The Synthesis of Some Dialkyl 4-(3-Substituted amino)phenyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylates

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Dialkyl 4-(3-aminophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylates **1** were transformed into alkyl 4-(3-(((2-benzoylamino-2-methoxycarbonyl)ethenyl)amino)phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylates **4** and with 2,2-disubstituted-1-dimethylaminoethenes **7** into dimethyl 4-(3-(((2,2-diacyl- or 2-acyl-2-alkoxycarbonyl)ethenyl)amino)phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylates **8** and their ethyl methyl analogues **9**.

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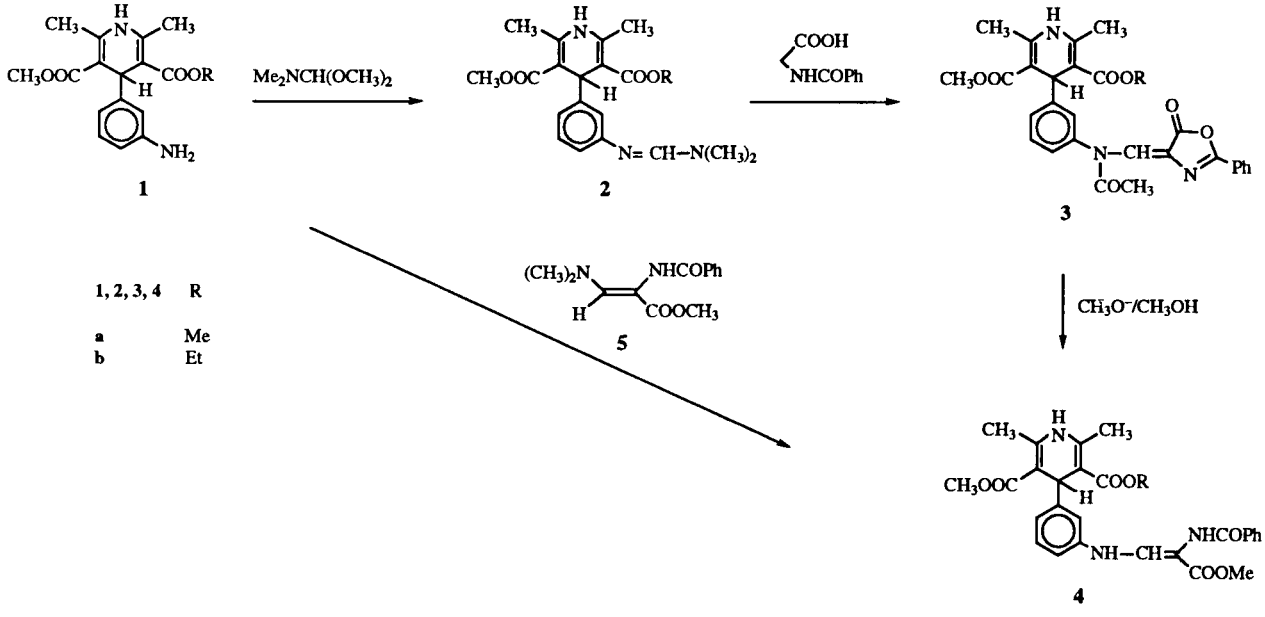
Dimethyl 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-pyridine-3,5-dicarboxylate was introduced in 1975 in medicinal praxis as the first calcium antagonist of the dihydropyridine type. Since then, this type of compounds has been the object of intensive studies in recent years, and many of them are used for the treatment of hypertension and other cardiovascular disorders [1].

In this paper we describe some transformations of dimethyl and ethyl methyl 4-(3-aminophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylates **1**, prepared from the corresponding nitro derivatives by catalytic hydrogenation as described earlier [2], and further transformed into derivatives with various substituents, such as substituted unsaturated amino acid or keto acid residue, attached to the amino group.

Compounds **1** were transformed with *N,N*-dimethylformamide dimethyl acetal into dimethyl (**2a**) and ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-(dimethylamino)methyleneamino)pyridine-3,5-dicarboxylate (**2b**). These compounds gave with hippuric acid in the presence of acetic anhydride the corresponding dimethyl (**3a**) and ethyl methyl 4-(3-(acetyl-((2-phenyl-5-oxooxazolinyl-4)methylene)amino)-phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**3b**). By treatment of the compound **3** with sodium methoxide in methanol the oxazolinyl part of the molecule was cleaved to give the corresponding dimethyl (**4a**) and ethyl methyl 4-(3-(((2-benzoylamino-2-methoxycarbonyl)-ethenyl)amino)phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**4b**) in 11% and 10% yield, respectively. The same compounds were also prepared from **1a** or **1b** and methyl (*Z*)-2-benzoylamino-3-dimethylaminopropenoate (**5**) in acetic acid at room temperature in 44% and 54% yield, respectively (Scheme 1).

