 H 6.82 N 10.75

Methyl 3-[Tetrahydro-3-(2-imidazolin-2-yl)-4,5-dimethyl-2-oxo-3-furanyl]-(E)-propenoate (**2c**):Like **2a** from 0.36 g (2.0 mmol) of **1c** and 0.17 g (2.0 mmol) of methyl propiolate in benzene or dioxane solution; **2c** is obtained as a viscous oil. – IR (film): 3380 (NH), 1762 (lactone C=O), 1722 (ester C=O), 1685, 1645, 1608 cm^{-1} (C=C, C=N). – MS: M^+ *m/e* = 266.

Methyl 3-[Tetrahydro-5,5-dimethyl-2-oxo-3-(1,4,5,6-tetrahydro-2-pyrimidinyl)-3-furanyl]-(E)-propenoate (**2d**): Like **2a** from 0.20 g (1.0 mmol) of **1d** and 0.085 g (1.0 mmol) of methyl propiolate in benzene or dioxane solution. Yield 0.26 g (93%), m.p. 108–112°C. – IR (KBr): 3210 (NH), 1760 (lactone C=O), 1722 (ester C=O), 1685, 1655, 1615 cm^{-1} (C=C, C=N). – MS: M^+ *m/e* = 280.

$C_{14}H_{20}N_2O_4$ (280.3) Calcd. C 59.98 H 7.19 N 10.00 **2d**: Found C 59.65 H 7.48 N 10.22
2e: Found C 59.61 H 7.49 N 10.19

Methyl 3-[Tetrahydro-4,5-dimethyl-2-oxo-3-(1,4,5,6-tetrahydro-2-pyrimidinyl)-3-furanyl]-(E)-propenoate (**2e**): Similar to **2a**, from 0.20 g (1.0 mmol) of **1e** and 0.085 g (1.0 mmol) of methyl propiolate in benzene or dioxane solution; yield 0.28 g (98%), m.p. 106–112°C. – IR (KBr): 3410, 3390 (NH), 1758 (lactone C=O), 1727 (ester C=O), 1642, 1630 cm^{-1} (C=C, C=N). – MS: M^+ *m/e* = 280.

Methyl 2,3,5,8-Tetrahydro-8-(2-hydroxypropyl)-5-oxoimidazo[1,2-a]pyridine-8-carboxylate (**3a**): A small amount of methanol was added to 0.25 g of the oily **2a**; after standing for some time a raw product crystallized, yield 0.24 g (96%), m.p. 177–180°C. – IR (KBr): 3150, 3084 (OH), 1735 (ester C=O), 1662 (amide C=O), 1560, 1540 cm^{-1} (C=C, C=N). – MS: M^+ *m/e* = 252.

$C_{12}H_{16}N_2O_4$ (252.3) Calcd. C 57.13 H 6.39 N 11.11 Found C 57.48 H 6.72 N 10.73

A mixture of 0.50 mmol of **1a** and 0.50 mmol of methyl propiolate in 5 ml of methanol was stirred at room temp. for 2 days. After removal of the solvent, a quantitative yield of **3a** was obtained; m.p. 179–182°C.

Methyl 2,3,5,8-Tetrahydro-8-(2-hydroxy-2-methylpropyl)-5-oxoimidazo[1,2-a]pyridine-8-carboxylate (**3b**): After standing of the methanolic solution of **2b** for some days or refluxing for 4 h, **3b** was obtained in quantitative yield; m.p. 145–152°C, from methylene chloride m.p. 154–157°C. – IR (KBr): 3150, 3090 (OH), 1738 (ester C=O), 1655 (amide C=O), 1560, 1540 cm^{-1} (C=C, C=N). – MS: M^+ *m/e* = 266.

$C_{13}H_{18}N_2O_4$ (266.3) Calcd. C 58.63 H 6.81 N 10.52 Found C 58.48 H 7.09 N 10.23

3b could be also directly obtained from **1b** and methyl propiolate in methanolic solution.

