The Synthesis of 5-Substituted 3-Benzoylamino-6-(2-substituted amino-1-ethenyl)-2*H*-pyran-2-ones and Their Transformations into 2*H*-Pyrano[3,2-*c*]pyridine Derivatives

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Dedicated to the memory of the late Professor Nicholas Alexandrou, Aristotelian University of Thessaloniki

A new approach to the 2*H*-pyrano[3,2-*c*]pyridine system is described. 5,6-Disubstituted 3-benzoylamino-2*H*-pyran-2-ones **3a,b**, prepared from the corresponding 1,3-dicarbonyl compounds **1a,b** and methyl (*Z*)-2-benzoylamino-3-dimethylaminopropenoate (**2**), were converted into 3-benzoylamino-6-(2-dimethylamino-1-ethenyl)-5-ethoxycarbonyl-2*H*-pyran-2-one (**4a**) and 5-acetyl derivative **4b**. The exchange of the dimethylamino group in **4a,b** with aromatic amines **5a-f,m**, heteroaromatic amines **5g-i**, and benzylamines **5j-l** produced 5-ethoxycarbonyl-3-benzoylamino-6-(2-arylamino- or heteroarylamino- or benzylamino-1-ethenyl)-2*H*-pyran-2-ones **6a-l**, and its 5-acetyl analog **6m**. The compounds **6** were cyclized in basic media into 2*H*-pyrano[3,2-*c*]pyridine derivatives **7a-h**. Analogously react also α-amino acid derivatives **8a-c** and **11** as nitrogen nucleophiles producing **9a-c**, **10** and **12**.

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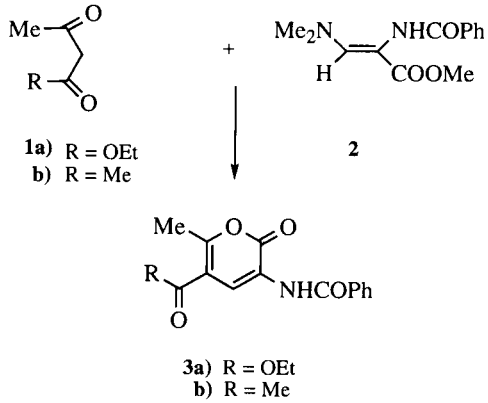
There are several synthetic approaches for the preparation of fused pyranopyridine derivatives described in the literature [1]. The methods to prepare 2*H*-pyrano-[3,2-*c*]pyridine system are limited and all of them are based on the suitably substituted pyridine derivatives as starting material, from which the fused pyranone ring has been constructed by condensation with a C-3 synthon. Recently, the interest for this bicyclic system has been arisen and many derivatives have been synthesized, due to their pharmacological activity [10,11].

In this report, we describe a new approach to 2*H*-pyrano[3,2-*c*]pyridine system starting from 5,6-disubstituted 3-benzoyl-amino-2*H*-pyran-2-ones **3a,b**, prepared from the corresponding 1,3-dicarbonyl compounds, such as ethyl acetoacetate (**1a**) and acetylacetone (**1b**), and methyl (*Z*)-2-benzoylamino-3-dimethylaminopropenoate

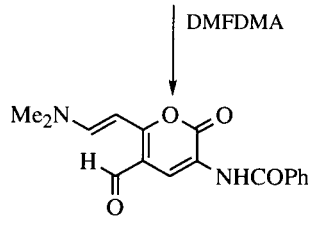
Scheme 1



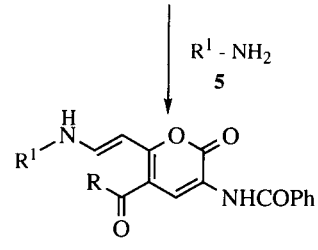
1a R = OEt
b R = Me

2

3a R = OEt
b R = Me



4a R = OEt
b R = Me



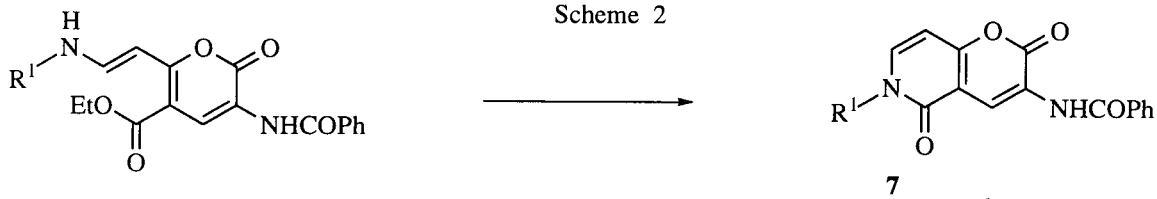
6

5,6	R	R[1]
a	OEt	phenyl
b	OEt	4-methylphenyl
c	OEt	4-bromophenyl
d	OEt	3-nitrophenyl
e	OEt	2,4-dinitrophenyl
f	OEt	4-methoxyphenyl
g	OEt	5-nitropyridyl-2
h	OEt	pyrimidyl-2
i	OEt	pyrazinyl-2
j	OEt	benzyl
k	OEt	4-methoxybenzyl
l	OEt	4-nitrobenzyl
m	Me	phenyl

(**2**) [12,13].