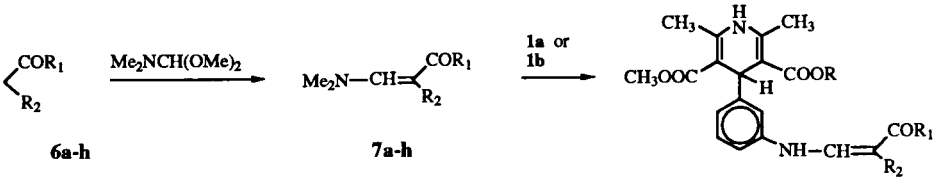
Since this alternative route resulted in better yields, various 2,2-disubstituted-1-dimethylaminoethenes [3], such as 1,1-diacetyl-2-dimethylaminoethene (**7a**) [4], methyl 2-acetyl-3-dimethylaminopropenoate (**7b**) and its ethyl ester analog (**7c**) [5,6], isopropyl 2-acetyl-3-dimethylaminopropenoate (**7d**), 2-methoxyethyl 2-acetyl-3-dimethylaminopropenoate (**7e**),

Scheme 1



1-acetyl-1-benzoyl-2-dimethylaminoethene (**7f**) [7], ethyl 2-benzoyl-3-dimethylaminopropenoate (**7g**) [7], and ethyl 1-(dimethylamino)-2-ethoxycarbonylpropenoate (**7h**) [8], were prepared. When the compounds **1** were treated with compounds **7** either in ethanol in the presence of hydrochloric acid or in acetic acid, the corresponding dimethyl (**8**) or ethyl methyl 4-(3-((2,2-disubstituted ethenyl)amino)-phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylates (**9**) were formed. The following compounds were prepared in this manner: dimethyl 4-(3-(((2,2-diacetyl)ethenyl)-amino)phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**8a**), dimethyl 4-(3-(((2-acetyl-2-methoxycarbonyl)ethenyl)amino)phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**8b**), dimethyl 4-(3-(((2-acetyl-2-ethoxycarbonyl)ethenyl)amino)phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**8c**), dimethyl 4-(3-(((2-acetyl-2-isopropoxycarbonyl)ethenyl)amino)phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**8d**), dimethyl 4-(3-(((2-acetyl-2-(2-methoxyethoxy)carbonyl)-ethenyl)amino)phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**8e**), dimethyl 4-(3-(((2-acetyl-2-benzoyl)ethenyl)amino)-phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**8f**), dimethyl 4-(3-(((2-benzoyl-2-ethoxycarbonyl)ethenyl)amino)phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**8g**), dimethyl 4-(3-(((2,2-diethoxycarbonyl)ethenyl)amino)phenyl)-1,4-dihydro2,6-dimethylpyridine-3,5-dicarboxylate (**8h**), ethyl methyl 4-(3-(((2,2-di-acetyl)ethenyl)amino)phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**9a**), ethyl methyl 4-(3-(((2-acetyl-2-methoxycarbonyl)ethenyl)-amino)phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**9b**), ethyl methyl 4-(3-(((2-acetyl-2-ethoxycarbonyl)ethenyl)amino)phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**9c**), ethyl methyl 4-(3-(((2-acetyl-2-isopropoxycarbonyl)ethenyl)amino)phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**9d**), ethyl methyl 4-(3-(((2-acetyl-2-methoxyethoxycarbonyl)ethenyl)-amino)phenyl)-1,4-dihydro-2,6-di-methylpyridine-3,5-dicarboxylate (**9e**), ethyl methyl 4-(3-(((2-acetyl-2-benzoyl)-ethenyl)amino)phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**9f**), ethyl methyl 4-(3-(((2-benzoyl-2-ethoxycarbonyl)ethenyl)amino)phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**9g**), ethyl methyl 4-(3-(((2,2-diethoxycarbonyl)ethenyl)amino)phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**9h**) (Scheme 2).

