Pergamon

Tetrahedron 54 (1998) 9799–9810

TETRAHEDRON

The Synthesis and Transformations of Substituted 2-Hydroxy-3-dimethylaminopropenoates. The Preparation of Condensed 3-Hydroxypyran-2-ones

Janez Smodiš and Branko Stanovnik*

Faculty of Chemistry and Chemical Technology, University of Ljubljana,
P. O. Box 537, Aškerčeva 5, 1001 Ljubljana, Slovenia

Dedicated to Professor Alan R. Katritzky, University of Florida, Gainesville, USA, on the occasion of his 70th birthday

Received 6 March 1998; revised 24 April 1998; accepted 29 May 1998

Abstract: A convenient synthesis of substituted 2-hydroxy-3-dimethylaminopropenoates is reported. They react with cyclic 1,3-diketones, with aromatic and heteroaromatic hydroxy compounds to afford the corresponding 3-substituted hydroxytetrahydro-*2H*-1-benzopyran-2-ones, benzo- and naphthopyran-2-ones and azolo- and azinopyran-2-ones, respectively. Catalytic debenzylation of 3-benzyloxy substituted fused pyran-2-ones gives free 3-hydroxy derivatives.

2H-Pyran-2-ones and fused pyran-2-ones are important biologically active compounds.[1a,b] Among condensed *2H*-pyran-2-ones derivatives, *2H*-1-benzopyran-2-one (coumarin) plays an important role. Derivatives of this ring system can be found in numerous plants as metabolites.[1c] They exhibit various pharmacological activities as hypnotics, insecticides, antimicrobial agents, diuretics,[1d,e] and anticoagulants.[1f]

Rapid progress in the field of *2H*-pyran-2-ones and condensed systems in recent years is due to the introduction of several drug receptor binding models leading to novel inhibitors of various enzymes, such as HIV protease,[2a-f] and α-chymotrypsin. 3,4-Dihydroxy-*2H*-benzopyran-2-ones and their hexahydro diastereomers show anti-lipidemic and platelet antiaggregatory properties.[1e]

However, from the synthetic point of view, the basic idea of construction of the coumarin system from the corresponding aromatic compound and C_2 or C_3 synthon has remained unchanged for many decades.[1a,3] Recently, substituted alkyl 2-acylamino-3-dimethylaminopropenoates and alkyl 2-(2,2-disubstituted)ethenyl-aminopropenoates, masked α-formyl-α-amino acid derivatives, have been used for the preparation of many heterocyclic systems, including *2H*-pyran-2-ones and fused pyran-2-ones with a protected amino group attached at position 3 of the pyranone ring.[4]

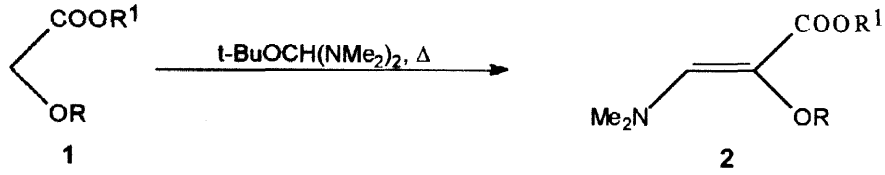
The synthesis of substituted 3-dimethylamino-2-hydroxypropenoates

It has been reported that 2-methoxy- and 2-ethoxy- 3-dimethylaminopropenoates have been prepared from 2-methoxy- or 2-ethoxy- acetoacetate and t-butoxy-bis(dimethylamino)methane. They have been used for the synthesis of derivatives of oxaloacetic acid in α–substituted tetronic acids.[5]

We now report, the synthesis of substituted 3-amino-2-hydroxypropenoates (**2**), α-formyl-α-hydroxy acid derivatives, as reagents for construction of fused pyran-2-ones with a hydroxy or substituted hydroxy group attached at position 3 in the newly formed ring. They were prepared from substituted 2-hydroxyacetic acid esters and t-butoxy-bis(dimethylamino)methane in 73-90% yield (Scheme 1). The structure of compounds **2a-d** were determined by ^{1}H NMR spectra, which show a singlet at δ= 6.95-7.25 ppm for H_3, indicating that only one isomer exists in solution. It was shown by X-ray analysis that methyl 2-benzoyloxy-3-dimethylaminopropenoate (**2a**) exists in the solid state in the (*Z*)-form.[6]

0040-4020/98/$ - see front matter
PII: S0040-4020(98)00534-1

Scheme 1



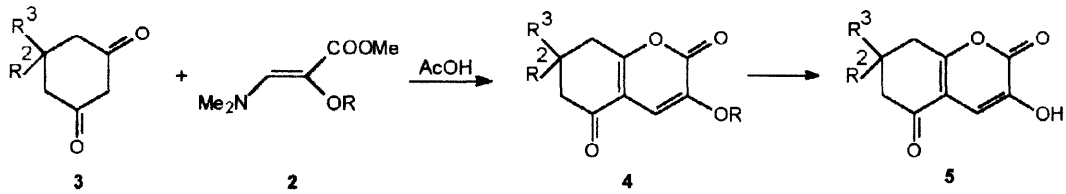
1 2

1, 2	R	R^1
a	COPh	Me
b	CH_2Ph	Me
c	Ph	Me
d	COPh	Et

Reactions of 3-aminopropenoates with 1,3-dicarbonyl compounds

Cyclic diones, such as cyclohexane-1,3-dione (**3a**) and dimedone (**3b**) react with 2-benzoyloxy- (**2a**) and 2-benzyloxy- 3-dimethylaminopropenoate (**2b**) when heated in acetic acid at 130°C for 2 hours to give 3-benzoyloxy-5-oxo-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-one (**4a**) and its 3-benzyloxy derivative (**4b**) in 26% and 45% yield, respectively (Scheme 2).

Scheme 2



3 2 4 5

3	R^2	R^3	4	R	R^2	R^3	5	R^2	R^3
a	H	H	**a**	COPh	H	H			
b	Me	H	**b**	COPh	Me	Me			
c	Me	Me	**c**	CH_2Ph	H	H	**c**	H	H
			d	CH_2Ph	Me	H			
			e	CH_2Ph	Me	Me	**e**	Me	Me