Methyl 3,4,6,9-Tetrahydro-9-(2-hydroxy-2-methylpropyl)-6-oxo-2H-pyrido[1,2-a]pyrimidine-9-carboxylate (**3d**): Refluxing the methanolic solution of **2d** for 6 h, **3d** was obtained in quantitative yield; m.p. 158–161°C. – IR (KBr): 3224, 3100 (OH), 1732 (ester C=O), 1645 (amide C=O), 1624, 1578, 1525 cm^{-1} (C=C, C=N). – MS: M^+ *m/e* = 280.

$C_{14}H_{20}N_2O_4$ (280.3) Calcd. C 59.98 H 7.19 N 10.00 **3d**: Found C 59.79 H 7.25 N 10.04
3e: Found C 59.38 H 7.17 N 10.00

3d was also directly obtained from **1d** and methyl propiolate in methanolic solution.

Methyl 3,4,6,9-Tetrahydro-9-(2-hydroxy-1-methylpropyl)-6-oxo-2H-pyrido[1,2-a]pyrimidine-9-carboxylate (**3e**): After refluxing of the methanolic solution of **2e** for 8 h, **3e** could not be obtained in pure state (lactone IR absorption was still present). Pure **3e** could be, however, directly obtained from 0.50 mmol of **1e** and 0.50 mmol of methyl propiolate in 5 ml of methanol, after stirring the mixture for 2 days at room temp.; the yield was quantitative, m.p. 182–185°C. – IR (KBr): 3210, 3100 (OH), 1740 (ester C=O), 1645 (amide C=O), 1630, 1572, 1520 cm^{-1} (C=C, C=N). – MS: M^+ *m/e* = 280.

Ethyl 2,3,5,8-Tetrahydro-8-(2-hydroxypropyl)-5-oxoimidazo[1,2-a]pyridine-8-carboxylate (**3f**): After refluxing of the ethanolic solution of **2a** for 6 h, **3f** was obtained in quantitative yield, m.p. 176–179°C, after recrystallization from methylene chloride m.p. 181–183°C. – IR (KBr): 3158, 3098 (OH), 1730 (ester C=O), 1660 (amide C=O), 1560, 1540 cm^{-1} (C=C, C=N). – MS: M^+ *m/e* = 266.

$C_{13}H_{18}N_2O_4$ (266.3) Calcd. C 58.63 H 6.81 N 10.52 Found C 58.35 H 6.76 N 10.51

Ethyl 2,3,5,8-Tetrahydro-8-(2-hydroxy-2-methylpropyl)-5-oxoimidazo[1,2-a]pyridine-8-carboxylate (**3g**): After refluxing of the ethanolic solution of **2b** for 6 h, **3g** was obtained in

quantitative yield; m.p. 169 – 171 °C (recryst. from ethanol). – IR (KBr): 3150, 3084 (OH), 1732 (ester C = O), 1652 (amide C = O), 1560, 1535 cm^{-1} (C = C, C = N). – MS: M^+ *m/e* = 280.

$C_{14}H_{20}N_2O_4$ (280.3) Calcd. C 59.98 H 7.19 N 10.00 **3g**: Found C 60.24 H 7.31 N 10.29
3h: Found C 59.51 H 7.02 N 10.07

Ethyl 2,3,5,8-Tetrahydro-8-(2-hydroxy-1-methylpropyl)-5-oxoimidazo[1,2-a]pyridine-8-carboxylate (**3h**): Like **3f** in quantitative yield; (8 h reflux); m.p. 176 – 178 °C (recryst. from methylene chloride). – IR (KBr): 3150, 3080 (OH), 1738 (ester C = O), 1648 (amide C = O), 1560, 1530 cm^{-1} (C = C, C = N). – MS: M^+ *m/e* = 280.