Scheme 2



6a-h **7a-h** **8a-h** **9a-h**

6, 7	R^1	R^2
a	Me	COMe
b	Me	COOMe
c	Me	COOEt
d	Me	COO-*i*-Pr
e	Me	$COOCH_2CH_2OMe$
f	Me	COPh
g	Ph	COOEt
h	OEt	COOEt

	R	R^1	R^2
8a	Me	Me	COMe
8b	Me	Me	COOMe
8c	Me	Me	COOEt
8d	Me	Me	COO-*i*-Pr
8e	Me	Me	$COOCH_2CH_2OMe$
8f	Me	Me	COPh
8g	Me	Ph	COOEt
8h	Me	OEt	COOEt
9a	Et	Me	COMe
9b	Et	Me	COOMe
9c	Et	Me	COOEt
9d	Et	Me	COO-*i*-Pr
9e	Et	Me	$COOCH_2CH_2OMe$
9f	Et	Me	COPh
9g	Et	Ph	COOEt
9h	Et	OEt	COOEt

Table 1
^{1}H NMR Chemical Shifts for Protons at the Substituted Amino Group for Compounds **8** and **9**

Compound	δ_1 (ppm)	δ_2 (ppm)	Ratio (*Z*:*E*)
8d	11.00	12.62	traces of Z
8e	10.71	12.15	1:11
8g	10.60	11.55	4:5
9b	10.56	12.48	1:5
9d	10.72	12.45	1:5
9e	10.40	12.48	1:6

δ_1, δ_2 -Chemical shift for amino group and ratio of integrals for signals of (*Z*)- and (*E*)-isomers.

The structures of all new compounds were determined by ^{1}H nmr spectra, elemental analyses for C, H, and N, and most of them also with mass spectra. The magnitude of coupling constants, $J_{NHCH} = 13$ Hz, indicates the *trans* orientation of protons in CHNH group. Beside this, two sets of signals for the side amino group protons are observed in high resolution (300 MHz) spectra for some compounds indicating that both, (*Z*)- and (*E*)-, orientations around the

Table 2

Physical and Analytical Data for Compounds **8** and **9**

Compound	Method	Yield (%)	Mp (°) (Solvent)	Molecular Formula (Molecular Weight)	Analysis (%) Calcd./Found C	H	N
8a	A	92.7	215-218 (Methanol/acetic acid)	$C_{23}H_{26}N_2O_6$ (426.18)	64.78 64.75	6.15 6.09	6.57 6.43
8b	A	91.6	188-189 (Methanol/acetic acid)	$C_{23}H_{26}N_2O_7$ (442.17)	62.42 62.69	5.93 5.70	6.33 6.14
8c	A	71.2	151-154 (Ethanol)	$C_{24}H_{28}N_2O_7$ (456.19)	63.15 63.26	6.18 6.04	6.14 5.99
8d	A	88.2	188-190 (Ethanol)	$C_{25}H_{30}N_2O_7$ (470.21)	63.80 63.97	6.43 6.82	5.96 5.90
8e	A	61.7	138-140 (Isopropanol)	$C_{25}H_{30}N_2O_8$ (486.20)	61.70 61.67	6.22 6.50	5.76 5.76
8f	A	53.3	190-192 (Toluene)	$C_{28}H_{28}N_2O_6$ (488.20)	68.82 68.75	5.78 5.64	5.74 5.53
8g	A	39.6	138-141 (Ethanol)	$C_{29}H_{30}N_2O_7$ (518.21)	67.15 67.46	5.83 6.24	5.40 5.42
8h	B	47.3	165-166 (Ethyl acetate)	$C_{25}H_{30}N_2O_8$ (486.52)	61.72 62.07	6.22 6.07	5.76 5.63
9a	B	27.2	137-141 (Ethanol)	$C_{24}H_{28}N_2O_6$ (440.50)	65.44 65.07	6.41 6.60	6.36 6.24
9b	A	88.7	158-160 (Ethanol/acetic acid)	$C_{24}H_{28}N_2O_7$ (456.50)	63.15 63.20	6.18 5.98	6.14 5.84
9c	B	13.8	127-129 (Ethanol)	$C_{25}H_{30}N_2O_7$ (470.53)	63.82 64.07	6.43 6.50	5.95 5.71
9d	B	89.2	158-159 (Ethanol)	$C_{26}H_{32}N_2O_7$ (484.22)	64.45 64.43	6.66 6.87	5.78 5.66
9e	A	71.0	132-135 (Ethanol)	$C_{26}H_{32}N_2O_8$ (500.213)	62.37 62.21	6.45 6.50	5.60 5.69
9f	A	28.9	150-153 (Ethanol)	$C_{29}H_{30}N_2O_6$ (502.21)	69.29 69.17	6.02 6.42	5.58 5.49
9g	A	69.5	176-179 (Ethanol)	$C_{30}H_{32}N_2O_7$ (532.22)	67.64 67.80	6.06 6.40	5.26 5.22
9h	B	83.9	168-170 (Ethanol)	$C_{26}H_{32}N_2O_8$ (500.22)	62.37 62.47	6.45 6.27	5.60 5.51