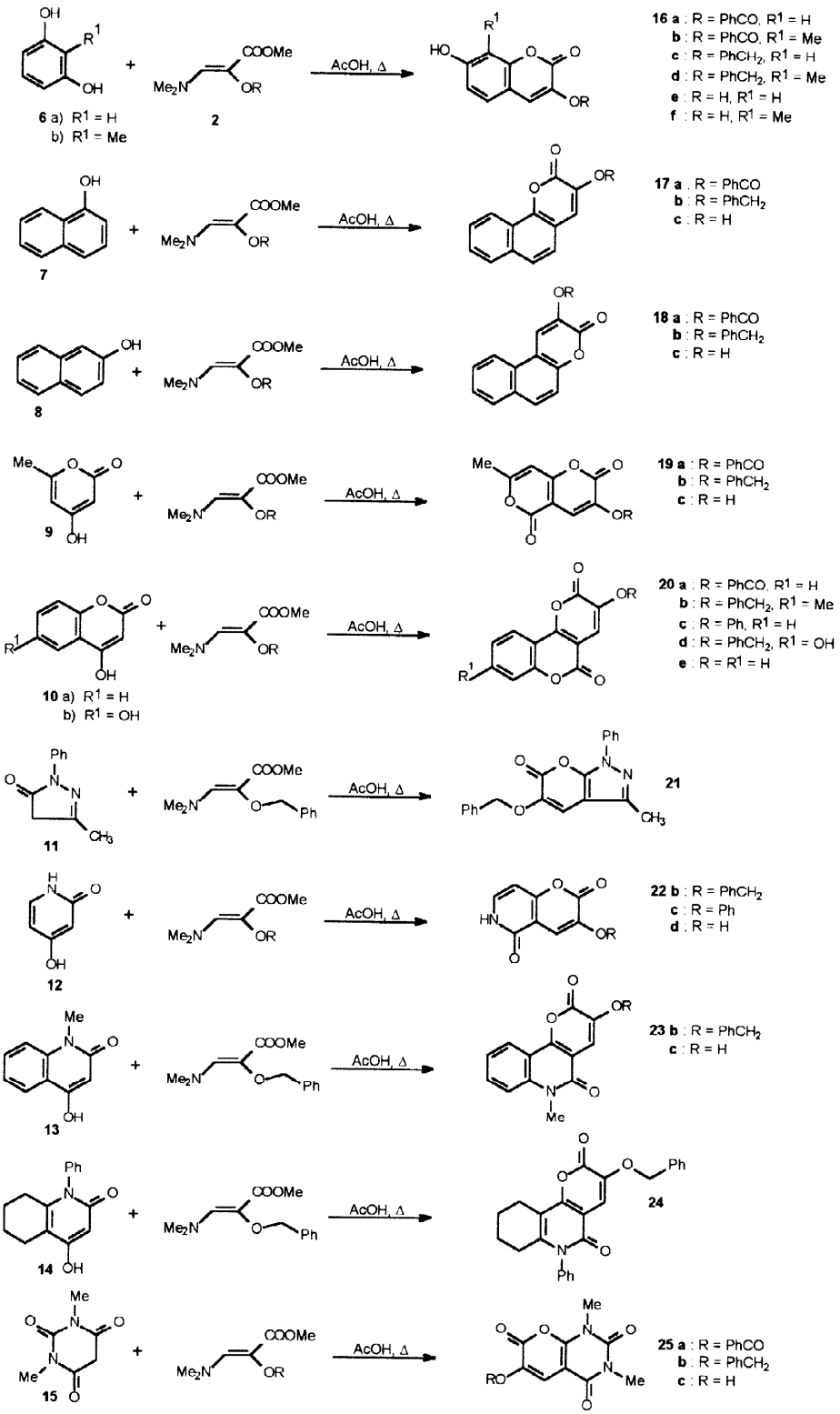
Reactions of 3-aminopropenoates with aromatic and heteroaromatic hydroxy compounds

Condensed 3-hydroxypyranones have been prepared from 3-amino or substituted 3-amino derivatives by hydrolysis,[7] while 3-phenoxy substituted coumarins have been prepared from acetamides and salicylaldehyde in the presence of phosphorous oxychloride.[8] 3-Hydroxycoumarins have been found among metabolites.[1c] They are chemically interesting compounds because of activation of the 4-position towards electrophilic substitution[9] and sigmatropic rearrangements.[10]

Activated aromatic and heteroaromatic hydroxy or potential hydroxy compounds react with compounds **2a-d** to form 3-substituted hydroxypyran-2-one systems fused to aromatic or heteroaromatic ring. The reactions were carried out in glacial acetic acid at reflux temperature. The following compounds were selected: **6a,b**, **7-9**,

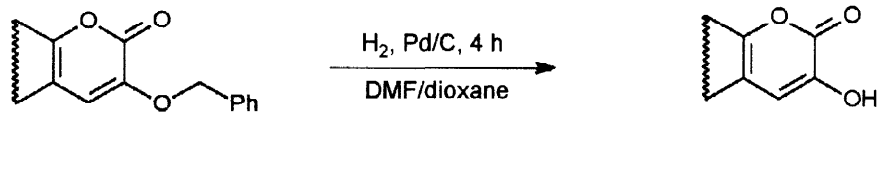
10a,b, **11-15** to give the following compounds **16a-d**, **17a,b**, **18a,b**, **19a,b**, **20a-d**, **21**, **22b,c**, **23b**, **24**, and **25a,b**, respectively (Scheme 3).

Scheme 3



Fused pyran-2-ones containing a 3-benzyloxy group, such as **16c,f**, **17c**, **18c**, **19c**, **20b**, **22b**, **23b**, **25b**, were catalytically debenzylated with hydrogen over Pd/C at 3 atm in a mixture of DMF and dioxane as solvent. The reaction was complete in 2-4 hours to give the products **16e,f**, **17c**, **18c**, **19c**, **20b**, **22c**, **23c**, and **25c**, respectively, with free hydroxy group at position 3, in 80-98% yield (Scheme 4).

Scheme 4

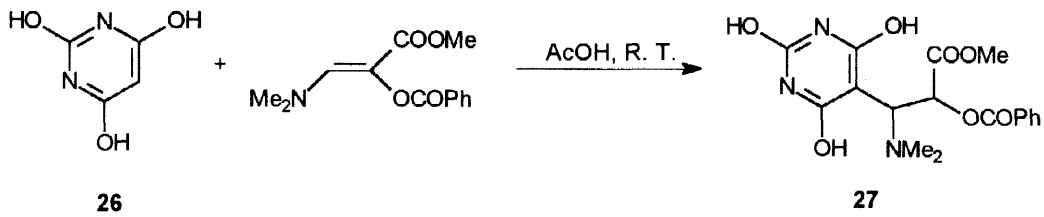


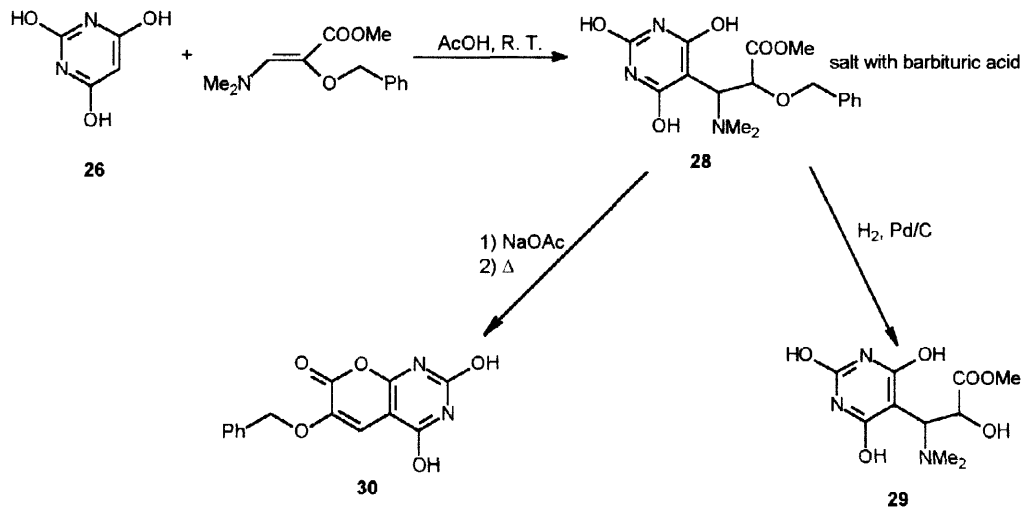
16c → **16e**		**20b** → **20e**	
16d → **16f**		**22b** → **22d**	
17b → **17c**		**23b** → **23c**	
18b → **18c**		**25b** → **25c**	
19b → **19c**			

Reactions of 3-aminopropenoates with barbituric acid and aminouracil

Barbituric acid (**26**) is insoluble in organic solvents, but it is soluble in acetic acid at boiling point. However, on reaction with 2-benzoyloxy-3-dimethylaminopropenoate (**2a**) a mixture of products was formed. When the reaction was carried out at room temperature only one product was formed in 24 hours.

