Rearrangements of 5-Acetyl-3-benzoylamino-6-(2-dimethylamino-1-ethenyl)-2*H*-pyran-2-one and 3-Benzoylamino-6-(2-dimethylamino-1-ethenyl)-5-ethoxycarbonyl-2*H*-pyran-2-one into 1-Amino-pyridine,Pyrano[2,3-*b*]pyridine and Isoxazole Derivatives

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Rearrangements of 5-acetyl-3-benzoylamino-6-(2-dimethylamino-1-ethenyl)-2*H*-pyran-2-one (**1**) and 3-benzoylamino-6-(2-dimethylamino-1-ethenyl)-5-ethoxycarbonyl-2*H*-pyran-2-one (**7**) in the presence of *N*-nucleophiles, such as ammonia, hydrazine, and hydroxylamine, into 1-aminopyridine, pyrano[2,3-*b*]-pyridine, and isoxazole derivatives **5**, **11**, and **15** is described. In the reaction of compounds **1** and **7** with *C*-nucleophiles, such as 5,5-dimethyl-1,3-cyclohexanedione and barbituric acid, only substitution of the dimethylamino group is taking place to give the compounds **17**, **18**, and **20**.

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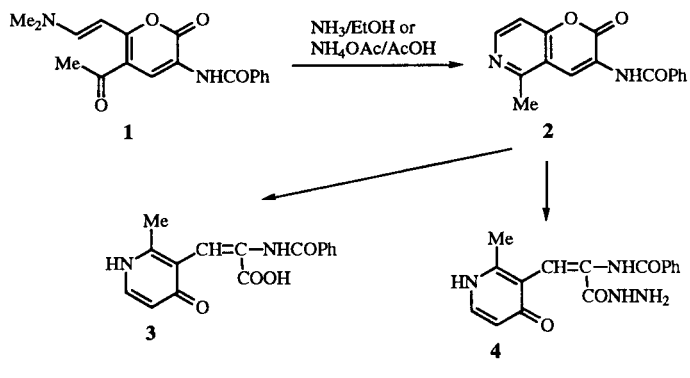
Recently, we have described the preparation of 5-acetyl-3-benzoylamino-6-(2-dimethylamino-1-ethenyl)-2*H*-pyran-2-one (**1**) and 3-benzoylamino-6-(2-dimethylamino-1-ethenyl)-5-ethoxycarbonyl-2*H*-pyran-2-one (**7**) [1], derived from 5,6-disubstituted 3-benzoylamino-2*H*-pyran-2-ones [2] and *N*,*N*-dimethylformamide dimethyl acetal, as intermediates in the synthesis of 2*H*-pyrano-[3,2-*c*]pyridine derivatives.

In this communication we report on some new transformations of 5-acetyl-3-benzoylamino-6-(2-dimethylamino-1-ethenyl)-2*H*-pyran-2-one (**1**) and 3-benzoylamino-6-(2-diemthylamino-1-ethenyl)-2*H*-pyran-2-one (**7**) with nitrogen and carbon nucleophiles.

The compound **1** reacts either with ammonia in ethanol at room temperature or ammonium acetate in acetic acid at reflux temperature by substitution of the dimethylamino group followed by cyclization to the adjacent carbonyl group to give 3-benzoylamino-5-methyl-2*H*-pyrano[3,2-*c*]pyridin-2-one (**2**) in 77% and 86% yield, respectively. By treatment of the compound **2** with sodium ethoxide in ethanol at room temperature the cleavage of the pyranone ring takes place to give 2-benzoylamino-3-(2-methyl-4-oxo-1,4-dihydropyridinyl-3)propenoic acid (**3**) in 28% yield, while the reaction of **2** with hydrazine hydrate at room temperature produces 2-benzoylamino-3-(2-methyl-4-oxo-1,4-dihydropyridinyl-3)propenoic acid hydrazide (**4**) in 78% yield (Scheme 1).