double bond are present. The signals in nmr spectra for that amino group for compounds **8a** and **9a**, both diacyl substituted at ethenyl group, occur at δ = 12.46 and δ = 12.50 ppm, respectively. On the other hand the signals for the same groups in compounds **8h** and **9h** occur at δ = 10.64 and δ = 10.70 ppm, respectively. On this basis it could be concluded that the chemical shift for the amino group depends on the strenght of the hydrogen bonding with carbonyl oxygen and that it is stronger in the case of keto than in alkoxycarbonyl group. From chemical shifts and the ratios of integrals for derivatives with different substitutents could be concluded that isomers with stronger hydrogen bonding (*E*-form) are predominant (see Table 1).

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^1H nmr spectra were obtained on a Varian VXR-300 or Varian 360 L spectrometers respectively, ir spectra on a Perkin-Elmer 1310 instrument, and microanalyses for C, H, and N on a Perkin-Elmer Analyser 2400. Mass spectra were recorded on a VG-Analytical Autospec Q.

The following compounds were prepared according to the procedures described in the literature: dimethyl 4-(3-aminophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**1a**) [9], ethyl methyl 4-(3-aminophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**1b**) [2], dimethyl 4-(3-(dimethylaminomethyleneamino)phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**2**) [2], and methyl (*Z*)-2-benzoylamino-3-dimethylaminopropenoate (**5**) [10], 1,1-diacetyl-2-dimethylaminoethene (**7a**) [4], methyl 2-acetyl-3-dimethylaminopropenoate (**7b**) and its ethyl ester analog **7c** [5,6], 1-acetyl-1-benzoyl-2-dimethylaminoethene (**7f**) [7], ethyl 2-benzoyl-3-dimethylaminopropenoate (**7g**) [7], and ethyl 1-(dimethylamino)-2-ethoxycarbonylpropenoate (**7h**) [8].

The Synthesis of Dimethyl and Ethyl Methyl 4-(3-(Acetyl((2-phenyl-5-oxooxazolinyl-4)methylene)amino)phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylates **3**.

General Procedure.

A mixture of compound **2** (2 mmoles), hippuric acid (0.36 g, 2 mmoles) and acetic anhydride (5 ml) was heated under reflux for 4 hours. The mixture was then left overnight at room temperature. The solid precipitate was collected by filtration.and recrystallized from the mixture of ethanol and chloroform.