Scheme 5



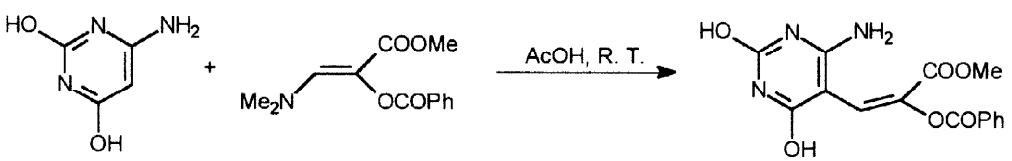


It was concluded on the basis of the ^{1}H NMR spectrum that nucleophilic addition of a *C*-nucleophile to the double bond of **2a** occured to give methyl 2-benzoyloxy-3-dimethylamino-3-(2,4,6-trihydroxy-5-pyrimidinyl)propanoate (**27**) in 70% yield. Similarly, **26** reacts with methyl 2-benzyloxy-3-dimethylaminopropenoate (**2b**) to give methyl 3-dimethylamino-2-hydroxy-3-(2,4,6-trihydroxypyrimidin-5-yl)propanoate (**28**), from which dimethylamine was eliminated, allowing cyclization to 6-benzyloxy-2,4-dihydroxy-7*H*-pyrano[2,3-*d*]pyrimidin-7-one (**30**). However, **28** is in fact a salt formed between the adduct and barbituric acid, from which the benzyl group can be easily removed to give 3-dimethylamino-2-hydroxy-3-(2,4,6-trihydroxypyrimidin-5-yl)propanoate (**29**). (Scheme 5).

6-Aminouracil (**31**) is less soluble in acetic acid. At higher temperature a complex mixture of products was formed from reaction with **2a**. However, when the reaction mixture was stirred at room temperature for 14 days, the *C*-substituted product 2-benzoyloxy-3-(6-amino-3*H*-dihydroxypyrimidin-5-yl)propenoate (**32**) was formed, indicating that addition to C_5 occurs in preference to addition-elimination of the 6-amino group. This is in agreement with other observations, that C_5 is more nucleophilic than group at the 6-position[11, 12] (Scheme 6).

The structure of **32** was confirmed by the ^{1}H NMR spectrum which shows a singlet at δ = 7.2 ppm for the olefinic proton (H3), two singlets at δ = 10.4 ppm and δ = 10.55 ppm for the 2- and 4- hydroxy groups at positions 2 and 6, and a broad singlet at δ = 6.75 ppm, integrating for two protons, assigned to the 6-amino group. After addition of deuterated water the last three peaks disappear.

Scheme 6



31 **32**

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^{1}H nmr spectra were obtained on a Varian EM 360 L and Bruker Avance 300 DPX spectrometers, mass spectra on an Autospeck Q spectrometer, and microanalyses for C, H, and N on a Perkin-Elmer Analyse 2400.

The following compounds were prepared according to the procedures described in the literature: methyl benzoyloxyacetate (**1a**),[13] methyl benzyloxyacetate (**1b**),[14] and methyl phenyloxyacetate (**1c**).[15]

General procedure for the synthesis of 2-hydroxy substituted-3-dimethylaminopropenoates. A mixture of 2-hydroxy substituted acetates (**1**; 10 mmole) and t-butoxy-bis(dimethylamino)methane (12.5 mmole) was stirred at 90°C in an argon atmosphere for 2 hours. t-Butanol and dimethylamine formed during the reaction were distilled off. After cooling, water (50 ml) was added and the suspension was extracted with dichloromethane (3x, 50 ml). The solvent was removed from the dried (Na_2SO_4) organic layer and the residue was purified by crystallization or distillation.

The following compounds were prepared in this manner:

Methyl 2-benzoyloxy-3-dimethylaminopropenoate (2a): from methyl benzoyloxyacetate (**1a**); yield 73%, mp 104-106°C (methanol). NMR ($CDCl_3$) δ: 2.95 (6H, s, N*Me*$_2$), 3.65 (3H, s, COO*Me*), 7.15 (1H, s, 3-*H*), 7.40-7.65 (3H, m, 3H(*Ph*)), 8.05-8.30 (2H, m, 2H(*Ph*)). *Anal.* Calcd. for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.87; H, 6.04; N, 5.75.

Methyl 2-benzyloxy-3-dimethylaminopropenoate (**2b**): from methyl benzyloxyacetate (**1b**); yield 90%, bp $_{0.1\ mm\ Hg}$= 140°C. NMR ($CDCl_3$) δ: 3.0 (6H, s, N*Me*$_2$), 3.75 (3H, s, COO*Me*), 4.75 (2H, s C*H*$_2$), 6. 95 (1H, s, 3-*H*), 7.30-7.65 (5H, m, *Ph*). *Anal.* Calcd. for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.46; H, 7.91; N, 5.94.

Methyl 3-dimethylamino-2-phenyloxyacetate (**2c**): from methyl phenyloxyacetate (**1c**); yield 84%, mp 82-84°C (cyclohexane/petroleter 2:1). NMR ($CDCl_3$) δ: 2.95 (6H, s, N*Me*$_2$), 3.6 (3H, s, COO*Me*), 6.90-7.40 (6H, m, *Ph*, =C*H*-). *Anal.* Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.94; H, 6.87; N, 6.41.

Ethyl 2-benzoyloxy-3-dimethylaminopropenoate (**2d**): from ethyl benzoyloxyacetate (**1d**); yield 74%, mp 100-104°C (diisopropylether/n-hexane 2:1). NMR ($CDCl_3$) δ: 1.2 (3H, t, *Me*CH_2, J_{MeCH2}= 7.0 Hz), 3.0 (6H, s, N*Me*$_2$), 4.2 (2H, q, MeC*H*$_2$), 7.25 (1H, s, =C*H*-), 7.5-7.7 (3H, m, 3H(*Ph*)), 8.15-8.35 (2H, m, 2H(*Ph*)). *Anal.* Calcd. for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.75; H, 6.50; N, 5.27.

Reactions of cyclohexane-1,3-diones with 2. General procedure: A mixture of cyclohexane-1,3-dione derivative (**3**, 1 mmole) and **2** (1 mmole) in glacial acetic acid (5 ml) was heated in an oil bath at 130°C in an argon atmosphere for two hours. The residue obtained after evaporation of volatile components under reduced pressure was recrystallized from appropriate solvent.

The following compounds were prepared in this manner:

3-Benzoyloxy-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2,5-dione (**4a**): from methyl 2-benzoyloxy-3-dimethylaminopropenoate (**2a**) and cyclohexane-1,3-dione (**3a**); yield 26%, mp 125-127°C (ethanol/water 1:1). NMR ($CDCl_3$) δ: 2.25 (2H, tt, 7-C*H*$_2$, $J_{6,7}$≅$J_{7,8}$=6.0 Hz), 2.7 and 2.95 (2x2H, 2xt, 6-C*H*$_2$ and 8-C*H*$_2$), 7.50-7.80 (3H, m, 3H(*Ph*)), 7.80 (1H, s, 4-*H*), 8.10-8.35 (2H, m, 2H(*Ph*)). *Anal.* Calcd. for $C_{16}H_{12}O_5$: C, 67.60; H, 4.25. Found: C, 67.45; H, 4.17.