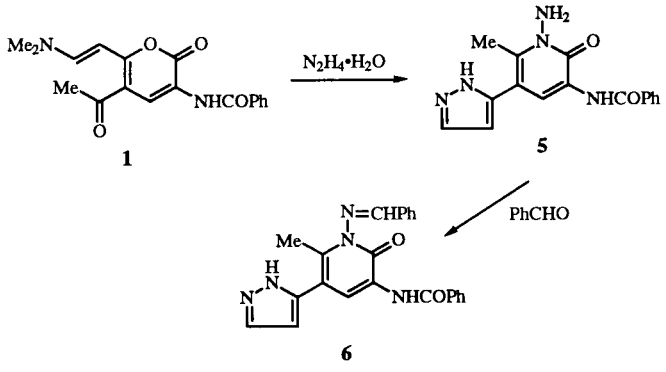
Scheme 1



In the reaction of **1** with excess of hydrazine hydrate in ethanol at room temperature a product was formed, for which the molecular formula $C_{16}H_{15}N_5O_2$ was established on the basis of its mass spectrum (ms: 309; M^+) and elemental analysis for C, H and N, indicating that two moles of hydrazine reacted with one mole of the starting material by elimination of dimethylamine. The ^1H nmr spectrum exhibits a singlet at δ = 8.41 ppm, two doublets at δ = 6.28 ppm and δ = 6.39 ppm, each integrating for one proton, with the coupling constant J = 2.0 Hz, a singlet at δ = 2.58 ppm for a methyl group, four exchangable protons, a singlet integrating for two protons at δ = 6.28 ppm, and two singlets at δ = 9.34 ppm and δ = 12.98 ppm, each integrating for one proton, and two multiplets at δ = 7.42-7.71 ppm and δ = 7.78-8.04 ppm, in the ratio of 3:2, characteristic for a benzoyl group. These data are consistent with 1-amino-3-benzoylamino-6-methyl-5-(pyrazolyl-3)-2*H*-pyridin-2-one (**5**). The compound **5** reacts with benzaldehyde to give the corresponding hydrazone, *i.e.* 1-benzalimino-3-benzoylamino-6-methyl-5-(pyrazolyl-3)-2*H*-pyridin-2-one (**6**), confirming thus the presence of a primary amino group in the compound **5** (Scheme 2).

In the reaction of the compound **7** with ammonia in ethanol at room temperature a compound was isolated with the molecular formula $C_{15}H_{10}N_2O_4$ in 62% yield, which was identified as 3-benzoylamino-2*H*-pyrano[2,3-*b*]pyridine-2,5-dione (**11**), isomeric with 3-benzoylamino-2*H*-pyrano[3,2-*c*]pyridine-2,5-dione (**9**) reported earlier [3]. The structure of **11** was determined on the basis of the ^1H nmr spectrum. Namely, it exhibits two doublets at δ = 7.48 ppm