Compounds **3a,b** have at position 6 the methyl group, which reacts with *N,N*-dimethylformamide dimethyl acetal (DMFDMA) by heating in toluene to give the corresponding 3-benzoylamino-6-(2-dimethylamino-1-ethenyl)-5-ethoxycarbonyl-2*H*-pyran-2-one (**4a**) and 5-acetyl-3-benzoylamino-6-(2-dimethylamino-1-ethenyl)-2*H*-pyran-2-one (**4b**), respectively. The most reactive group in the compounds **4** is the dimethylamino group, which could be exchanged with nitrogen nucleophiles, such as aromatic amines **5a-f, m,** heteroaromatic amines **5g-i,** and benzylamines **5j-l**, to give the corresponding 5-ethoxycarbonyl-3-benzoylamino-6-(2-arylamino- or heteroarylamino- or benzylamino-1-ethenyl)-2*H*-pyran-2-ones **6a-l**, and its 5-acetyl analog **6m** (Scheme 1). Further cyclization of the compounds **6** into 2*H*-pyrano[3,2-*c*]pyridine derivatives **7a-h** was carried out in ethanol in the presence of sodium ethoxide at room temperature. The cyclization can be explained as a nucleophilic attack of the anion formed

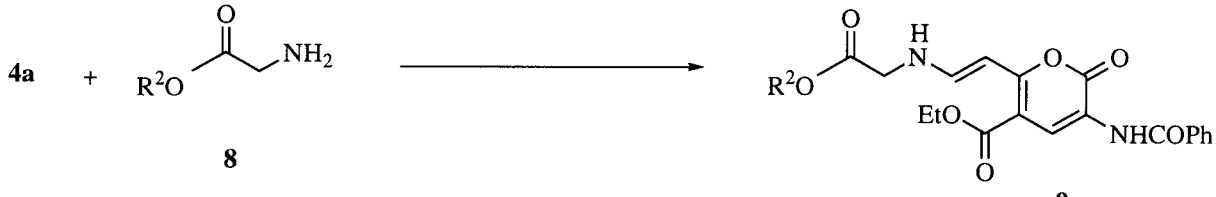
Scheme 2



6 **7**

R^1	
a	phenyl
b	4-methylphenyl
c	4-bromophenyl
d	3-nitrophenyl
e	4-methoxyphenyl
f	pyrimidinyl-2
g	benzyl
h	4-nitrobenzyl

Scheme 3

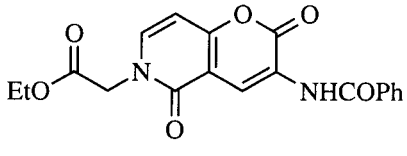


8

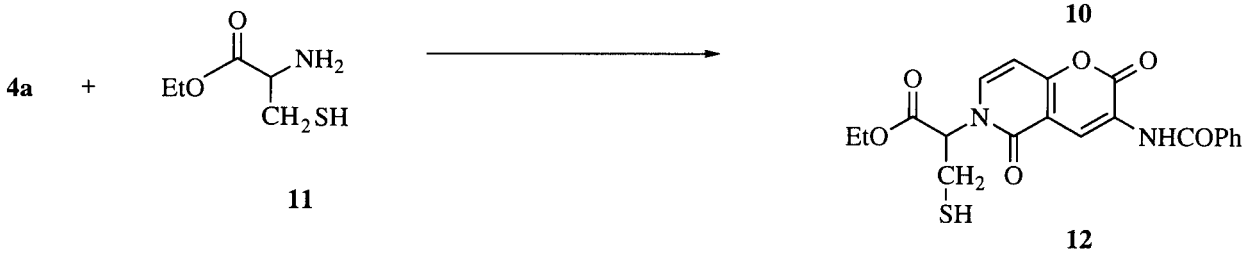
8,9a)	$R^2 = H$
b)	$R^2 = Me$
c)	$R^2 = Et$

9

$R^2 = Et$



10



11 **12**

from NH group of the side chain attached at position 6 of the pyranone ring to the ester group at positon 5 to form the compounds **7** (Scheme 2).

The compound **4a** reacts also with α-amino acids and their derivatives. Glycine (**8a**) and its methyl (**8b**) and ethyl ester (**8c**) give by heating in acetic acid or ethanol the corresponding compounds **9a-c**. The compound **9c** was converted into pyrano[3,2-*c*]pyridine derivative **10** by heating in pyridine solution. On the other hand, the compound **4a** was transformed with ethyl (L)-cisteinate (**11**) directly into the derivative of the bicyclic systems **12** by heating in acetic acid (Scheme 3).

The structure of all new compounds was established on the basis of their elemental analyses and ^{1}H nmr spectral characteristics. The olefinic protons of the exocyclic double bond appear as two doublets at δ = 6.34 ppm and δ = 7.85 ppm (partially overlapped by signals of the phenyl group) with the coupling constant $J_{CH=CH}$ = 13.5 Hz for **4a**, and as two doublets at δ = 6.66 ppm and δ = 7.80 ppm with the coupling constants $J_{CH=CH}$ 13.5 Hz for **4b**, showing that the orientation around the double bond is (*E*). In compounds **6**, the olefinic protons close to the pyranone ring appear as doublets in the range δ = 6.93-7.26 ppm, while the protons close to the amino substituent are overlaped with the multiplets of the phenyl group, with the coupling constants $J_{CH=CH}$ = 13.5-15 Hz. The pyrano-[3,2-*c*]pyridine derivatives **7**, **10**, and **12** show besides the signals characteristic for substituents, a singlet in the range of δ = 8.26-9.17 ppm for H_4 in the pyranone ring and two doublets in the range δ = 6.31-6.74 ppm for H_8 and δ =7.28-8.21 ppm for H_7, partially overlapped with the multiplets of the phenyl group. The magnitude of the coupling constant $J_{H7,H8}$ = 7.8 Hz is in agreement with the coupling constants in similar systems [14].