3-Benzoyloxy-7,7-dimethyl-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2,5-dione (**4b**): from ethyl 2-benzoyloxy-3-dimethylaminopropenoate (**2d**) and 5,5-dimethylcyclohexane-1,3-dione (**3c**); yield 34%, mp 135-136°C (diisopropyl ether). NMR ($CDCl_3$) δ: 1.20 (6H, s, 2x7-*Me*), 2.45 (2H, s, 6-C*H*$_2$), 2.75 (2H, s, 8-C*H*$_2$), 7.40-7.70 (3H, m, 3H(*Ph*)), 7.75 (1H, s, 4-*H*), 8.10-8.30 (2H, m, 2H(*Ph*)). *Anal.* Calcd. for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16. Found: C, 69.28; H, 4.97.

3-Benzyloxy-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2,5-dione (**4c**): from methyl 2-benzyloxy-3-dimethylaminopropenoate (**2b**) and cyclohexane-1,3-dione (**3a**); yield 45%, mp 135-137°C (ethanol). NMR ($CDCl_3$) δ: 2.15 (2H, tt, 7-C*H*$_2$, $J_{6,7}$≅$J_{7,8}$=6.0 Hz), 2.65 and 2.85 (2x2H, 2xt, 6-C*H*$_2$ and 8-C*H*$_2$), 5.20 (2H, s, PhC*H*$_2$), 7.10 (1H, s, 4-H), 7.45 (5H, brs, *Ph*). *Anal.* Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 70.90; H, 5.19.

3-Benzyloxy-7-methyl-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2,5-dione (**4d**): from methyl 2-benzyloxy-3-dimethylaminopropenoate (**2b**) and 5-methylcyclohexane-1,3-dione (**3d**); yield 51%, mp 128-131°C (ethanol). NMR (DMSO-d_6) δ: 1.00-1.20 (3H, d, 7-*Me*, J_{MeCH}= 4.0 Hz), 2.30-2.85 (5H, m, 7-H, 6-CH_2, 8-CH_2), 5.15 (2H, s, PhC*H*$_2$), 7.15 (1H, s, 4-H), 7.50 (5H, brs, Ph). *Anal.* Calcd. for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.95; H, 5.70.

3-Benzyloxy-7,7-dimethyl-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2,5-one (**4e**): from methyl 2-benzyloxy-3-dimethylaminopropenoate (**2b**) and 5,5-dimethylcyclohexane-1,3-dione (**3c**); yield 52%, mp 149-152°C (ethanol). NMR ($CDCl_3$) δ: 1.10 (6H, s, 2x7-*Me*), 2.40 (2H, s, 6-C*H*$_2$), 2.65 (2H, s, 8-C*H*$_2$), 5.1 (2H, s, PhC*H*$_2$), 7.05 (1H, s, 4-*H*), 7.45 (5H, brs, *Ph*). *Anal.* Calcd. for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.29; H, 5.93.

Reactions of 2 with aromatic and heterocyclic hydroxy compounds. General procedure: To a solution of aromatic or heteroaromatic hydroxy compound (2 mmole) in glacial acetic acid (10 ml), propenoate **2** (2 mmole) was added. The mixture was heated on an oil bath at 130°C for two hours in an argon atmosphere. The volatile components were evaporated *in vacuo* and the residue recrystallized from an appropriate solvent.

In this manner, the following compounds were prepared:

3-Benzoyloxy-7-hydroxy-2*H*-1-benzopyran-2-one (16a): from **2a** and 1,3-dihydroxybenzene (**6a**); yield 20%, mp 220-221°C (ethanol/water 5:1). NMR (DMSO-d_6) δ: 6.85 (1H, d, 8-*H*, $J_{6,8}$= 2.0 Hz), 6.95 (1H, dd, 6-*H*, $J_{5,6}$= 6.5 Hz), 7.6 (1H, d, 5-H), 7.6-7.9 (3H, m, 3H(*Ph*)), 8.1 (1H, s, 4-*H*), 8.05-8.30 (2H, m, 2H(*Ph*)). *Anal.* Calcd. for $C_{16}H_{10}O_5$: C, 68.09; H, 3.57. Found: C, 68.38; H, 3.36.

3-Benzoyloxy-7-hydroxy-8-methyl-2*H*-1-benzopyran-2-one (16b): from **2a** and 1,3-dihydroxy-2-methylbenzene (**6b**); yield 42%, mp 260-262°C (DMF/ethanol 1:2). NMR (DMSO-d_6) δ: 2.25 (3H, s, 8-*Me*), 3.20-4.50 (1H, brs, O*H*), 7.00 (1H, d, 6-*H*, $J_{5,6}$= 8.5 Hz), 7.5 (1H, d, 5-*H*), 7.65-7.95 (3H, m, 3H(*Ph*)), 8.1 (1H, s, 4-*H*), 8.10-8.35 (2H, m, 2H(*Ph*)). *Anal.* Calcd. for $C_{17}H_{12}O_5$: C, 68.92; H, 4.08. Found: C, 68.84; H, 4.25.

3-Benzyloxy-7-hydroxy-2*H*-1-benzopyran-2-one (16c): from **2b** and 1,3-dihydroxybenzene (**6a**); yield 13%, mp 242-245°C (ethanol). NMR (DMSO-d_6) δ: 5.15 (2H, s, PhCH_2), 6.75 (1H, s, 8-*H*), 6.85 (1H, dd, 6-*H*, $J_{5,6}$= 8 Hz, $J_{6,8}$= 1.5 Hz), 7.30-7.70 (7H, brs, Ph, 4-H, 5-H). *Anal.* Calcd. for $C_{16}H_{12}O_4$: C, 71.64; H, 4.51. Found: C, 71.11; H, 4.40.

3-Benzyloxy-7-hydroxy-8-methyl-2*H*-1-benzopyran-2-one (16d): from **2b** and 1,3-dihydroxy-2-methylbenzene (**6b**); yield 44%, mp 232-238°C (ethanol). NMR (DMSO-d_6) δ: 2.20 (3H, s, 8-*Me*), 5.15 (2H, s, PhCH_2), 6.90 (1H, d, 6-*H*, $J_{5,6}$= 8.5 Hz), 7.30 (1H, d, 5-*H*), 7.50 (1H, s, 4-*H*), 7.50 (5H, brs, *Ph*), 9.00-10.00 (1H, brs, O*H*). *Anal.* Calcd. for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.54; H, 4.96.

3-Benzoyloxy-2*H*-naphtho[1,2-*b*]pyran-2-one (17a): from **2a** and 1-hydroxynaphthalene (**7**); yield 12%, mp 203-205°C (ethanol). NMR ($CDCl_3$) δ: 7.35-8.05 (9H, m, 3H(*Ph*), 4,5,6,7,8,9-*H*), 8.15-8.40 (2H, m, 2H(*Ph*)), 8.45-8.75 (1H, m, 10-*H*). *Anal.* Calcd. for $C_{20}H_{12}O_4$: C, 75.95; H, 3.82. Found: C, 75.90; H, 4.01.

3-Benzyloxy-2*H*-naphtho[1,2-*b*]pyran-2-one (17b): from **2b** and 1-hydroxynaphthalene (**7**); yield 23%, mp 164-166°C (ethanol). NMR ($CDCl_3$) δ: 5.25 (2H, s, PhCH_2), 7.05 (1H, s, 4-*H*), 7.40 (1H, d, 5-*H*, $J_{5,6}$= 9 Hz), 7.7 (1H, d, 6-*H*), 7.25-8.00 (8H, m, 5H(*Ph*), 7,8,9-*H*), 8.35-8.65 (1H, m, 10-*H*). *Anal.* Calcd. for $C_{20}H_{14}O_3$: C, 79.46; H, 4.67. Found: C, 79.26; H, 4.63.