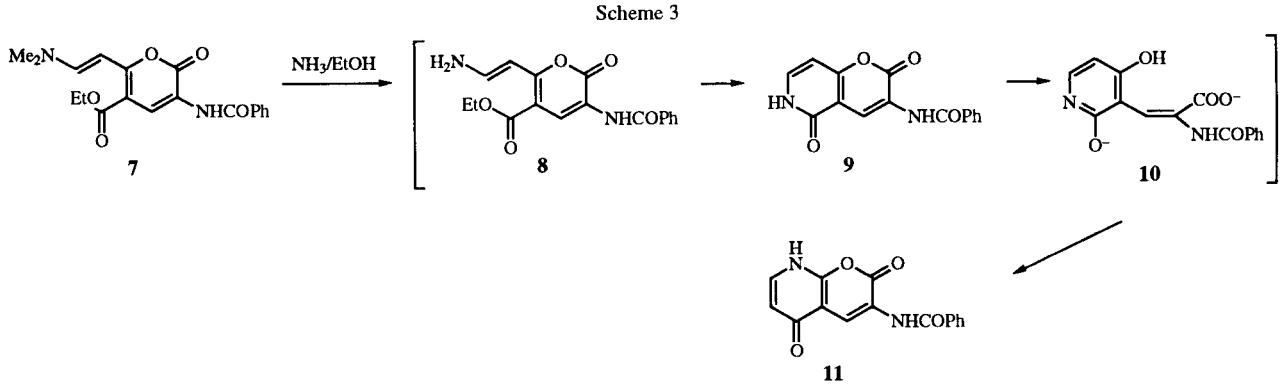
Scheme 2



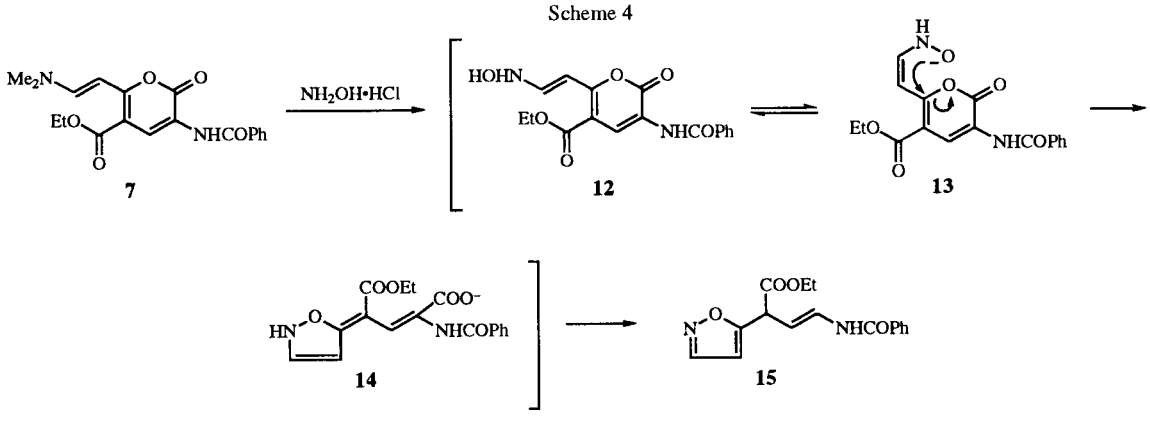
(H_6) and δ =8.46 ppm (H_7), each integrating for one proton, with the coupling constant $J_{H6,H7}$ = 7.8 Hz, a singlet at δ = 8.94 ppm (H_4) integrating for one proton, two multiplets at δ = 7.57-7.76 ppm and δ = 8.01-8.22 ppm, in ratio 3:2, typical for a benzoyl group, and a broad singlet at δ = 9.84 ppm for NH group. The pyridine protons in the compound **11** appear downfield in comparison to protons H_7 (δ = 6.36 ppm) and H_8 (δ = 7 50 ppm) for the compound **9**. This isomerization is explained in the following manner. The compound **8** cyclizes into **9**. In basic media the pyranone ring is cleaved to give the intermediate **10**, which cyclizes into **11** (Scheme 3).

By the reaction of the compound **7** with hydroxylamine hydrochloride in boiling methanol a compound was isolated in 59% yield, for which molecular formula $C_{16}H_{16}N_2O_4$ was established on the basis of elemental analysis and mass spectrum (ms: 300; M^+). Its ^1H nmr spectrum shows a triplet at δ = 1.29 ppm and a quartet at δ = 4.27 ppm, with the coupling constant J_{CH3CH2} =7.0 Hz, characteristic for the ester ethyl group, a doublet at δ = 5.01 ppm with the coupling constant J = 9 Hz, a doublet of doublet at δ = 5.74 ppm with the coupling constants J_{CH-CH} = 9 Hz and $J_{CH=CH}$ = 14 Hz, a doublet of doublet at δ = 7.29 ppm with the coupling constant J_{CHNH} = 10 Hz, two doublets at δ = 6.43 ppm and δ = 8.57 ppm, with the coupling constant J = 2 Hz, characteristic for ortho protons in a five membered heterocyclic ring, two multiplets at δ = 7.45-7.72 ppm and δ =7.85-8.09 ppm, in the ratio 3:2, characteristic for a benzoyl group, and one exchangable proton at δ =11.41 ppm for NH group. After addition of deuterium oxide, the signal at δ = 11.41 ppm disappeared, while the doublet of doublet at δ = 7.29 ppm appeared as a doublet with the coupling constant $J_{CH=CH}$ = 14.0 Hz. The reaction proceeds as a substitution of the dimethylamino group in **7** with hydroxylamino group to give **12**, isomerization around the double bond to give **13**, followed by the attack of hydroxylamino group to C_6 of the pyranone ring, as has been previously reported for some other nucleo-