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^{1}H nmr spectra were obtained on a Varian EM 360 L spectrometer, ir spectra on a Perkin-Elmer 1310 instrument, and microanalyses for C, H and N on a Perkin-Elmer Analyser 2400.

The following compounds were prepared according to the procedures described in the literature: methyl 2-benzoylamino-3-dimethylaminopropenoate (**2**) [15], 3-benzoylamino-5-ethoxycarbonyl-6-methyl-2*H*-pyran-2-one (**3a**) [12], and 5-acetyl- 3-benzoylamino-6-methyl-2*H*-pyran-2-one (**3b**) [12].

The Synthesis of 5,6-Disubstituted-3-benzoylamino-2*H*-pyran-2-ones (**4**).

3-Benzoylamino-6-(2-dimethylamino-1-ethenyl)-5-ethoxycarbonyl-2*H*-pyran-2-one (**4a**).

To a solution of 3-benzoylamino-5-ethoxycarbonyl-6-methyl-2*H*-pyran-2-one (**3a**) (1 mmole) in toluene (4 ml) *N,N*-dimethylformamide dimethyl acetal (DMFDMA) (0.2 ml) was added and the mixture was heated under reflux for 7 hours. The solid product was recrystallized from ethanol to give **4a** in 69% yield, mp 201-202°; ^{1}H nmr (deuteriochloroform): δ 1.35 (t, CH_2CH_3), 3.07 (s, NMe_2), 4.28 (q, CH_2CH_3), 6.34 (d, CH=CHNMe$_2$), 7.42-7.61 (m, 3H, Ph, CH=CHNMe$_2$), 7.81-7.98 (m, 2H, Ph), 8.37 (br s, NHCOPh), 8.98 (s, H_4), $J_{CH_2CH_3}$ = 7.1 Hz, $J_{CH=CH}$ = 13.5 Hz.

Anal. Calcd. for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86. Found: C, 64.06; H, 5.88; N, 7.93.

5-Acetyl-3-benzoylamino-6-(2-dimethylamino-1-ethenyl)-2*H*-pyran-2-one (**4b**).

To a solution of 5-acetyl-3-benzoylamino-6-methyl-2*H*-pyran-2-one (**3b**) (1 mmole) in toluene (2 ml) *N,N*-dimethylformamide dimethyl acetal (DMFDMA) (0.15 ml) was added and the mixture was heated under reflux for 3 hours. The solid product was recrystallized from a mixture of ethanol and toluene to give **4b** in 74% yield, mp 204-206°; ^{1}H nmr (deuteriochloroform): δ 2.50 (s, CH_3CO), 3.07 (br s, NMe_2), 6.66 (d, CH=CHNMe$_2$), 7.42-7.60 (m, 3H, Ph), 7.80 (d, CH=CHNMe$_2$), 7.84-7.95 (m, 2H, Ph), 8.39 (br s, NHCOPh), 8.99 (s, H_4), $J_{CH=CH}$ = 13.5 Hz.

Anal. Calcd. for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.23; H, 5.61; N, 8.52.

The Reaction between Arylamines **5a-f** and 5,6-Disubstituted-3-benzoylamino-2*H*-pyran-2-ones **4**. The Synthesis of 5-Acetyl- or 5-Ethoxycarbonyl-3-benzoyl-amino-6-(2-arylamino-1-ethenyl)-2*H*-pyran-2-ones **6a-f, m**.

General Procedure.

To a mixture of arylamine **5a-f** (0.001 mole) and compound **4** (0.001 mole) in ethanol (5 ml) hydrochloric acid (0.1 ml) was added and the mixture was heated under reflux for several hours. The reaction was followed by tlc (DC-Alufolien Kieselgel 60 F 254, 0.2 mm, E. Merck, and chloroform/methanol, 5:1 and 25:1, as a solvent). After the reaction was completed, the reaction mixture was cooled to room temperature and the solid product was collected by filtration and recrystallized from an appropriate solvent to give **6a-f, m**.

The following compounds were prepared in this manner:

3-Benzoylamino-6-(1-ethenyl-2-phenylamino)-5-ethoxycarbonyl-2*H*-pyran-2-one (**6a**).

This compound was prepared from **4a** and **5a**, 3 hours of reflux, in 86% yield, mp 191-193° (from toluene); ^{1}H nmr (DMSO-d$_6$): δ 1.29 (t, CH_2CH_3), 4.26 (q, CH_2CH_3), 6.77-8.23 (m, 5H, PhCO, 5H, PhNH, CH=CH), 8.36 (s, H_4), 9.51 (s, NHCOPh), 10.35 (br s, CHNH).

Anal. Calcd. for $C_{23}H_{20}N_2O_5$: C, 68.31; H, 4.98; N, 6.93. Found: C, 68.18; H, 4.93; N, 7.05.

3-Benzoylamino-6-[2-(4-methylphenylamino)-1-ethenyl]-5-ethoxycarbonyl-2*H*-pyran-2-one (**6b**).

This compound was prepared from **4a** and **5b**, 3 hours of reflux, in 92% yield, mp 204-205° (from toluene); ^{1}H nmr (DMSO-d$_6$): δ 1.33 (t, CH_2CH_3), 2.28 (s, 4´-CH_3), 4.29 (q, CH_2CH_3), 6.93 (d, CH=CHNH), 7.09-7.26 (m, 4H, Ar), 7.47-7.76 (m, 3H, Ph), 7.89-8.12 (m, 2H, Ph, CH=CHNH), 8.46

(s, H_4), 9.57 (s, NHCOPh), 10.36 (br s, CHNH).