2-Benzoyloxy-3*H*-naphtho[2,1-*b*]pyran-2-one (18a): from **2a** and 2-hydroxynaphthalene (**8**); yield 47%, mp 175-178°C (n-propanol). NMR ($CDCl_3$) δ: 7.40-7.95 (7H, 3H(*Ph*), 7,8,9,10-*H*), 7.50 (1H, d, 5-*H*, $J_{5,6}$= 9.0 Hz), 8.05 (1H, d, 6-*H*), 8.20-8.40 (2H, m, 2H(*Ph*)), 8.50 (1H, s, 1-*H*). *Anal.* Calcd. for $C_{20}H_{12}O_4$: C, 75.94; H, 3.82. Found: C, 75.79; H, 3.88.

2-Benzyloxy-3*H*-naphtho[2,1-*b*]pyran-2-one (18b): from **2b** and 2-hydroxynaphthalene (**8**); yield 41%, mp 190-192°C (ethanol). NMR ($CDCl_3$) δ: 5.3 (2H, s, PhCH_2), 7.30-8.20 (9H, m, 5H(*Ph*), 7,8,9,10-*H*), 7.40 (1H, d, 5-*H*, $J_{5,6}$= 9.0 Hz), 7.65 (1H, s, 1-*H*), 7.85 (1H, d, 6-*H*). *Anal.* Calcd. for $C_{20}H_{14}O_3$: C, 79.46; H, 4.67. Found: C, 79.46; H, 4.66.

3-Benzoyloxy-7-methyl-2*H*,5*H*-pyrano[4,3-*b*]pyran-2,5-dione (19a): from **2a** and 4-hydroxy-6-methyl-2*H*-pyran-2-one (**9**); yield 28%, mp 200-202°C (n-propanol). NMR (DMSO-d_6) δ: 2.35 (3H, s, 7-*Me*), 6.75 (1H, s, 8-*H*), 7.40-7.90 (3H, m, 3H(*Ph*)), 8.05 (1H, s, 4-*H*), 8.00-8.30 (2H, m, 2H(*Ph*)). *Anal.* Calcd. for $C_{16}H_{10}O_6$: C, 64,43; H, 3.38. Found: C, 64.63; H, 3.07.

3-Benzyloxy-7-methyl-2*H*,5*H*-pyrano[4,3-*b*]pyran-2,5-dione (19b): from **2b** and 4-hydroxy-6-methyl-2*H*-pyran-2-one (**9**); yield 91%, mp 223-225°C (ethanol). NMR (DMSO-d_6) δ: 2.30 (3H, s, 7-*Me*), 5.2 (2H, s, PhCH_2), 6.65 (1H, s, 8-*H*), 7.15 (1H, s, 4-*H*), 7.50 (5H, brs, 5H(*Ph*)). *Anal.* Calcd. for $C_{16}H_{12}O_6$: C, 67.60; H, 4.25. Found: C, 67.56; H, 4.15.

3-Benzoyloxy-2*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-2,5-dione (20a): from **2a** and 4-hydroxycoumarin (**10a**); yield 16%, mp 234-236°C (DMF/ethanol 1:2). NMR (DMSO-d_6) δ: 7.50-8.00 (6H, m, 3H(*Ph*), 7,8,9-*H*), 8.00-8.30 (4H, m, 2H(*Ph*), 4,10-H). *Anal.* Calcd. for $C_{19}H_{10}O_6$: C, 68.27; H, 3.02. Found: C, 68.05; H, 2.87.

3-Benzyloxy-2*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-2,5-dione (20b): from **2b** and 4-hydroxycoumarin (**10a**); yield 22%, mp 239-243°C (DMF/ethanol 1:3). NMR (DMSO-d_6) δ: 5.25 (2H, s, PhCH_2), 7.30 (1H, s, 4-*H*), 7.40-7.80 (8H, m, 5H(*Ph*), 7,8,9-H), 7.85-8.20 (1H, m, 10-*H*). *Anal.* Calcd. for $C_{19}H_{12}O_5$: C, 71.25; H, 3.87. Found: C, 71.05; H, 3.66.

3-Phenyloxy-2*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-2,5-dione (20c): from **2c** and 4-hydroxycoumarin (**10a**); yield 32%, mp 230-231°C (DMF/ethanol 1:1). NMR (DMSO-d_6) δ: 7.10-8.20 (10H, m, 5H(*Ph*), 4,7,8,9,10-*H*). *Anal.* Calcd. for $C_{18}H_{10}O_5$: C, 70.59; H, 3.29. Found: C, 70.80; H, 3.05.

3-Benzyloxy-9-hydroxy-2*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-2,5-dione (20d): from **2b** and 4,6-dihydroxycoumarin (**10b**); yield 29%, mp 297-300°C (DMF/ethanol 2:5). NMR (DMSO-d_6) δ: 5.25 (2H, s, PhCH_2), 6.90 (1H, d, 10-*H*, $J_{8,10}$=2.0 Hz), 6.95 (1H, dd, 8-*H*, $J_{7,8}$=2.0 Hz), 7.55 (5H, s, *Ph*), 7.80 (1H, d, 7-*H*), 10.40-11.40 (1H, brs, 9-O*H*). *Anal.* Calcd. for $C_{19}H_{12}O_6$: C, 67.86; H, 3.60. Found: C, 67.70; H, 3.24.

5-Benzyloxy-3-methyl-1-phenyl-1*H*,6*H*-pyrazolo[3,4-*b*]pyran-6-one (21): from 3-methyl-1-phenylpyrazol-5(4*H*)-one (**11**) and **2b**; yield 15%, mp 226-230°C (ethanol). NMR (DMSO-d_6) δ: 2.20 (3H, s, 3-*Me*), 4.20 (2H, s, PhCH_2), 7.20-7.95 (11H, m, 2xPh, 4-*H*). *Anal.* Calcd. for $C_{20}H_{16}N_2O_3$: C, 72.28; H, 4.85; N, 8.43. Found: C, 72.41; H, 4.86; N, 8.47.

3-Benzyloxy-5,6-dihydro-2*H*-pyrano[2,3-*c*]pyridine-2,5-dione (22b): from **2b** and 4-hydroxypyridin-2(1*H*)-one (**12**); yield 72%, mp 285-287°C (ethanol). NMR (DMSO-d_6) δ: 5.2 (2H, s, PhCH_2), 6.4 (1H, s, 8-*H*, $J_{7,8}$= 7.5 Hz), 7.3 (1H, s, 4-*H*), 7.50 (5H, brs, Ph), 7.50 (1H, d, 7-*H*), 11.60-12.30 (1H, brs, N*H*). *Anal.* Calcd. for $C_{15}H_{11}NO_4$: C, 66.91; H, 4.12; N, 5.20. Found: C, 66.51; H, 3.99; N, 5.29.

3-Phenyloxy-5,6-dihydro-2*H*-pyrano[2,3-*c*]pyridine-2,5-dione (22c): from **2c** and 4-hydroxypyridin-2(1*H*)-one (**12**); yield 62%, mp 228-230°C (ethanol). NMR (DMSO-d_6) δ: 6.45 (1H, s, 8-*H*, $J_{7,8}$= 7.0 Hz), 7.10-7.70 (6H, m, 5H(*Ph*), 4-H), 7.65 (1H, d, 7-*H*), 11.40-12.70 (1H, brs, N*H*). *Anal.* Calcd. for $C_{14}H_9NO_4$: C, 65.88; H, 3.55; N, 5.49. Found: C, 65.70; H, 3.37; N, 5.40.