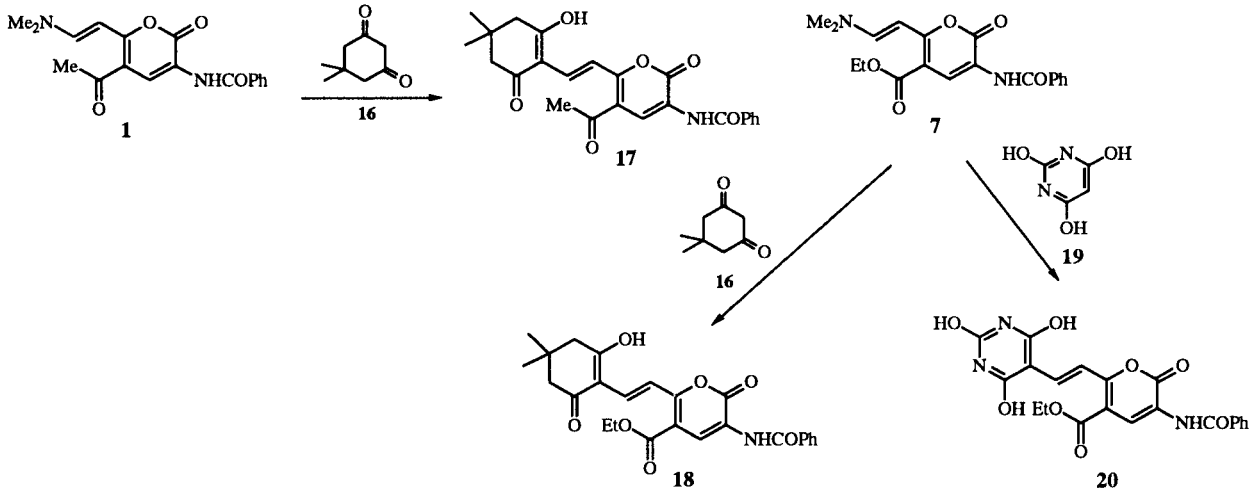
Scheme 3



Scheme 4



Scheme 5



philes [4]. The *trans* orientation around the C=C double bond indicates that pyranone ring in the intermediate **13** was cleaved under the reaction conditions to give the intermediate **14**, which produced after decarboxylation ethyl 4-benzoylamino-2-(isoxazolyl-5)buten-3-oate (**15**) (Scheme 4).

Compounds **1** and **7** react also with *C*-nucleophiles in boiling acetic acid, such as 5,5-dimethyl-1,3-cyclohexanedione (**16**) and barbituric acid (**19**) by the exchange of the dimethylamino group to give the compounds **17**, **18**, and **20**, respectively (Scheme 5).

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: 5-acetyl-3-benzoylamino-6-(2-dimethylamino-1-ethenyl)-2*H*-pyran-2-one (**1**) [1], and 3-benzoylamino-6-(2-dimethylamino-1-ethenyl)-5-ethoxycarbonyl-2*H*-pyran-2-one (**7**) [1].

3-Benzoylamino-5-methyl-2*H*-pyrano[3,2-*c*]pyridin-2-one (**2**).

Method A.