Anal. Calcd for $C_{24}H_{22}N_2O_5$: C, 68.89; H, 5.30; N, 6.69. Found: C, 68.70; H, 5.20; N, 6.44.

3-Benzoylamino-6-[2-(4-bromophenylamino)-1-ethenyl]-5-ethoxycarbonyl-2*H*-pyran-2-one (**6c**).

This compound was prepared from **4a** and **5c**, 10 minutes of reflux, in 89% yield, mp 220-221° (from ethanol); ^{1}H nmr (DMSO-d_6): δ 1.29 (t, CH_2CH_3), 4.27 (q, CH_2CH_3), 6.98 (d, CH=CHNH), 7.16 (d, $H_{2'}$,$H_{6'}$), 7.41-7.74 (m, 3H, Ph, $H_{3'}$,$H_{5'}$), 7.86-8.21 (m, Ph, CH=CHNH), 8.47 (s, H_4), 9.62 (br s, NHCOPh), 10.40 (br s, CHNH), $J_{CH=CH}$ = 14 Hz, $J_{H2',H3'}$ = $J_{H5',H6'}$ = 9 Hz.

Anal. Calcd. for $C_{23}H_{19}N_2O_5Br$: C, 57.16; H, 3.96; N, 5.80. Found: C, 57.22; H, 4.05; N, 5.85.

3-Benzoylamino-6-[2-(4-nitrophenylamino)-1-ethenyl]-5-ethoxy carbonyl-2*H*-pyran-2-one (**6d**).

This compound was prepared from **4a** and **5d**, 4 hours of reflux, in 89% yield, mp 197-199° (from ethanol); ^{1}H nmr (DMSO-d_6): δ 1.30 (t, CH_2CH_3), 4.29 (q, CH_2CH_3), 6.95 (d, CH=CHNH), 7.41-8.15 (m, 5H, PhCO, 4H, Ar, CH=CHNH), 8.36 (s, H_4), 9.43 (br s, NHCOPh), 10.31 (br s, CHNH), $J_{CH=CH}$ = 13.5 Hz.

Anal. Calcd. for $C_{23}H_{19}N_3O_7$: C, 61.47; H, 4.26; N, 9.35. Found: C, 61.36; H, 4.12; N, 9.58.

3-Benzoylamino-6-[2-(2,4-dinitrophenylamino)-1-ethenyl]-5-ethoxycarbonyl-2*H*-pyran-2-one (**6e**).

This compound was prepared from **4a** and **5e**, 9 hours of reflux, in 29% yield, mp 230-232° (from ethanol); ^{1}H nmr (DMSO-d_6): δ 1.31 (t, CH_2CH_3), 4.37 (q, CH_2CH_3), 7.39-7.67 (m, 3H, Ph, CH=CHNH), 7.69-8.07 (m, 2H, Ph, CH=CHNH, $H_{6'}$, 8.50 (dd, $H_{5'}$), 8.54 (s, H_4), 8.91 (d, $H_{3'}$), 9.66 (br s, NHCOPh), CHNH exchanged, $J_{H3',H5'}$ = 3 Hz, $J_{H5',H6'}$ = 9 Hz.

Anal. Calcd. for $C_{23}H_{18}N_4O_9$: C, 55.87; H, 3.67; N, 11.23. Found: C, 55.76; H, 3.58; N, 11.09.

3-Benzoylamino-6-[2-(4-methoxyphenylamino)-1-ethenyl]-5-ethoxycarbonyl-2*H*-pyran-2-one (**6f**).

This compound was prepared from **4a** and **5f**, 3 hours of reflux, in 87% yield, mp 199-200° (from toluene); ^{1}H nmr (DMSO-d_6): δ 1.29 (t, CH_2CH_3), 3.76 (s, CH_3O), 4.25 (q, CH_2CH_3), 6.87 (d, CH=CHNH), 6.95 (d, $H_{2'}$, $H_{6'}$), 7.18 (d, $H_{3'}$, $H_{5'}$), 7.46-8.09 (m, 5H, Ph, CH=CHNH), 8.33 (s, H_4), 9.54 (br s, NHCOPh), 10.32 (br d, CH=CHNH), $J_{CH_2CH_3}$ = 7.0 Hz, J_{CHNH} = 13.0 Hz, $J_{CH=CH}$ = 14.0 Hz, $J_{H2',H3'}$ = $J_{H5',H6'}$ = 9.0 Hz).

Anal. Calcd. for $C_{24}H_{22}N_2O_6$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.36; H, 4.90; N, 6.57.

5-Acetyl-3-benzoylamino-6-(1-ethenyl-2-phenylamino)-2*H*-pyran-2-one (**6m**).

This compound was prepared from **4b** and **5m**, 4 hours of reflux, in 48% yield, mp 250° dec (from toluene); ^{1}H nmr (DMSO-d_6): δ 2.47 (s, CH_3), 7.23-8.34 (m, 5H, PhCO, 5H, PhNH, CH=CH), 8.72 (s, H_4), 9.85 (br s, NHCOPh), 10.73 (br s, CHNH).

Anal. Calcd. for $C_{22}H_{18}N_2O_4$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.59; H, 4.71; N, 7.19.

The Reaction between Heteroarylamines **5g-i** and 3-Benzoylamino-6-(2-dimethylamino-1-ethenyl)-5-ethoxycarbonyl-2*H*-pyran-2-one (**4a**). The Synthesis of 3-Benzoylamino-5-ethoxycarbonyl-6-(2-heteroarylamino-1-ethenyl)-2*H*-pyran-2-ones (**5g-i**).