3-Benzyloxy-6-methyl-5,6-dihydro-2*H*-pyrano[3,2-*c*]quinoline-2,5-dione (23b): from **2b** and 4-hydroxy-1-methylquinolin-2(1*H*)-one (**13**); yield 63%, mp 186-189°C (ethanol). NMR (DMSO-d_6) δ: 3.65 (3H, s, 6-*Me*), 5.20 (2H, s, PhCH_2), 7.30 (1H, s, 4-*H*), 7.20 -7.80 (8H, m, 5H(*Ph*), 7,8,9-*H*), 7.95 (1H, dd, 10-*H*, $J_{8,10}$= 1.5 Hz, $J_{9,10}$= 8.0 Hz). *Anal.* Calcd. for $C_{20}H_{15}NO_4$: C, 72.06; H, 4.54; N, 4.20. Found: C, 72.29; H, 4.44; N, 4.20.

3-Benzyloxy-6-phenyl-5,6,7,8,9,10-hexahydro-2*H*-pyrano[3,2-*c*]quinoline-2,5-dione (24): from **2b** and 4-hydroxy-1-phenyl-6,7,8,9-tetrahydroquinolin-2(1*H*)-one (**14**); yield 38%, mp 273-275°C (DMF/n-propanol 2:5). NMR (DMSO-d_6) δ: 1.50-1.85 (4H, m, 8,9-CH_2), 2.00-2.25 (2H, m, 7-CH_2), 2.55-2.80 (2H, m, 10-CH_2), 5.20 (2H, s, PhCH_2), 7.20-7.65 (11H, m, 2xPh, 4-*H*). *Anal.* Calcd. for $C_{25}H_{21}NO_4$: C, 75.17; H, 5.30; N, 3.51. Found: C, 75.02; H, 5.22; N, 3.43.

6-Benzoyloxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-7*H*-pyrano[2,3-*d*]pyrimidin-7-one (25a): from **2a** and 1,3-dimethylbarbituric acid (**15**); yield 17%, mp 194°C (n-propanol). NMR ($CDCl_3$) δ: 3.45 and 3.60 (2x3H,

2xs, 1-*Me*, 3-*Me*), 7.50-7.85 (3H, m, 3H(*Ph*)), 7.90 (1H, s, 5-*H*), 8.10-8.35 (2H, m, 2H(*Ph*)). *Anal.* Calcd. for $C_{16}H_{12}N_2O_6$: C, 58.54; H, 3.68; N, 8.53. Found: C, 58.13; H, 3.40; N, 8.40.

6-Benzyloxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-7*H*-pyrano[2,3-*d*]pyrimidin-7-one (25b): from **2b** and 1,3-dimethylbarbituric acid (**15**); yield 39%, mp 185-186°C (n-propanol). NMR ($CDCl_3$) δ: 3.40 and 3.55 (2x3H, 2xs, 1-Me, 3-Me), 5.10 (2H, s, PhCH_2), 7.25 (1H, s, 5-*H*), 7.45 (5H, brs, *Ph*). *Anal.* Calcd. for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49; N, 8.91. Found: C, 60.82; H, 4.50; N, 8.83.

General procedure for debenzylation. To a solution of benzyloxy derivative (2 mmole) in a mixture of DMF and dioxane (1:1, 30 ml), Pd/C (10%, 100 mg) was added and the mixture was hydrogenated in a Parr autoclave at 3 atm. The reaction was finished in 4 hours. The catalyst was removed by filtration, the solvent was evaporated *in vacuo*, and the solid residue recrystallized from an appropriate solvent.
In this manner, the following compounds were prepared:

3-Hydroxy-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2,5-dione (5c): from **4c**; yield 86%, mp 155-162°C (toluene/cyclohexane 4:1). NMR (DMSO-d_6) δ: 2.10 (2H, tt, 7-CH_2, $J_{6,7}$=$J_{7,8}$= 6.0 Hz), 2.5 (2H, t, 6-CH_2), 2.8 (2H, t, 8-CH_2), 6.9 (1H, s, 4-*H*), 10.1 (1H, brs, OH). *Anal.* Calcd. for $C_9H_8O_4$: C, 60.00; H, 4.48. Found: C, 59.89; H, 4.37.

3-Hydroxy-7,7-dimethyl-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2,5-dione (5e): from **4e**; yield 92%, mp 138-140°C. NMR (DMSO-d_6) δ: 1.50 (6H, s, 2x7-Me), 2.45 (2H, s, 6-CH_2), 2.7 (2H, s, 8-CH_2), 7.2 (1H, s, 4-*H*). *Anal.* Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.24; H, 5.85.

3,7-Dihydroxy-2*H*-1-benzopyran-2-one (16e): from **16c**; yield 80%, mp 285-290°C (toluene/cyclohexane 1:2). NMR (DMSO-d_6) δ: 6.75 (1H, d, 8-*H*, $J_{6,8}$= 1.5 Hz), 6.80 (1H, dd, 6-*H*, $J_{5,6}$= 9.5 Hz), 7.15 (1H, s, 4-*H*), 7.40 (1H, d, 5-*H*), 10.00 (2H, brs, 3,7-O*H*). *Anal.* Calcd. for $C_9H_6O_4$: C, 60.68; H, 3.39. Found: C, 60.39; H, 3.43.

3,7-Dihydroxy-8-methyl-2*H*-1-benzopyran-2-one (16f): from **16d**; yield 88%, mp 250-254°C (toluene). NMR (DMSO-d_6) δ: 2.20 (3H, s, 8-*Me*), 6.85 (1H, d, 6-*H*, $J_{5,6}$= 8.5 Hz), 7.10 (1H, s, 4-*H*), 7.25 (1H, d, 5-*H*), 9.70-10.20 (2H, brs, 3,7-O*H*). *Anal.* Calcd. for $C_{10}H_8O_4$: C, 62.50; H, 4.20. Found: C, 62.67; H, 4.17.

3-Hydroxy-2*H*-naphtho[1,2-*b*]pyran-2-one (17c): from **17b**; yield 95%, mp 248-250°C (dioxane/n-propanol 1:5). NMR (DMSO-d_6) δ: 7.35 (1H, s, 4-*H*), 7.50-8.20 (5H, m, 5,6,7,8,9-*H*), 8.20-8.50 (1H, m, 10*H*), 10.60 (1H, brs, 3-O*H*). *Anal.* Calcd. for $C_{13}H_8O_3$: C, 73.58; H, 3.80. Found: C, 73.17; H, 3.70.

2-Hydroxy-3*H*-naphtho[2,1-*b*]pyran-2-one (18c): from **18b**; yield 59%, mp 241-243°C (ethanol). NMR (DMSO-d_6) δ: 5.80-7.30 (1H, brs, 2-O*H*), 8.55 (1H, d, 5-*H*, $J_{5,6}$= 9.0 Hz), 8.55-8.80 (2H, m, 8,9-*H*), 8.90-9.20 (1H, m, 7-*H*), 9.00 (1H, s, 1-*H*), 9.30-9.55 (1H, m, 10-*H*). *Anal.* Calcd. for $C_{13}H_8O_3$: C, 73.58; H, 3.80. Found: C, 73.61; H, 3.58.

3-Hydroxy-7-methyl-2*H*,5*H*-pyrano[4,3-*b*]pyran-2,5-dione (19c): from **19b**; yield 80%, mp 277-279°C (ethanol). NMR (DMSO-d_6) δ: 2.20 (3H, s, 7-*Me*), 6.60 (1H, s, 8-*H*), 6.90 (1H, s, 4-*H*). *Anal.* Calcd. for $C_9H_6O_5$: C, 55.68; H, 3.12. Found: C, 55.79; H, 2.85.

3-Hydroxy-2*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-2,5-dione (20e): from **20b**; yield 88%, mp 319-320°C (n-propanol). NMR (DMSO-d_6) δ: 7.00 (1H, s, 4-*H*), 7.30-7-80 (3H, m, 7,8,9-*H*), 7.80-8.05 (1H, m, 10-*H*). *Anal.* Calcd. for $C_{12}H_6O_5$: C, 62.62; H, 2.63. Found: C, 62.64; H, 2.44.