Table 3

Spectral Data for Compounds **8** and **9**

Compound	^{1}H-NMR (DMSO-d_6) δ (ppm)	Mass Spectra (EI) m/z, (% intensity)
8a [a]	2.28 (6H, s, 2x Het-CH_3), 2.36 (3H, s, $COCH_3$), 2.40 (3H, s, $COCH_3$), 3.57 (6H, s, 2x $COOCH_3$), 4.93 (1H, s, C*H*-Ph), 6.9-7.4 (4H, m, Ph), 8.33 (1H, d, J 13Hz, NH-C*H*=C), 8.96 (1H, br s, cycl. NH), 12.46 (1H, d, J 13 Hz, N*H*-CH=C)	426 (12, M^+), 367 (5), 238 (8), 224 (100)
8b [b]	2.30 (6H, s, 2x Het-CH_3), 2.40 (3H, s, $COCH_3$), 3.60 (6H, s, 2x $COOCH_3$), 3.70 (3H, s, C=C-$COOCH_3$), 4.95 (1H, s, C*H*-Ph), 6.9-7.4 (4H, m, Ph), 8.40 (1H, d, J 13 Hz, NH-C*H*=C), 8.95 (1H, br s, cycl. NH), 12.45 (1H, d, J 13 Hz, N*H*-CH=C)	
8c [b, d]	1.30 (3H, t, $COOCH_2CH_3$), 2.30 (6H, s, 2x Het-CH_3), 2.40 (3H, s, $COCH_3$), 3.60 (6H, s, 2x $COOCH_3$), 4.20 (2H, q, $COOCH_2CH_3$), 4.95 (1H, s, C*H*-Ph), 6.9-7.5 (4H, m, Ph), 8.40 (1H, d, J 13Hz, NH-C*H*=C), 8.95 (1H, br s, cycl. NH), 12.45 (1H, d, J 13 Hz, N*H*-CH=C)	457 (57, M^++1), 411 (8), 335 (5), 233 (6), 224 (100)
8d [c]	1.32 (6H, d, J 6 Hz, $CH(CH_3)_2$), 2.35 (6H, s, 2x Het-CH_3), 2.55 (3H, s, $COCH_3$), 3.66 (6H, s, 2x $COOCH_3$), 5.02 (1H, s, C*H*-Ph), 5.15 (1H, p, J 6 Hz, $CH(CH_3)_2$), 6.9-7. 4 (4H, m, Ph), 8.44 and 8.60 (traces) (1H, d, J 13 Hz, NH-C*H*=C), 6.03 (1H, br s, cycl. NH), 11.00 and 12.62 (traces) (1H, d, J 13 Hz, N*H*-CH=C)	470 (6, M^+), 411 (5), 351 (4), 247 (9), 224 (100)
8e [c]	2.35 (6H, s, 2x Het-CH_3), 2.56 (3H, s, $COCH_3$), 3.42 (3H, s, OCH_3), 3.66 (6H, s, 2x $COOCH_3$), 3.69 (2H, t, J 4.8 Hz, OCH_2CH_2OCO), 4.35 and 4.42 (ratio 11:1, 2H, t, J 4.8 Hz, OCH_2CH_2OCO), 5.01 (1H, s, C*H*-Ph), 6.05 and 6.15 (ratio 1:11, 1H, br s, cycl. NH), 6.95-7.30 (4H, m, Ph), 8.49 and 8.63 (ratio 11:1, 1H, d, J 13 Hz, NH-C*H*=C), 10.71 and 12.15 (ratio 1:11, 1H, d, J 13 Hz, N*H*-CH=C)	486 (6, M^+), 427 (3), 411 (4), 351 (6), 263 (12), 224 (100)
8f [b]	2.25 (6H, s, 2x Het-CH_3), 2.40 (3H, s, $COCH_3$), 3.45 (6H, s, 2x $COOCH_3$), 4.95 (1H, s, C*H*-Ph), 6.8-7.4 (4H, m, Ph), 7.5-7.8 (5H, m, COPh), 7.80 (1H, d, J 13 Hz, NH-C*H*=C), 8.90 (1H, br s, cycl. NH), 12.40 (1H, d, J 13 Hz, N*H*-CH=C)	488 (11, M^+), 429 (5), 265 (12), 224 (100)
8g [a]	0.90 and 0.95 (3H, t, J 7 Hz, $COOCH_2CH_3$), 2.27 and 2.29 (6H, s, 2x Het-CH_3), 3.55 and 3.58 (ratio 5:4, 6H, s, 2x $COOCH_3$), 3.95 and 4.02 (2H, q, J 7 Hz, $COOCH_2CH_3$), 4.91 and 4.94 (ratio 5:4, 1H, s, C*H*-Ph), 6.9-7.6 (9H, m, Ph, COPh), 8.10 and 8.35 (ratio 4:5, 1H, d, J 13 Hz, NH-C*H*=C), 8.94 and 8.96 (ratio 4:5, 1H, br s, cycl. NH), 10.60 and 11.55 (ratio 4:5, 1H, d, J 13 Hz, N*H*-CH=C)	518 (10, M^+), 295 (25), 249 (9), 224 (100)
8h [a, d]	1.24 (3H, t, J 7, $COOCH_2CH_3$), 1.26 (3H, t, J 7 Hz, $COOCH_2CH_3$), 2.28 (6H, s, 2x Het-CH_3), 3.57 (6H, s, 2x $COOCH_3$), 4.12 (2H, q, J 7 Hz, $COOCH_2CH_3$), 4.20 (2H, q, J 7 Hz, $COOCH_2CH_3$), 4.92 (1H, s, C*H*-Ph), 6.9-7.3 (4H, m, Ph), 8.32 (1H, d, J 13 Hz, NH-C*H*=C),8.96 (1H, br s,cycl. NH), 10.64 (1H, d, J 13 Hz, N*H*-CH=C)	487 (49, M^++1), 441 (34), 365 (9), 307 (6), 263 (8), 224 (100)