Ethyl 3,4,6,9-Tetrahydro-9-(2-hydroxy-2-methylpropyl)-6-oxo-2H-pyrido[1,2-a]pyrimidine-9-carboxylate (**3i**): Like **3h**, **3i** was obtained in quantitative yield in refluxing ethanol; m.p. (recryst. from methylene chloride) 138 – 142 °C. – IR (KBr): 3270, 3110 (OH), 1735 (ester C = O), 1648 (amide C = O), 1560, 1535 cm^{-1} (C = C, C = N). – MS: M^+ *m/e* = 294.

$C_{15}H_{22}N_2O_4$ (294.4) Calcd. C 61.20 H 7.54 N 9.52 **3i**: Found C 60.70 H 7.71 N 9.56
3j: Found C 59.64 H 7.32 N 9.16

Ethyl 3,4,6,9-Tetrahydro-9-(2-hydroxy-1-methylpropyl)-6-oxo-2H-pyrido[1,2-a]pyridine-9-carboxylate (**3j**): By refluxing the ethanolic solution of **2e** or by reacting **1e** with methyl propiolate in ethanol, pure **3j** was hardly obtained; always a semi-solid product was formed; for this reason the elemental analysis showed some deviation. – IR (KBr): 3270, 3110 (OH), 1738 (ester C = O), 1645 (amide C = O), 1580, 1530 cm^{-1} (C = C, C = N). – MS: M^+ *m/e* = 294.

2-(3-Bromotetrahydro-5-methyl-2-oxo-3-furanyl)-2-imidazolinium Bromide Hydrobromide (**4a**): 0.32 g (2.0 mmol) of bromine in 10 ml of CH_2Cl_2 was added dropwise to a solution of 0.34 g (2.0 mmol) of **1a** in 20 ml of CH_2Cl_2 while the mixture was stirred at 0 °C. After 0.5 h the reaction mixture was further stirred at 0 °C for 0.5 h, and then at ambient temp. for 1 h. After removal of the solvent the residue was recrystallized from ethanol. Yield 0.38 g (46%) of orange-yellow crystals with m.p. 120 – 123 °C. – IR (KBr): 3340, 3190, 3070, 2740 (NH, $=\overset{+}{N}H$), 1767 (lactone C = O), 1595 cm^{-1} (C = N). – MS: *m/e* = 246 [M – 2 HBr]$^+$.

$C_8H_{13}Br_3N_2O_2$ (409.0) Calcd. C 23.49 H 3.20 N 6.85 Found C 23.64 H 2.89 N 7.04

2-(3-Bromotetrahydro-5,5-dimethyl-2-oxo-3-furanyl)-3,4,5,6-tetrahydropyrimidinium Bromide Hydrobromide (**4b**): Using the same procedure as above, 0.27 g (62%) of **4b** was obtained as yellow crystals with m.p. 130 – 133 °C. – IR (KBr): 3320, 3202, 3110, 2700 (NH, $=\overset{+}{N}H$), 1744 (lactone C = O), 1650, 1600 cm^{-1} (C = N). – MS: *m/e* = 274 [M – 2 HBr]$^+$.

$C_{10}H_{17}Br_3N_2O_2$ (437.0) Calcd. C 27.48 H 3.92 N 6.41 **4b**: Found C 29.75 H 4.05 N 6.70
4c: Found C 27.89 H 3.80 N 6.50

2-(3-Bromotetrahydro-4,5-dimethyl-2-oxo-3-furanyl)-3,4,5,6-tetrahydropyrimidinium Bromide Hydrobromide (**4c**): Like **4a** from 1.0 mmol of **1e** and 1.0 mmol of bromide in CH_2Cl_2 solution; yield 0.40 g (91%), orange-red crystals, m.p. 80 – 83 °C. – IR (KBr): 3340, 3300, 3105, 2740 (NH, $=\overset{+}{N}H$), 1766 (lactone C = O), 1652, 1596 cm^{-1} (C = N). – MS: *m/e* = 356 [M – HBr]$^+$.