A mixture of the pyranone **1** (0.326 g, 0.001 mmole) and ammonium acetate (0.154 g, 0.002 mmole) in acetic acid (5 ml) was heated under reflux for 1 hour. The volatile components were evaporated *in vacuo*. To the residue water (2 ml) was added and the precipitate was collected by filtration and recrystallized from a mixture of methanol and water to give **2** in 86% yield, mp 170-171°; ^{1}H nmr (DMSO-d_6): δ 2.73 (s, CH_3), 7.31 (d, H_8), 7.43-7.71 (m, 3H-Ph), 7.83-8.06 (m, 2H-Ph), 8.47 (d, H_7), 8.72 (s, H_4), 9.85 (br s, N*H*COPh), $J_{H7,H8}$ = 6.0 Hz.

Anal. Calcd. for $C_{16}H_{12}N_2O_3$; C, 68.57; H, 4.32; N, 10.00. Found: C, 68.65; H, 4.05; N, 9.98.

Method B.

To a solution of ammonia in absolute ethanol (10 ml) the pyranone **1** was added and the mixture was stirred at room temperature for 12 hours. The precipitate was collected by filtration and recrystallized from a mixture of acetonitrile and water to give **2** in 77% yield. The compound was identical with that obtained according to the method A.

2-Benzoylamino-3-(2-methyl-4-oxo-1,4-dihydropyridinyl-3)propenoic Acid (**3**).

To a solution of sodium ethoxide in ethanol (0.060 g sodium in 10 ml of absolute ethanol) compound **2** (0.280 g, 0.001 mmole) was added and the mixture was stirred at room temperature for 45 minutes. The solid (sodium salt) was collected by filtration, dissolved in water and adjusted with hydrochloric acid to *p*H 3. The precipitate was again collected by filtration and recrystallized from a mixture of ethanol and water to give **3** in 28% yield. The compound cyclized by heating above 102° into **2**; ^{1}H nmr (DMSO-d_6): δ 2.23 (s, Me), 6.35 (d, $H_{5'}$), 6.41 (s, C*H*-Het), 7.40-8.09 (m, 5H-Ph, $H_{6'}$), 10.12 (br s, N*H*COPh), OH,COOH exchanged, $J_{H5',H6'}$ = 7.2 Hz.

Anal. Calcd. for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.55; H, 4.58; N, 9.47.

2-Benzoylamino-3-(2-methyl-4-oxo-1,4-dihydropyridinyl-3)propenoic Acid Hydrazide (**4**).

To a suspension of the compound **2** (0.280 g, 0.001 mmole) in ethanol (10 ml) hydrazine hydrate (80%, 0.6 ml) was added and the mixture was stirred at room temperature for 15 minutes. The precipitate was collected by filtration and recrystallized from ethanol to give **4** in 78% yield, mp 152-153°; ms: 312 (M^+); ^{1}H nmr (DMSO-d_6): δ 2.23 (s, Me), 4.15 (br s, NHNH_2), 6.06 (d, $H_{5'}$), 6.37 (s, C*H*-Het), 7.36-7.61 (m, 3H-Ph, $H_{6'}$), 7.78-7.99 (m, 2H-Ph), 9.43 (br s, N*H*COPh), 9.86 (br s, N*H*NH$_2$), NH exchanged, $J_{H5',H6'}$ = 7.2 Hz.

Anal. Calcd. for $C_{16}H_{16}N_4O_3$ x H_2O: C, 58.17; H, 5.49; N, 16.96. Found: C, 57.89; H, 5.61; N, 16.67.

1-Amino-3-benzoylamino-6-methyl-5-(pyrazolyl-3)-2*H*-pyridin-2-one (**5**).

To a suspension of the pyranone **1** (0.326 g, 0.001 mmole) in ethanol (5 ml) hydrazine hydrate (99%, 1 ml) was added and the

mixture was stirred at room temperature for 1 hour. The precipitate was collected by filtration and recrystallized from a mixture of ethanol and water to give **5** in 47% yield, mp 209-211°; ms: 309 (M^+); ^1H nmr (DMSO-d_6): δ 2.58 (br s, Me, DMSO), 6.28 (s, NH_2), 6.39 (d, $H_{5'}$), 7.42-7.71 (m, 3H-Ph), 7.78-8.04 (m, 2H-Ph, $H_{4'}$), 8.41 (s, H_4), 9.34 (bs, N*H*COPh), 12.98 (br s, N*H*NH_2), $J_{H4',H5'}$ = 2.0 Hz.