9a [b]	1.15 (3H, t, J 7 Hz, $COOCH_2CH_3$), 2.30 (6H, s, 2x Het-CH_3), 2.40 (3H, s, $COCH_3$), 2.45 (3H, s, $COCH_3$), 3.55 (3H, s, $COOCH_3$), 4.05 (2H, q, J 7 Hz, $COOCH_2CH_3$), 4.95 (1H, s, C*H*-Ph), 6.9-7.5 (4H, m, Ph), 8.35 (1H, d, J 13 Hz, NH-C*H*=C), 8.90 (1H, br s, cycl. NH), 12.50 (1H, d, J 13 Hz, N*H*-CH=C)	440 (9, M^+), 367 (3), 238 (100)
9b [a]	1.16 (3H, t, J 7 Hz, $COOCH_2CH_3$), 2.29 (6H, s, 2x Het-CH_3), 2.40 (3H, s, $COCH_3$), 3.56 (3H, s, $COOCH_3$), 3.70 (3H, s, =C-$COOCH_3$), 4.05 (2H, m, J 7 Hz, $COOCH_2CH_3$), 4.90 (1H, s, C*H*-Ph), 6.9-7.4 (4H, m, Ph), 8.36 and 8.40 (1H, d, J 13 Hz, NH-C*H*=C), 8.94 (1H, br s, cycl. NH), 10.56 and 12.48 (ratio 1:5, 1H, d, J 13 Hz, N*H*-CH=C)	
9c [b]	1.20 (3H, t, J 7 Hz, $COOCH_2CH_3$), 1.30 (3H, t, J 7 Hz, $COOCH_2CH_3$), 2.30 (6H, s, 2x Het-CH_3), 2.45 (3H, s, $COCH_3$), 3.60 (3H, s, $COOCH_3$), 4.05 (2H, m, $COOCH_2CH_3$), 4.20 (2H, m, $COOCH_2CH_3$), 4.95 (1H, s, C*H*-Ph), 6.9-7.5 (4H, m, Ph),8.40 (1H, d, J 13 Hz, NH-C*H*=C), 8.95 (1H, br s, cycl. NH), 12.50 (1H, d, J 13 Hz, N*H*-CH=C)	
9d [a]	1.16 (3H, t, J 7 Hz, $COOCH_2CH_3$), 1.28 (6H, d, J 6 Hz, $COOCH_2(CH_3)_2$), 2.28 and 2.29 (6H, s, 2x Het-CH_3), 2.42 (3H, s, $COCH_3$), 3.56 (3H, s, $COOCH_3$), 4.05 (4H, m, $COOCH_2CH_3$), 4.91 (1H, s, C*H*-Ph), 5.02 (1H, s, $COOCH(CH_3)_2$), 6.95-7.35 (4H, m, Ph), 8.34 and 8.38 (1H, d, J 13 Hz, NH-C*H*=C), 8.93 (1H, br s, cycl. NH), 10.72 and 12.45 (ratio 1:5, 1H, d, J 13 Hz, N*H*-CH=C)	484 (6, M^+), 425 (4), 247 (6), 238 (100)
9e [a, d]	1.15 (3H, t, J 7 Hz, $COOCH_2CH_3$), 2.28 (6H, s, 2x Het-CH_3), 2.43 (3H, s, $COCH_3$), 3.30 (3H, s, OCH_3), 3.56 (3H, s, $COOCH_3$), 3.63 (2H, t, J 4.8 Hz, OCH_2CH_2OCO), 4.02 (2H, m, $COOCH_2CH_3$), 4.25 (2H, t, J 4.8 Hz, OCH_2CH_2OCO), 4.90 (1H, s, C*H*-Ph), 6.95-7.35 (4H, m, Ph), 8.38 and 8.42 (1H, d, J 13 Hz, NH-C*H*=C), 8.92 (1H, br s, cycl. NH), 10.40 and 12.48 (ratio 1:6, 1H, d, J 13 Hz, N*H*-CH=C)	501 (64, M^++1), 425 (10), 263 (8), 238 (100)
9f [b]	1.15 (3H, t, J 7 Hz, $COOCH_2CH_3$), 2.25 (6H, s, 2x Het-CH_3), 2.40 (3H, s, $COCH_3$), 3.55 (3H, s, $COOCH_3$), 3.95 (2H, q, J 7 Hz, $COOCH_2CH_3$), 4.90 (1H, s, C*H*-Ph), 6.8-7.4 (4H, m, Ph), 7.5-7.75 (5H, m, COPh), 7.85 (1H, d, J 13 Hz, NH-C*H*=C), 8.85 (1H, br s, cycl. NH), 12.50 (1H, d, J 13 Hz, N*H*-CH=C)	502 (8, M^+), 429 (3), 265 (6), 238 (100)
9g [a]	0.90 and 0.95 (3H, t, J 7 Hz, $COOCH_2CH_3$), 1.14 and1.16 (3H, t, J 7 Hz, $COOCH_2CH_3$), 2.28 (6H, s, 2x Het-CH_3), 3.54 and 3.56 (ratio 4:6, 3H, s, $COOCH_3$), 3.6-4.3 (4H, m, 2x $COOCH_2CH_3$), 4.89 and 4.91 (ratio 4:6, 1H, s, C*H*-Ph), 6.9-7.6 (9H, m, Ph, COPh), 8.10 and 8.36(ratio 4:6, 1H, d, J 13 Hz, NH-C*H*=C), 8.90 and 8.93 (ratio 4:6, 1H, br s, cycl. NH), 10.59 and 11.58 (ratio 4:6, 1H, d, J 13 Hz, N*H*-CH=C)	532 (7, M^+), 295 (18), 249 (7), 238 (100)
9h [b]	1.1-1.5 (9H, t, 3x $COOCH_2CH_3$), 2.30 (6H, s, 2x Het-CH_3), 3.60 (3H, s, $COOCH_3$), 3.9-4.5 (6H, m, 3x $COOCH_2CH_3$), 4.95 (1H, s, C*H*-Ph), 6.9-7.4 (4H, m, Ph), 8.35 (1H, d, J 12 Hz, NH-CH=C), 8.90 (1H, br s, cycl. NH), 10.70 (1H, d, J 12 Hz, NH-CH=C)	