General procedure:

To a mixture of heteroarylamine **5g-i** (0.001 mole) and the compound **4a** (0.001 mole) in ethanol (5 ml) hydrochloric acid (0.1 ml) was added and the mixture was heated under reflux for several hours. The reaction was followed by tlc (DC-Alufolien Kieselgel 60 F 254, 0.2 mm, E. Merck, and chloroform/methanol, 5:1 and 25:1, as a solvent). After the reaction was completed, the reaction mixture was cooled to room temperature and the solid product was collected by filtration and recrystallized from an appropriate solvent to give **6g-i**.

The following compounds were prepared in this manner:

3-Benzoylamino-5-ethoxycarbonyl-6-[1-ethenyl-2-(5-nitro-2-pyridylamino)]-2*H*-pyran-2-one (**6g**).

This compound was prepared from **5g**, 4 hours of reflux, in 62% yield, mp 232-234° dec (from chloroform); ^{1}H nmr (DMSO-d_6): δ 1.33 (t, CH_2CH_3), 4.39 (q, CH_2CH_3), 7.05 (d, $H_{3'}$), 7.26 (d, CH=CHNH), 7.57-7.81 (m, 3H, Ph), 7.98-8.21 (m, 2H, Ph), 8.24 (d, CH=CHNH), 8.56 (dd, $H_{4'}$), 8.36 (s, H_4) 9.31 (d, $H_{6'}$), 9.78 (s, NHCOPh), 11.47 (br s, CHNH), $J_{CH=CH}$ = 14.0 Hz, $J_{H3'H4'}$ = 9 Hz, $J_{H4',H6'}$ = 3 Hz.

Anal. Calcd. for $C_{22}H_{18}N_4O_7$: C, 58.67; H, 4.03; N, 12.44. Found: C, 58.66; H, 3.79; N, 12.23.

3-Benzoylamino-5-ethoxycarbonyl-6-[1-ethenyl-2-(2-pyrimidinylamino)]-2*H*-pyran-2-one (**6h**).

This compound was prepared from **5h**, 4 hours of reflux, in 72% yield, mp 262-264°dec (from chloroform); ^{1}H nmr (DMSO-d_6): δ 1.34 (t, CH_2CH_3), 4.33 (q, CH_2CH_3), 7.17 (d, CH=CHNH),7.18 (d, $H_{5'}$), 7.56-7.76 (m, 3H, Ph), 7.93-8.17 (m, 2H, Ph), 8.53 (s, H_4), 8.54 (d, CH=CHNH), 8.70 (d, $H_{4'}$,$H_{6'}$), 9.71 (br s, NHCOPh), 13.04 (br d, CHNH), $J_{CH=CH}$ = 14.0 Hz, J_{CHNH} = 11.0 Hz, $J_{H4'H5'}$ = $J_{H5',H6'}$ = 5 Hz.

Anal. Calcd. for $C_{21}H_{18}N_4O_5$: C, 62.06; H, 4.46; N, 13.79. Found: C, 61.86; H, 4.13; N, 13.54.

The Reaction between Alkylamine (**5j-l**) and 3-Benzoylamino-6-(2-dimethylamino-1-ethenyl)-5-ethoxycarbonyl-2*H*-pyran-2-one (**4a**). The Synthesis of 3- Benzoylamino-5-ethoxycarbonyl-6-(2-alkylamino-1-ethenyl)-2*H*-pyran-2-ones **6j-l**.

General procedure:

To a mixture of alkylamine **5j-l** (0.001 mole) and the compound **4a** (0.001 mole) in ethanol (5 ml) hydrochloric acid (0.1 ml) was added and the mixture was heated under reflux for several hours. The reaction was followed by tlc (DC-Alufolien Kieselgel 60 F 254, 0.2 mm, E. Merck, and chloroform/methanol, 5:1 and 25:1, as a solvent). After the reaction was completed, the reaction mixture was cooled to room temperature and the solid product was collected by filtration and recrystallized from an appropriate solvent to give **6j-l**.

The following compounds were prepared in this manner:

3-Benzoylamino-6-[2-(benzylamino)-1-ethenyl]-5-ethoxycarbonyl-2*H*-pyran-2-one (**6j**).

This compound was prepared from **5j**, 3 hours of reflux, in 75% yield, mp 209-210° (from toluene); ^{1}H nmr (DMSO-d_6): δ 1.25 (t, CH_2CH_3), 3.97-4.58 (m, CH_2CH_3, CH_2Ph), 6.44 (d, C*H*=CHNH), 7.43-8.07 (m, 5H, PhCO, CH=C*H*NH), 7.45 (s, *Ph*CH_2), 8.21 (s, H_4), 8.44 (br s, CH=CHN*H*), 9.45 (br s, N*H*COPh), $J_{CH_2CH_3}$ = 7.0 Hz, $J_{CH=CH}$ = 14.0 Hz.

Anal. Calcd. for $C_{24}H_{22}N_2O_5$: C, 68.89; H, 5.30; N, 6.69. Found: C, 68.78; H, 5.13; N, 6.79.

3-Benzoylamino-6-[2-(4-methoxybenzylamino)-1-ethenyl]-5-ethoxycarbonyl-2*H*-pyran-2-one (**6k**).