Anal. Calcd. for $C_{16}H_{15}N_5O_2$: C, 62.13; H, 4.89; N, 22.64. Found: C, 62.41; H, 4.90; N, 22.39.

1-Benzalimino-3-benzoylamino-6-methyl-5-(pyrazolyl-3)-2*H*-pyridin-2-one (**6**).

To a suspension of the compound **5** (0.309 g, 0.001 mmole) in absolute ethanol (5 ml) with catalytic amount of trifluoroacetic acid benzaldehyde (0.001 mmole) was added and the mixture was heated under reflux for 1 hour. The precipitate was, after cooling to room temperature, collected by filtration to give **6** in 97% yield, mp 243-245° (from ethanol); ms: 397 (M^+); ^1H nmr (DMSO-d_6): δ 2.47 (bs, Me, DMSO), 6.42 (d, $H_{4'}$), 7.44-7.67 (m, 3H-PhCO, 3H-PhCH), 7.77 (d, $H_{5'}$), 7.79-8.06 (m, 2H-PhCO, 2H-PhCH), 8.46 (s, H_4), 8.89 (s, C*H*-Ph), 9.34 (br s, N*H*COPh), NH exchanged, $J_{H4',H5'}$ = 2.0 Hz.

Anal. Calcd. for $C_{23}H_{19}N_5O_2$: C, 69.51; H, 4.82; N, 17.62. Found: C, 69.93; H, 4.46; N, 17.51.

3-Benzoylamino-2*H*-pyrano[2,3-*b*]pyridine-2,5-dione (**11**).

To a solution of ammonia in absolute ethanol (10 ml) pyranone **7** (0.356 g, 0.001 mmole) was added and a suspension was stirred at room temperature for 48 hours. The precipitate was collected by filtration and washed with ethanol to give **11** in 62% yield, mp 245-247° (from DMF); ^1H nmr (DMF-d_7): δ 7.48 (d, H_6), 7.57-7.76 (m, 3H-Ph), 8.01-8.22 (m, 2H-Ph, DMF), 8.46 (d, H_7), 8.94 (s, H_4), 9.84 (br s, N*H*COPh), $J_{H6,H7}$ = 7.8 Hz.

Anal. Calcd. for $C_{15}H_{10}N_2O_4$: C, 63.83; H, 3.57; N, 9.93. Found: C, 63.60; H, 3.58; N, 9.58.

Ethyl 4-Benzoylamino-2-(isoxazolyl-5)but-3-enoate (**15**).

A suspension of the pyranone **7** (0.356 g, 0.001 mmole) and hydroxylamine hydrochloride (0.076 g, 0.001 mmole) in methanol (5 ml) was heated under reflux for 30 minutes. The volatile components were evaporated *in vacuo*. The oily residue was dissolved in chloroform (30 ml) and extracted with water (3 X 10 ml). The organic phase was dried over anhydrous sodium sulphate and evaporated *in vacuo*, methanol (3 ml) and water (1 ml) was added to the residue and the precipitate was collected by filtration and recrystallized from a mixture of methanol and water to give **15** in 59% yield, mp 115-117°; ms: 300 (M^+); ^1H nmr (DMSO-d_6): δ 1.29 (t, CH_2CH_3), 4.27 (q, CH_2CH_3), 5.01 (d, C*H*COOEt), 5.74 (dd, CH-C*H*=CH), 6.43 (d, $H_{4'}$), 7.29 (dd, CH=C*H*-NHCOPh), 7.45-7.72 (m, 3H-Ph), 7.85-8.09 (m, 2H-Ph), 8.57 (d, $H_{3'}$), 11.41 (d, N*H*COPh), J_{CH2CH3} = 7.0 Hz, J_{CHNH} = 10.0 Hz, $J_{CH=CH}$ = 14.0 Hz, J_{CH-CH} = 9.0 Hz, $J_{H3',H4'}$ = 2.0 Hz.