2-(3-Bromotetrahydro-5,5-dimethyl-2-oxo-3-furanyl)-2-imidazolinium Bromide (**5a**): Using the same procedure as above, 0.27 g (79%) of **5a** were obtained from 0.18 g (1.0 mmol) **1b** and 0.16 g (1.0 mmol) of bromine in CH_2Cl_2 solution; colourless crystals, m.p. 255 – 258 °C. – IR (KBr): 3300, 3200, 2740 (NH, $=\overset{+}{N}H$), 1760 (lactone C = O), 1610, 1590 cm^{-1} (C = N). – MS: *m/e* = 260 [M – HBr]$^+$.

$C_9H_{14}Br_2N_2O_2$ (342.1) Calcd. C 31.60 H 4.13 N 8.19 Found C 31.50 H 4.07 N 8.30

5a was also obtained from the reaction of **1b** with *N*-bromosuccinimide (NBS), as follows: 0.22 g (1.2 mmol) of NBS was added portionwise to a solution of 0.18 g (1.0 mmol) of **1b** in 10 ml of CH_2Cl_2 at room temperature. Then the mixture was stirred for additional 2 h at room temp. After removal of the solvent 0.20 g (59%) of **5a** were obtained.

2-(3-Chlorotetrahydro-5,5-dimethyl-2-oxo-3-furanyl)-2-imidazolinium Chloride (**5b**): Chlorine gas was passed at 0°C for 1 h into the solution of 0.18 g (1.0 mmol) of **1b** in 10 ml of CH_2Cl_2. After removal of the solvent the residue was recrystallized from ethanol; yield 0.13 g (52%), m.p. ca. 160°C (transformation into cubic plate crystals); 250–260°C sublimation. – IR (KBr): 3320, 3200, 2720 (NH, $=\overset{+}{N}H$), 1765 (lactone C=O), 1612, 1590 cm^{-1} (C=N). – MS: *m/e* = 216 $[M - HCl]^+$.

$C_9H_{14}Cl_2N_2O_2$ (253.1) Calcd. C 42.70 H 5.57 N 11.07 Found C 42.21 H 6.23 N 11.30

5b could also be obtained in 60% yield from **1b** and *N*-chlorosuccinimide (NCS) in CH_2Cl_2 solution following the same procedure as **1b** → **5a** in the presence of NBS.

2-(3-Chlorotetrahydro-5,5-dimethyl-2-oxo-3-furanyl)-3,4,5,6-tetrahydropyrimidinium Chloride (**5c**): Similar to **5b** from 0.20 g (1.0 mmol) of **1d** and chlorine. m.p. 160–170°C (transformation into another crystal form); 266–270°C melting. – IR (KBr): 3250, 3160, 3070, 2700 (NH, $=\overset{+}{N}H$), 1765 (lactone C=O), 1650, 1590 cm^{-1} (C=N). – MS: *m/e* = 230 $[M - HCl]^+$.

$C_{10}H_{16}Cl_2N_2O_2$ (267.2) Calcd. C 44.95 H 6.04 N 10.49 Found C 44.56 H 6.00 N 10.57

2-(Tetrahydro-4,5-dimethyl-2-oxo-3-furanyl)-2-imidazolinium Bromide (**6**): From 0.18 g (1.0 mmol) of **1c** and 0.16 g (1.0 mmol) of bromine in CH_2Cl_2 solution. Yield 0.17 g (65%), m.p. 232–235°C. – IR (KBr): 3220, 3080, 2760 (NH, $=\overset{+}{N}H$), 1760 (lactone C=O), 1600 cm^{-1} (C=N). – MS: *m/e* = 182 $[M - HBr]^+$.