Notes: [a] nmr at 300MHz in DMSO-d_6. [b] nmr at 60MHz in DMSO-d_6. [c] nmr at 300MHz in $CDCl_3$. [d] ms FAB method.

Dimethyl 4-(3-(Acetyl((2-phenyl-5-oxooxazolinyl-4)methylene)amino)phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**3a**).

This compound was prepared from **1a** in 69% yield, mp 271-273°; ^{1}H nmr (DMSO-d_6, 60 MHz): δ 2.00 (3H, s, $COCH_3$), 2.20 (6H, s, 2x Het-CH_3), 3.40 (6H, s, 2x $COOCH_3$), 4.90 (1H, s, C*H*-Ph), 7.0-7.5 (9H, m, 2 x Ph), 8.10 (1H, s, N-C*H*=C), 8.8 (1H, br s, cycl. NH).

Anal. Calcd. for $C_{29}H_{27}N_3O_7$: C, 65.77; H, 5.14; N, 7.94. Found: C, 65.54; H, 5.13; N, 7.85.

Ethyl Methyl 4-(3-(Acetyl((2-phenyl-5-oxooxazolinyl-4)methylene)amino)phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**3b**).

This compound was prepared from **1b** in 69% yield, mp 252-254°; ^{1}H nmr (DMSO-d_6, 300 MHz): δ 1.05 (3H, t, J 7 Hz, $COOCH_2CH_3$), 2.03 (3H, s, $COCH_3$), 2.25 (6H, s, 2x Het-CH_3), 3.39 (3H, s, $COOCH_3$), 3.81 (2H, q, J 7 Hz, $COOCH_2CH_3$), 4.91 (1H, s, C*H*-Ph), 7.1-7.2 and 7.3-8.05 (9H, m, 2 x Ph), 8.1 (1H, s, N-C*H*=C), 8.68 (1H, br s, cycl. NH).

Anal. Calcd. for $C_{30}H_{29}N_3O_7$: C, 66.29; H, 5.38; N, 7.73. Found: C, 66.12; H, 5.24; N, 7.85.

The Synthesis of Dimethyl and Ethyl Methyl 4-(3-(((2-Benzoylamino-2-methoxycarbonyl)ethenyl)amino)phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylates **4**.

General Procedure. Method A.

Sodium (23 mg, 1 mmole) was dissolved in methanol (10 ml). After addition of compound **3** (0.75 mmoles) the mixture was stirred for one hour at room temperature. The volatile components were evaporated *in vacuo*. The residue was extracted with methylene chloride (10 ml) and water (5 ml) at *p*H 6 (adjusted with 1 *M* hydrochloric acid). Methylene chloride solution was then dried over sodium sulfate, evaporated to the solid residue and recrystallized from ethanol to give compound **4**.

Dimethyl 4-(3-(((2-Benzoylamino-2-methoxycarbonyl)ethenyl)amino)phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**4a**).