Anal. Calcd. for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.82; H, 5.29; N, 9.32.

5-Acetyl-3-benzoylamino-6-[1-ethenyl-2-(5,5-dimethyl-1-hydroxy-3-oxocyclohexenyl-2)]-2*H*-pyran-2-one (**17**).

A suspension of the pyranone **1** (0.326 g, 0.001 mmole) and 5,5-dimethyl-1,3-cyclohexanedione (**16**) (0.142 g, 0.001 mmole) in acetic acid (4 ml) was heated under reflux for 30 minutes. The precipitate was, after cooling to room temperature, collected by filtration to give **17** in 57% yield, mp 243-245° (washed with chloroform); ^1H nmr (DMSO-d_6): δ 1.03 (s, 5',5'-CH_3), 2.34-2.61 (m, 2 x CH_2, CH_3CO, DMSO), 7.52-7.81 (m, 3H-Ph, C*H*=CH), 7.92-8.07 (m, 2H-Ph), 8.22 (d, CH=C*H*), 8.59 (s, H_4), 9.71 (s, N*H*COPh), $J_{CH=CH}$ = 15.0 Hz.

Anal. Calcd. for $C_{24}H_{23}NO_6$: C, 68.40; H, 5.50; N, 3.33. Found: C, 68.58; H, 5.28; N, 3.58.

3-Benzoylamino-5-ethoxycarbonyl-6-[1-ethenyl-2-(5,5-dimethyl-1-hydroxy-3-oxocyclohexenyl-2)]-2*H*-pyran-2-one (**18**).

A suspension of the pyranone **7** (0.356 g, 0.001 mmole) and 5,5-dimethyl-1,3-cyclohexanedione (**16**) (0.142 g, 0.001 mmole) in acetic acid (5 ml) was heated under reflux for 20 minutes. The precipitate was, after cooling to room temperature, collected by filtration to give **18** in 90% yield, mp 245-247° (washed with ethanol); ^1H nmr (DMSO-d_6): δ 1.05 (s, 5',5'-CH_3), 1.38 (t, CH_2CH_3), 2.37-2.65 (m, 2 x CH_2, DMSO), 4.19-4.93 (m, CH_2CH$_3$, OH, H_2O), 7.56-7.78 (m, 3H-Ph), 7.72 (d, C*H*=CH), 7.96-8.17 (m, 2H-Ph), 8.48 (d, CH=C*H*), 8.62 (s, H_4), 9.71 (bs, N*H*COPh), $J_{CH=CH}$ = 15.0 Hz.

Anal. Calcd. for $C_{25}H_{25}NO_7$: C, 66.51; H, 5.58; N, 3.10. Found: C, 66.25; H, 5.47; N, 3.32.

3-Benzoylamino-5-ethoxycarbonyl-6-[1-ethenyl-2-(2,4,6-trihydroxypyrimidinyl-5)]-2*H*-pyran-2-one (**20**).

A suspension of the pyranone **7** (0.356 g, 0.001 mmole) and barbituric acid hydrate (**19**) (0.180 g, 0.0011 mmole) in acetic acid (5 ml) was heated under reflux for 45 minutes. The precipitate was, after cooling to room temperature, collected by filtration to give **20** in 97% yield, mp 276-279° dec (washed with ethanol); ^1H nmr (DMSO-d_6): δ 1.36 (t, CH_2CH_3), 4.33 (q, CH_2CH_3), 7.59-8.35 (m, 5H-Ph, C*H*=C*H*), 8.52 (s, H_4), 9.68 (br s, N*H*COPh), 10.23 (br s, 2 x N*H* or O*H*).

Anal. Calcd. for $C_{21}H_{17}N_3O_8$: C, 57.41; H, 3.90; N, 9.56. Found: C, 57.46; H, 3.77; N, 9.77.

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