3-Hydroxy-5,6-dihydro-2*H*-pyrano[2,3-*c*]pyridine-2,5-dione (22d): from **22b**; yield 73%, mp >350°C (DMF). NMR (DMSO-d_6) δ: 6.35 (1H, d, 8-*H*, $J_{7,8}$= 5.5 Hz), 7.05 (1H, s, 4-*H*), 7.40 (1H, d, 7-*H*), 9.80-11.80 (2H, brs, N*H*, O*H*). *Anal.* Calcd. for $C_8H_5NO_4$: C, 53.64; H, 2.81; N, 7.82. Found: C, 53.39; H, 2.91; N, 7.92.

3-Hydroxy-6-methyl-5,6-dihydro-2*H*-pyrano[3,2-*c*]quinoline-2,5-dione (23c): from **23b**; yield **84%** , mp 310-313°C (DMF). NMR (DMSO-d_6) δ: 3.65 (3H, s, 6-*Me*), 7.5 (1H, s, 4-*H*), 7.20-7.80 (3H, m, 7,8,9-*H*), 7.95 (1H, dd, 10-*H*, $J_{9,10}$= 8.0 Hz, $J_{8,10}$= 1.5 Hz), 10.40-11.30 (1H, brs, 3-O*H*). *Anal.* Calcd. for $C_{13}H_9NO_4$: C, 64.20; H, 3.73; N, 5.76. Found: C, 63.97; H, 3.59; N, 5.73.

1,3-Dimethyl-7-hydroxy-1,2,3,4-tetrahydro-7*H*-pyrano[2,3-*d*]-pyrimidin-2,4,7-trione (25c): from **25b**; yield 98%, mp 195-197°C (toluene). NMR (DMSO-d_6) δ: 3.25 and 3.35 (2x3H, 2xs, 1,3-*Me*), 7.05 (1H, s, 5-*H*), 10.15 (1H, s, O*H*). MS: m/z= 224 (M^+, 100%). *Anal.* Calcd. for $C_9H_8N_2O_5$: C, 58.22; H, 3.60; N, 12.50. Found: C, 48.22; H, 3.93; N, 12.73.

Methyl 2-benzoyloxy-3-dimethylamino-3-(2,4,6-trihydroxypyrimidin-5-yl)propanoate (27). A mixture of **2a** (1 mmol) and barbituric acid (**26**, 1 mmole) in acetic acid (5 ml) was stirred at room temperature for 24 hours. The solvent was removed *in vacuo* at 40°C. The residue was suspended in ethanol (10 ml) and the solid was collected by filtration to give **27** in 70% yield, mp 270°C (decomp). NMR (DMSO-d_6) δ: 2.55 (6H, s, N*Me*$_2$), 3.20-3.60 (2H, m, 2,3-*H*), 3.60 (3H, s, COO*Me*), 7.40-7.60 (3H, m, 3H(*Ph*)), 7.85-8.20 (2H, m, 2H(*Ph*)), 8.30-9.2 (1H, brs, O*H*), 9.8-10.3 (1H, brs, O*H*). *Anal.* Calcd. for $C_{17}H_{19}N_3O_7$: C, 54.11; H, 5.08; N, 11.14. Found: C, 54.01; H, 4.96; N, 11.43.

Methyl 2-benzyloxy-3-dimethylamino-3-(2,4,6-trihydroxypyrimidin-5-yl)propanoate salt with barbituric acid (28). A mixture of **2b** (1 mmole) and barbituric acid (1 mmole) in acetic acid (5 ml) was stirred at room temperature for 6 hours. The solvent was removed *in vacuo* at 40°C. The residue was suspended in ethanol (5 ml) and the solid collected by filtration to give **28** in 45% yield, mp 197-200°C (water). NMR (DMSO-d_6) δ: 2.55 (6H, s, N*Me*$_2$), 3.55 (3H, s, COO*Me*), 3.20-3.60 (1H, brs, 3-*H*), 4.35 (1H, brs, 2-*H*), 4.80 (2H, s, PhC*H*$_2$), 7.15 (1H, s, 5-*H* of barbituric acid), 7.25 (5H, s, *Ph*), 7.35 (1H, brs, O*H*), 7.8-8.5 (2H, brs, 2xO*H*), 9.45 (1H, brs, O*H*), 9.95 (1H, brs, O*H*), 10.05 (1H, brs, O*H*). *Anal.* Calcd. for $C_{21}H_{25}N_5O_9$: C, 51.32; H, 5.13; N, 14.23. Found: C, 51.08; H, 5.12; N, 13.98.

Methyl 3-dimethylamino-2-hydroxy-3-(2,4,6-trihydroxypyrimidin-5-yl)propanoate (29). To a solution of **28** (700 mg) in a mixture of dioxane (7 ml) and water (15 ml), Pd/C (10%, 120 mg) was added and the mixture was hydrogenated (3 atm) in a Parr autoclave for three days. The catalyst was removed by filtration, the solvent evaporated to dryness. Ethanol (10 ml) was added to the residue nd filtered to give **29** in 71% yield, mp 260°C (decomp). NMR (DMSO-d_6) δ: 2.60 (6H, s, N*Me*$_2$), 3.30-4.10 (m, COO*Me*, 2,3-*H*, H_2O), 8.0 10.0 (3H, brs, 3xO*H*), 12.20 (1H, brs, O*H*). *Anal.* Calcd. for $C_{10}H_{15}N_3O_6$: C, 43.96; H, 5.53; N, 15.38. Found: C, 43.80; H, 5.26; N, 15.09.

6-Benzyloxy-2,4-dihydroxy-7*H*-pyrano[2,3-*d*]pyrimidin-7-one (30). To a solution of **28** (1 mmole) in acetic acid (5 ml), sodium acetate (1 mmol) was added and the mixture stirred in an argon atmosphere at room temperature for 24 hours, then the mixture was heated at reflux temperature for 2 hours. The precipitate was, after cooling, collected by filtration to give **30** in 63% yield, mp 325°C (decomp). NMR (DMSO-d_6) δ: 3.70-4.80 (1H, brs, O*H*), 5.12 (2H, s, PhC*H*$_2$), 7.25 (1H, s, 5-*H*), 7.55 (5H, s, *Ph*), 11.25 (1H, brs, O*H*). MS: m/z 286 (M^+ 14%), MS: calcd. for $C_{14}H_{10}N_2O_5$: m/z= 286.0590. Found: m/z= 286.0600. *Anal.* Calcd. for $C_{14}H_{10}N_2O_5$: C, 58.75; H, 3.52; N, 9.79. Found: C, 58.90; H, 2.87; N, 9.67.

Methyl 2-benzoyloxy-3-(6-amino-2,4-dihydroxypyrimidin-5-yl)propenoate (32). A suspension of 6-aminouracil (**31**, 1 mmole) and **2a** (1 mmole) in acetic acid (10 ml) was stirred at room temperature for 14 days. The solid was collected by filtration to give **32** in 69% yield, mp>300°C (acetic acid). NMR (DMSO-d_6) δ: 3.75 (3H, s, COO*Me*), 6.75 (2H, brs, 4-N*H*$_2$), 7.20 (1H, s, 3-*H*), 7.50-7.80 (3H, m, 3H(*Ph*)), 8.00-8.25 (2H, m, 2H(*Ph*)), 10.40 and 10.55 (2x1H, 2xbrs, 2', 6'-O*H*). *Anal.* Calcd. for $C_{15}H_{13}N_3O_6$: C, 54.38; H, 3.96; N, 12.68. Found: C, 54.26; H, 3.99; N, 12.36.