This compound was prepared from **3b** in 11% yield, mp 212-216° (mp 215-218°, from ethanol, prepared by Method B); ir spectrum was identical with the spectrum of the substance prepared by Method B.

Ethyl Methyl 4-(3-(((2-Benzoylamino-2-methoxycarbonyl)ethenyl)amino)phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**4b**).

This compound was prepared from **3b** in 10% yield, mp 162-165° (mp 168-171°, from ethyl acetate, prepared by Method B); ir and ms spectra were identical with the spectrum of the substance prepared by Method B.

The Synthesis of Dimethyl and Ethyl Methyl 4-(3-(((2-Benzoylamino-2-methoxycarbonyl)ethenyl)amino)phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**4**).

General Procedure. Method B.

A mixture of compound **5** (0.50 g, 2 mmoles), amine **1** (2 mmoles) and acetic acid (5 ml) was stirred at room temperature for 4 hours. The volatile components were evaporated *in vacuo*. To the oily residue ethanol (4 ml) was added and left in cold overnight. The precipitate was collected by filtration to give compound **4**.

Dimethyl 4-(3-(((2-Benzoylamino-2-methoxycarbonyl)ethenyl)-amino)phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**4a**).

This compound was prepared from amine **1a** in 44% yield, mp 215-218° (from ethanol); ^{1}H nmr (DMSO-d_6, 60 MHz): 2.30 (6H, s, 2x Het-CH_3), 3.60 (6H, s, 2x $COOCH_3$), 3.65 (3H, s, C=C-$COOCH_3$), 4.90 (1H, s, C*H*-Ph), 6.6-8.2 (10H, m, 2x Ph, CH=C), 8.8-9.2 (3H, m, 3x NH).

Anal. Calcd. for $C_{28}H_{29}N_3O_7$: C, 64.71; H, 5.63; N, 8.09. Found: C, 64.64; H, 5.42; N, 8.30.

Ethyl Methyl 4-(3-(((2-Benzoylamino-2-methoxycarbonyl)-ethenyl)amino)phenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridine-dicarboxylate (**4b**).

This compound was prepared from amine **1b** in 54% yield, mp 168-171° (from ethanol); ^{1}H nmr (DMSO-d_6, 60 MHz): δ 1.15 (3H, t, J 7 Hz, $COOCH_2CH_3$), 2.30 (6H, s, 2x Het-CH_3), 3.55 (3H, s, $COOCH_3$), 3.65 (3H, s, C=C-$COOCH_3$), 4.05 (2H, q, J 7 Hz, $COOCH_2CH_3$), 4.90 (1H, s, C*H*-Ph), 6.7-8.2 (10H, m, 2x Ph, CH=C), 8.7-9.2 (3H, m, 3x NH); ms: (EI) m/z = 533.5 (M^+, 24%), 296 (10%), 238 (100%).

Anal. Calcd. for $C_{29}H_{31}N_3O_7$: C, 65.26; H, 5.86; N, 7.88. Found: C, 65.54; H, 5.64; N, 8.20.

The Synthesis of 2,2-Disubstituted-1-dimethylaminoethenes **7**.

General Procedure.

To a mixture of dicarbonyl compound **6a-h** (25 mmoles) and chloroform (20 ml) *N,N*-dimethylformamide dimethyl acetale (27.5 mmoles, 3.7 ml) was added. The mixture was heated under reflux for 1 hour. The volatile components were removed by evaporation *in vacuo* to gave oily or solid compound. All these substances were used without further purification for preparation of **8a-h** and **9a-h**.

The Synthesis of Dimethyl and Ethyl Methyl 4-(3-((2,2-Disubstituted-ethenyl)amino)phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylates **8** and **9**.

General Procedure A.

To a mixture of amine **1** (2 mmoles), dimethylaminoethene derivatives **7** (3 mmoles), and ethanol (5 ml) a few drops of concentrated hydrochloric acid were added and stirred at room temperature overnight. Then the solid was collected by filtration or volatile components removed *in vacuo* and an appropriate solvent (2-3 ml) was added for crystallization of the products. For the analyses the product were recrystallized from the same solvent.

General Procedure B.

A mixture of amine **1** (2 mmoles), dimethylaminoethene derivatives **7** (3 mmoles), and acetic acid (5 ml) was stirred at room temperature overnight. The volatile components were removed by evaporation *in vacuo* and the solvent (2-3 ml) was added. Then the solid was collected by filtration and recrystallized for analyses.

Experimental details are given in Tables 2 and 3.

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