$C_9H_{15}BrN_2O_2$ (263.1) Calcd. C 41.06 H 5.75 N 10.65 Found C 40.48 H 5.59 N 10.43

2-(Tetrahydro-5-methyl-2-oxo-3-furanyl)-2-imidazolinium Chloride (**7a**): A solution of 0.17 g (1.0 mmol) of **1a** and 10 drops of conc. hydrochloric acid in 10 ml of methanol was left at room temp. for 3 days. After removal of the solvent 0.20 g (98%) of **7a** were obtained as colorless crystals, m.p. 167–170°C. – IR (KBr): 3360, 3060, 2770 (NH, $=\overset{+}{N}H$), 1760 (lactone C=O), 1600 cm^{-1} (C=N). – MS: *m/e* = 168 $[M - HCl]^+$.

$C_8H_{13}ClN_2O_2$ (204.7) Calcd. C 46.95 H 6.40 N 13.69 Found C 46.28 H 6.34 N 13.60

7a could be converted back to **1a** by treatment with methanolic potassium hydroxide.

2-(Tetrahydro-5,5-dimethyl-2-oxo-3-furanyl)-2-imidazolinium Chloride (**7b**): From 0.18 g (1.0 mmol) of **1b** and 10 drops of conc. hydrochloric acid in methanol **7b** is obtained in quantitative yield; m.p. 239–243°C. – IR (KBr): 3230, 3090, 2780 (NH, $=\overset{+}{N}H$), 1760 (lactone C=O), 1610 cm^{-1} (C=N). – MS: *m/e* = 182 $[M - HCl]^+$.

$C_9H_{15}ClN_2O_2$ (218.7) Calcd. C 49.43 H 6.91 N 12.81 **7b**: Found C 48.88 H 7.10 N 12.69
7c: Found C 48.43 H 7.10 N 12.73

7b could be converted back to **1b** by treatment with 33% aqueous ammonia in methanolic solution.

2-(Tetrahydro-4,5-dimethyl-2-oxo-3-furanyl)-2-imidazolinium Chloride (**7c**): From 0.18 g (1.0 mmol) of **1c** and 10 drops of conc. hydrochloric acid in methanol; yield quantitative, m.p. 230–233°C. – IR (KBr): 3210, 3070, 2770 (NH, $=\overset{+}{N}H$), 1760 (lactone C=O), 1600 cm^{-1} (C=N). – MS: *m/e* = 182 $[M - HCl]^+$.

7c could be converted back to **1c** by treatment with 33% aqueous ammonia in methanolic solution.

2-(Tetrahydro-5,5-dimethyl-2-oxo-3-furanyl)-3,4,5,6-tetrahydropyrimidinium Chloride (**7d**): From 0.50 mmol of **1d** and 5 drops of conc. hydrochloric acid in methanol; **7d** was obtained in quantitative yield, m.p. 256–260°C. – IR (KBr): 3270, 3130, 2800 (NH, $=\overset{+}{N}H$), 1760 (lactone C=O), 1655, 1612 cm^{-1} (C=N). – MS: *m/e* = 196 $[M - HCl]^+$.

$C_{10}H_{17}ClN_2O_2$ (232.7) Calcd. C 51.61 H 7.37 N 12.04 **7d**: Found C 51.37 H 7.46 N 12.07
7e: Found C 51.29 H 7.10 N 11.94

7d could be converted back to **1d** by treatment with excess DBN in methanolic solution.

2-(Tetrahydro-4,5-dimethyl-2-oxo-3-furanyl)-3,4,5,6-tetrahydropyrimidinium Chloride (**7e**): Like **7d** from **1e** in quantitative yield, m.p. 224–227°C. – IR (KBr): 3280, 3150, 2820 (NH, $=\overset{+}{N}H$), 1768 (lactone C=O), 1655, 1614 cm^{-1} (C=N). – MS: *m/e* = 196 $[M - HCl]^+$.

7e could be converted back to **1e** by treatment with excess DBN or potassium hydroxide in methanolic solution.

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