This compound was prepared from **5k**, 3 hours of reflux, in 73% yield, mp 178-179° (from toluene); ^{1}H nmr (deuteriochloroform): δ 1.29 (t, CH_2CH_3), 3.77 (s, CH_3O), 4.04-4.51 (m, CH_2CH_3, CH_2NH), 6.48 (d, C*H*=CHNH), 6.96 (d, $H_{2'}$, $H_{6'}$), 7.34 (d, $H_{3'}$, $H_{5'}$), 7.49-7.73 (m, 5H, Ph, CH=C*H*NH), 8.27 (s, H_4), 8.41 (br s, CH_2N*H*), 9.52 (br s, N*H*COPh), $J_{CH_2CH_3}$ = 13.0 Hz, $J_{CH=CH}$ = 14.0 Hz, $J_{H2',H3'} = J_{H5',H6'}$ = 9.0 Hz.

Anal. Calcd. for $C_{25}H_{24}N_2O_6$: C, 66.95; H, 5.39; N, 6.25. Found: C, 66.66; H, 5.22; N, 6.48.

3-Benzoylamino-6-[2-(4-nitrobenzylamino)-1-ethenyl]-5-ethoxycarbonyl-2*H*-pyran-2-one (**6l**).

This compound was prepared from **5l**, 3 hours of reflulx, 89° yield, mp 240-241° (from EtOH/DMF); ^{1}H nmr (DMSO-d_6): δ 1.22 (t, CH_2CH_3), 3.97-4.74 (m, CH_2CH_3, CH_2NH), 6.35 (br d, C*H*=CHNH), 7.49-8.12 (m, 5H, Ph, $H_{2'}$, $H_{6'}$, CH=C*H*NH), 8.26 (s, H_4), 8.33 (d, $H_{3'}$, $H_{5'}$), 8.57 (br s, CH_2N*H*), 9.56(br s, N*H*COPh), $J_{CH_2CH_3}$ = 7.0 Hz, $J_{H2',H3'}$ = 7.0 Hz, $J_{H2',H3'} = J_{H5',H6'}$ = 9.0 Hz.

Anal. Calcd. for $C_{24}H_{21}N_3O_7$: C, 62.20; H, 4.57; N, 9.07. Found: C, 61.99; H, 4.41; N, 9.22.

The Reaction of 3-Benzoylamino-6-(2-dimethylamino-1-ethenyl)-5-ethoxycarbonyl-2*H*-pyran-2-one (**4a**) with Amino Acids **8a,11** and Derivatives **8b,c**. The Synthesis of *N*-[(1-Ethenyl-2-(3-benzoylamino-5-ethoxycarbonyl-2-oxo-2*H*-pyran-6-yl)]glycine (**9a**), Alkyl *N*-[1-Ethenyl-2-(3-benzoylamino-5-ethoxycarbonyl-2-oxo-2*H*-pyran-6-yl)] glycinate **9b,c** and Ethyl 3-Mercapto-2-(3benzoylamino-5,6-dihydro-2,5-dioxo-2*H*-pyrano[3,2-*c*]piridyl-6)propanoate (**12**).

N-[(1-Ethenyl-2-(3-benzoylamino-5-ethoxycarbonyl-2-oxo-2*H*-pyran-6-yl)glycine (**9a**).

The mixture of **8a** (0.001 mole) and compound **4a** (0.001 mole) in acetic acid (5 ml) was heated under reflux for 1 hour. After the reaction mixture was cooled to room temperature, the precipitate was collected by filtration, washed with ethanol and recrystallized from a mixture of ethanol and DMF to give **9a** in in 53% yield, mp 237-239; ^{1}H nmr (DMSO-d_6): δ 1.29 (t, CH_2CH_3), 3.75-4.44 (m, CH_2CH_3, CH_2NH), 5.21 (br s, COO*H*, H_2O), 6.43 (br d, C*H*=CHNH), 7.59-8.29 (m, 5H, Ph, CH=C*H*NH, CH_2N*H*), 8.42 (s, H_4), 9.67 (br s, N*H*COPh), NH exchanged, $J_{CH_2CH_3}$ = 7.0 Hz, $J_{CH=CH}$ = 14.0 Hz.

Anal. Calcd. for $C_{19}H_{18}N_2O_7$: C, 59.07; H, 4.70; N, 7.25. Found: C, 59.14; H, 4.97; N, 7.24.

Methyl *N*-[1-Ethenyl-2-(3-benzoylamino-5-ethoxycarbonyl-2-oxo-2*H*-py-ran-6-yl)] glycinate (**9b**).

A mixture of **8b** (0.001 mole) and compound **4a** (0.001 mole) in ethanol (5 ml) was heated under reflux for 3.5 hours. After the reaction mixture was cooled to room temperature, the precipitate was collected by filtration and recrystallized from a mixture of ethanol and water to give **9b** in 52% yield, mp 246-248°; ^{1}H nmr (DMSO-d_6): δ 1.29 (t, CH_2CH_3), 3.47 (s, CH_3O), 4.01-4.39 (m, CH_2CH_3, CH_2NH), 6.35 (br d, C*H*=CH), 7.42-8.21 (m, 5H, Ph, CH=C*H*, CH_2N*H*), 8.26 (s, H_4), 9.51 (s, N*H*COPh), $J_{CH=CH}$ = 14.0 Hz.

Anal. Calcd. for $C_{20}H_{20}N_2O_7$: C, 60.00; H, 5.03; N, 7.00. Found: C, 59.93; H, 4.91; N, 6.91.

Ethyl *N*-[1-ethenyl-2-(3-benzoylamino-5-ethoxycarbon-yl-2-oxo-2*H*-pyran-6-yl)] glycinate (**9c**).