ACKNOWLEDGEMENT

The authors would like to express their gratitude to the Ministry for Science and Technology, Slovenia, for financial support of this investigation.

REFERENCES AND NOTES

1. a) Hepworth, J. D. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W.; Eds.; Pergamon Press, Oxford, 1984, Vol. 3, pp.737-883; b) Geen, G. R.; Evens, J.M.; Vong, A. K. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V.; Eds.; Elsevier Science Ltd, Oxford, 1996, Vol. 5, pp. 469-500; c) Feuer, G. In *Progress in Medicinal Chemistry*; Ellis, G. P.; West, G. B.; Eds.; North Holland Publishing Company, New York, 1974, pp. 85-158; d) Deana, A. A.; Stokker, G.E.; Schultz, E.M.; Smith, E.J.; Cragoe, E. J. Jr.; Russo, H.F.; Watson, L.S. *J. Med. Chem.* **1983**, *26*, 580-585; e) Witiak, D. T.; Kim, S. K.; Tehim, A. K.; Sternitzke, K. D.; McCreery, R. L.; Kim, S. U.; Feller, D. R.; Romstedt, K. J.; Kamanna, V. S.; Newman, H. A. I. *J. Med. Chem.* **1988**, *31*, 1437-1445; f) Cairns, H.; Cox, D.; Gould, K. J.; Ingall, A. H.; Suschitzky, J. L. *J. Med. Chem,* **1985**, *28*, 1832-1843.

2. a) Thaisrivongs, S.; Watenpaugh, K. D.; Howe, W. J.; Tomich, P. K.; Dolak, L. A.; Chong, K.-T.; Tomich C.-S.; Tomasselli, A. G.; Turner, S. R.; Strohbach, J. W.; Mulichak, A. M.; Janakiraman, M. N.; Moon, J. B.; Lynn, J. C.; Horng M.-M.; Hinshaw, R. R.; Curry, K. A.; Rothrock, D. J. *J. Med. Chem.* **1995**, *38*, 3624-3637; b) Vara Prasad, J. V. N.; Lunney, E. A.; Ferguson, D.; Tummino, P. J.; Rubin, J. R.; Reyner, E. L.; Stewart, B. H.; Guttendorf, R. J.; Domagala, J. M.; Suvorov, L. I.; Gulnik, S. V.; Topol, I. A.; Bhat, T. N.; Erickson, J. W. *J. Amer. Chem. Soc.* 1995, *117*, 11070-11074; c) Romines, K. R.; Watenpaugh, K. D.; Tomich, P. K.; Howe, W. J.; Morris, J. K.; Lovasz, K. D.; Mulichak, A. M.; Finzel, B. C.; Lynn, J. C.; Horng, M.-M.; Schwende, F. J.; Ruwart, M. J.; Zipp, G. L.; Chong, K.-T.; Dolak, L. A.; Toth, L. N.; Howard, G. M.; Rush, B. D., Wilkinson, K. F.; Possert, P. L.; Dalga, R. J.; Hinshaw, R. R. *J. Med. Chem.* **1995**, *38*, 1884-1891; d) Thaisrivongs, S.; Janakiraman, M. N.; Chong, K.-T.; Tomich, P. K.; Dolak, L. A.; Turner, S. R.; Strohbach, J. W.; Lynn, J. C.; Horng, M.-M.; Hinshaw, R. R.; Watenpaugh, K. D. *J. Med. Chem.* **1996**, *39*, 2400-2410; e) Wang, S.; Milne, G. W. A.; Yan, X.; Posey, I. J.; Nicklaus, M. C.; Graham, L.; Rice, W. G. *J. Med. Chem.* **1996**, *39*, 2047-2054; f) Mazumder, A.; Wang, S.; Neamati, N.; Nicklaus, M.; Sunder, S.; Chen, J.; Milne, W. A.; Rice, W. G.; Burke, T. R. Jr.; Pommier, Y. *J. Med. Chem.* **1996**, *39*, 2472-2481; g) Pochet, L.; Doucet, C.; Schynts, M.; Thierry, N.; Boggetto, N.; Pirotee, B.; Jiang, K. Y.; Masereel, B.; de Tulio, P.; Delarge, J.; Reboud-Ravaux, M. *J. Med. Chem.* **1996**, *39*, 2579-2585.

3. Hepworth; J. D.; Gabbutt, C. D.; Heron, B. M. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Elsevier Science Ltd., Oxford, 1996, Vol.5, pp. 351-468.

4. a) Stanovnik, B. In *Progress of Heterocyclic Chemistry*; Suschitzky, H.; Scriven, E. F. V., Eds.; Vol. 5, Pergamon Press, Oxford,, 1993, pp. 34-53; b) Stanovnik, B. *Molecules* **1996**, *1*, 123-127; c) Selič, L.; Golič Grdadolnik, S.; Stanovnik, B. *Helv. Chim. Acta* **1997**, *80*, 2418-2425; d) Toplak, R.; Selič, L.; Soršak, G.; Stanovnik, B. *Heterocycles* **1997**, *45*, 555-565; e) Pizzioli, L.; Ornik, B.; Svete, J.; Stanovnik, B. *Helv. Chim. Acta* **1998**, *81*, 231-235.

5. a) Bredereck, H.; Simchen, G.; Griebenow W. *Chem. Ber.* **1974**, *107*, 1545-1554; b) Schmidt, R. R.; Talbiersky, J.; Betz, R. *Chem. Ber.* **1982**, *115*, 2674-2678; c) Schmidt, R. R.; Betz, R. *Synthesis* **1982**, 748.

6. The X-ray analysis of compound **2a** will be reported elsewhere.

7. a) Trivedi, K. N.; Sethna, S. *J. Org. Chem.* **1960**, *25*, 1817-1819; b) Kokotos, G.; Tzougraki, C. *J. Heterocyclic Chem.* **1986**, *23*, 86-92; c) Ornik, B.; Stanovnik, B.; Tišler, M. *J. Heterocyclic Chem.* **1992**, *29*, 1241-1244;.

8. Salunke, P. S.; Phadke, C. P.; Kelkar, S. L.; Wadia, M. S. *Synthesis* **1985**, 111-112.

9. Ahluwalia, V.K.; Bhat, K.; Prakash, C. *Heterocycles* **1979**, *12*, 1203-1206.

10. a) Majumdar, K. C.; Khan, A. T.; De, R. N. *Synth. Commun.* **1988**, *18*, 1589-1595; b) Majumdar, K. C.; Khan, A. T.; Das, D. P. *Synth. Commun.* **1989**, *19*, 917-930; c) Majumdar, K. C.; De, R. *J. Chem. Soc. Perkin Trans. 1* **1989**, 1901-1905; d) Majumdar, K. C.; Khan, A. T.; Chattopadhyay, S. K. *Heterocycles* **1989**, *29*, 1573-1576.

11. Traube, W. *Chem. Ber.* **1900**, *33*, 1371-1383 ; **1900**, *33*, 3035-3056.

12. Lister, J. H. *Purines*, J. Wiley, New York, 1971, pp. 31-90.

13. Ringshaw, D. J.; Smith, H. J. *J. Chem. Soc.* **1964**, 1559-1562.

14. Hammond, K. M.; Fisher, N.; Morgan, E. N.; Tanner, E. M.; Franklin, C. *J. Chem. Soc.* **1957**, 1062-1067.

15. Niederl, J. B.; Lederer, S. J. *J. Org. Chem.* **1952**, *17*, 1617-1620.