A mixture of **8c** (0.001 mole) and compound **4a** (0.001 mole) in ethanol (5 ml) was heated under reflux for 3 hours. After the reaction mixture was cooled to room temperature, the precipitate was collected by filtration and recrystallized from ethanol to give **9c** in 52% yield, mp 227-228°; ^{1}H nmr (DMSO-d_6): δ 1.02-1.38 (m, 2 x CH_2CH_3), 3.92-4.47 (m, 2 x CH_2CH_3, CH_2NH), 6.31 (br d, C*H*=CH), 7.41-8.08 (m, 5H, Ph, CH=C*H*, CH_2N*H*), 8.24 (s, H_4), 9.47 (s, N*H*COPh), $J_{CH=CH}$ = 14.0 Hz.

Anal. Calcd. for $C_{21}H_{22}N_2O_7$: C, 60.86; H, 5.35; N, 6.76. Found: C, 60.74; H, 5.19; N, 6.64.

Ethyl 3-Mercapto-2-(3-benzoylamino-5,6-dihydro-2,5-dioxo-2*H*-pyrano[3,2-*c*]pyridinyl-6)propanoate (**12**).

A mixture of **11** (0.001 mole) and compound **4a** (0.001 mole) in acetic acid (5 ml) was heated under reflux for 1.5 hours. The volatile components were evaporated *in vacuo*. To oily residue water (2 ml) was added. After the solid product was collected by filtration and recrystallized from the mixture of ethanol and water to give **12** in 53% yield, mp 93-95°; ms: 414 (M^+); ^{1}H nmr (DMSO-d_6): δ 1.19 (t, CH_2CH_3), 3.09-3.48 (m, CH_2CH, SH, H_2O), 4.17 (q, CH_2CH_3), 5.24 (t, CH_2CH), 6.56 (d, H8), 7.43-7.67 (m, 3H, Ph), 7.79-8.04 (m, 2H, Ph, H7), 8.53 (s, H4), 9.66 (br s, N*H*COPh), $J_{H7,H8}$ = 7.8 Hz.

Anal. Calcd. for $C_{20}H_{18}N_2O_6S$: C, 57.96; H, 4.38; N, 6.76. Found: C, 57.52; H, 4.03; N, 7.24.

Synthesis of 2*H*-Pyrano[3,2-*c*]pyridine Derivatives **7, 10**.

General Procedure:

To a solution of sodium etoxide in ethanol (0.080 g, 0.002 mg atom of sodium in 5 ml of absolute ethanol) pyranone **6** (1 mmole) was added . A mixture was stirred at room temperature. The reaction was followed by tlc (DC-Alufolien Kieselgel 60 F 254, 0.2 mm, E. Merck, and chloroform/methanol, 5:1 and 25:1, as a solvent). After the reaction was completed, the volatile components were evaporated *in vacuo*. The oily residue was dissolved in water (3 ml) and 10% hydrochloric acid was added to *p*H = 3-4. The mixture was extracted with chloroform (3 x 30 ml). The organic phase was dried over anhydrous sodium sulphate and evaporated *in vacuo*. A solid residue was recrystallized from an appropriate solvent to give **7**.

The following compounds were prepared in this manner:

3-Benzoylamino-5,6-dihydro-6-phenyl-2*H*-pyrano[3,2-*c*]pyridine-2,5-dione (**7a**).

This compound was prepared from **6a**, 30 minutes of stirring at room temperature, in 48% yield, mp 242-243° (from ethanol); ^{1}H nmr (DMSO-d_6): δ 6.54 (d, H_8), 7.35-7.69 (m, 3H, PhCO, 5H, PhNH), 7.76-8.04 (m, 2H, Ph, H_7), 8.57 (s, H_4), 9.64 (br s, N*H*COPh), $J_{H7,H8}$ = 7.8 Hz.

Anal. Calcd. for $C_{21}H_{14}N_2O_4$: C, 70.39; H, 3.94; N, 7.82. Found: C, 70.02; H, 3.82; N, 7.99.

3-Benzoylamino-5,6-dihydro-6-(4-methylphenyl)-2*H*-pyrano-[3,2-*c*]pyridine-2,5-dione (**7b**).

This compound was prepared from **6b**, 30 minutes of stirring at room temperature, in 43% yield, mp 270-273° (from ethanol/chloroform); ^{1}H nmr (DMSO-d_6): δ 2.43 (s, 4′-Me), 6.35 (d, H_8), 7.29 (s, 4H, PhNH), 7.46-7.67 (m, 3H, PhCO), 7.76-8.04 (m, 2H, Ph, H_7), 8.69 (br s, N*H*COPh), 9.17 (s, H_4), $J_{H7,H8}$ = 7.8 Hz.

Anal. Calcd. for $C_{22}H_{16}N_2O_4$: C, 70.96; H, 4.33; N, 7.52. Found: C, 70.67; H, 4.18; N, 7.61.

3-Benzoylamino-6-(4-bromophenyl)-5,6-dihydro-2*H*-pyrano[3,2-*c*]-pyridine-2,5-dione (**7c**).

This compound was prepared from **6c**, 15 minutes of stirring at room temperature, in 62% yield, mp >290° (from acetic acid); ^{1}H nmr (DMSO-d_6): δ 6.74 (d, H_8), 7.28-8.01 (m, 5H, PhCO, 4H, PhNH, H_7), 8.54 (s, H_4), 9.65 (br s, NHCOPh), $J_{H7,H8}$ = 7.8 Hz.

Anal. Calcd. for $C_{21}H_{13}N_2O_4Br$: C, 57.68; H, 2.99; N, 6.41. Found: C, 57.85; H, 2.88; N, 6.60.

3-Benzoylamino-5,6-dihydro-6-(3-nitrophenyl)-2*H*-pyrano[3,2-*c*]-pyridine-2,5-dione (**7d**).

This compound was prepared from **6d**, 1 hour of stirring at room temperature, in 61% yield, mp 286-289° dec (from a mixture of acetic acid and water); ^{1}H nmr (DMSO-d_6): δ 6.73 (d, H_8), 7.56-7.78 (m, 3H, Ph), 7.91-8.19 (m, 2H PhCO, 2H ArN, H_7), 8.37-8.59 (m, 2H Ar), 8.72 (s, H_4), 9.85 (br s, N*H*COPh), $J_{H7,H8}$ = 7.8 Hz.

Anal. Calcd. for $C_{21}H_{13}N_3O_6$: C, 62.53; H, 3.25; N, 10.42. Found: C, 62.25; H, 3.03;N, 10.15.

3-Benzoylamino-5,6-dihydro-6-(4-methoxylphenyl)-2*H*-pyrano-[3,2-*c*]pyridine- 2,5-dione (**7e**)

This compound was prepared from **6f**, 30 minutes of stirring at room temperature, in 63% yield, mp 264-265° (from ethanol/DMF); ^{1}H nmr (deuteriochloroform): δ 3.88 (s, 4′-OMe), 6.37 (d, H_8), 6.94-7.72 (m, 3H, PhCO, 4H, ArN, H_7), 7.84-8.06 (m, 2H, Ph), 8.70 (br s,N*H*COPh), 9.15 (s, H_4), $J_{H7,H8}$ =7.8 Hz.

Anal. Calcd. for $C_{22}H_{16}N_2O_5$: C, 68.04; H, 4.15; N, 7.21. Found: C, 68.32; H, 3.90; N, 7.41.

3-Benzoylamino-6-(2-pyrimidinyl)-5,6-dihydro-2*H*-pyrano[3,2-*c*]-pyridine-2,5-dione (**7f**).

This compound was prepared from **6h**, 1.5 hours of stirring at room temperature, in 47% yield, mp 265-267° (from ethanol); ^{1}H nmr (DMSO-d_6): δ 6.70 (d, H_8), 7.46-8.15 (m, 5H, Ph, H_7), 8.63 (d, $H_{5'}$), 8.67 (s, H_4), 9.11 (d, $H_{4'}$, $H_{6'}$), 9 78 (br s, N*H*COPh), $J_{H7,H8}$ = 7.8 Hz, $J_{H5',H6'} = J_{H4',H5'}$ = 5.0 Hz.

Anal. Calcd. for $C_{19}H_{12}N_4O_4$: C, 63.33; H, 3.36; N, 15.55. Found: C, 63.37; H, 3.05; N, 15.48.

3-Benzoylamino-6-benzyl-5,6-dihydro-2*H*-pyrano[3,2-*c*]pyridine-2,5-dione (**7g**).

This compound was prepared from **6j**, 30 minutes of stirring at room temperature, in 72% yield, mp 239-240° (from ethanol); ^{1}H nmr (deuteriochloroform): δ 5.21 (s, CH_2Ph), 6.26 (d, H_8), 7.37 (s, 5H, PhCH_2), 7.43-7.71 (m, 3H, PhCO, H_7), 7.82-8.08 (m, 2H, PhCO), 8.66 (br s, N*H*COPh), 9.15 (s, H_4), $J_{H7,H8}$ = 7.8 Hz.

Anal. Calcd. for $C_{22}H_{16}N_2O_4$: C, 70.96; H, 4.33; N, 7.52. Found: C, 70.69; H, 4.16; N, 7.48.

3-Benzoylamino-5,6-dihydro-6-(4-nitrobenzyl)-2*H*-pyrano[3,2-*c*]-pyridine-2,5-dione (**7h**).

This compound was prepared from **6l**, 1.5 hours of stirring at room temperature, in 62% yield, mp 280-281° (from ethanol/-DMF); ^{1}H nmr (DMSO-d_6):δ 5.38 (s, CH_2Ar), 6.62 (d, H_8), 7.47-8.39 (m, 5H, Ph, 4H, Ar, H_7), 8.65 (s, H_4), 9.60 (br s, N*H*COPh), $J_{H7,H8}$ = 7.8 Hz.

Anal. Calcd. for $C_{22}H_{15}N_3O_6$: C, 63.31; H, 3.62; N, 10.07. Found: C, 63.17; H, 3.60; N, 10.09.

Ethyl 3-Benzoylamino-5,6-dihydro-2,5-dioxo-2*H*-pyrano-[3,2-*c*]pyridinyl-6)acetate (**10**).

A solution of **9c** (0.0005 mole) in pyridine (6 ml) was heated under reflux for 3 hours. The volatile components were evaporated *in vacuo*. To oily residue ethanol (4 ml) was added . After the solid product was collected by filtration and washed with ethanol to give **10** in 68% yield, mp 215-216°; ^{1}H nmr (DMSO-d_6): δ 1.23 (t, CH_2CH_3), 4.24 (q, CH_2CH_3), 4.69 (s, CH_2), 6.31 (d, H8), 7.30 (d, H_7), 7.45-7.66 (m, 3H, Ph), 7.79-8.01 (m, 2H, Ph), 8.65 (br s, N*H*COPh, H4), 9.09 (s, H_4), $J_{H7,H8}$ = 7.8 Hz.

Anal. Calcd. for $C_{19}H_{16}N_2O_6$: C, 61.69; H, 4.38; N, 7.61. Found: C, 61.90; H, 4.17; N, 7.56.

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