The Synthesis of Ethyl 2-[(2,2-Dibenzoyl)ethenyl]amino-3-dimethylaminopropenoate and its Application to the Synthesis of Fused 3-Aminopyran-2-ones and 3-Aminoazolo- and -azinopyrimidin-4(4*H*)-ones

Gorazd Soršak [a], Simona Golič Grdadolnik [b] and Branko Stanovnik* [a]

[a] Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, 1000 Ljubljana, Slovenia. [b] L01, Department of NMR and Molecular Modelling, National Institute of Chemistry, Hajdrihova 19, POB 3440, 1001 Ljubljana, Slovenia

Received April 10, 1998

Ethyl 2-[(2,2-dibenzoyl)ethenyl]amino-3-dimethylaminopropenoate (**3**) was prepared from dibenzoylmethane (**1**) in two steps, and used as a reagent for preparation of fused substituted 3-aminopyranones **12-15** in over 90% yield, quinolizin-4-one **16** in over 79% yield, and fused pyrimidin-4-ones **17-19** in 40-50% yield. Deprotection of (2,2-dibenzoyl)ethenyl group with either diethylamine or hydrazine hydrate produced free amino compounds **20**, **21** and **22** in 35%, 91% and 71% yield, respectively.

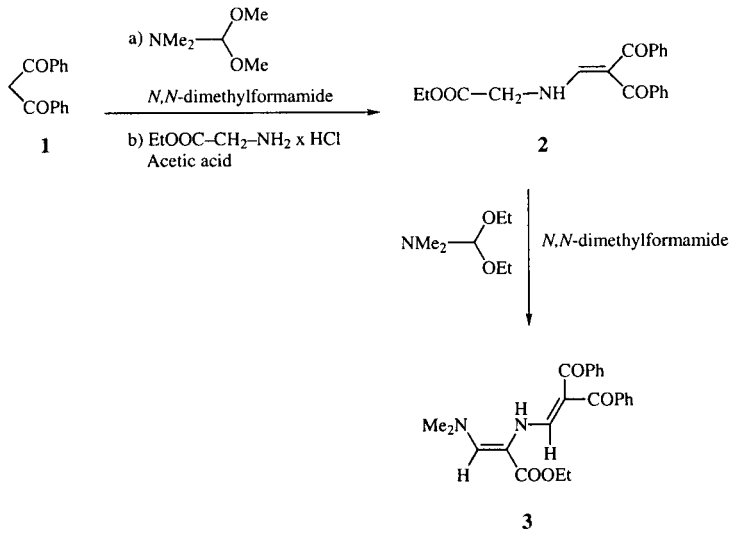
J. Heterocyclic Chem., **35**, 1275 (1998).

Recently, alkyl 2-(2,2-disubstituted-ethenylamino)-3-dimethylaminopropenoates, such as ethyl 2-[2,2-bis(ethoxycarbonyl)vinyl]amino-3-dimethylaminopropenoate [1,2], alkyl 2-(2-benzoyl-2-ethoxycarbonyl-1-ethenyl)amino-3-dimethylaminopropenoate [3-5], methyl 2-[2,2-bis(acetyl)ethenyl]aminopropenoate [6], methyl 2-acetyl-3-[2-(dimethylamino)-1-(methoxycarbonyl)-ethenyl]aminopropenoate [7], methyl 2-[2,2-bis(ethoxycarbonyl)ethenyl]amino-3-dimethylaminobut-2-enoate [8], and methyl 2-acylamino-3-cyanopropanoates [9] have been synthesized and used as reagents for preparation of many heterocyclic systems, especially fused pyran-2-ones and pyrimidin-4-ones with 2,2-disubstituted-1-ethenylamino group attached at the 3-position of the newly formed ring.

On the other hand, when we have tried to apply ethyl 2-(2-acetyl-2-benzoyl-1-ethenyl)amino-3-dimethylaminopropenoate in the reaction with 2-aminothiazole for preparation of the corresponding 6-substituted-amino-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine, we have observed that 4-benzoyl-2-ethoxycarbonyl-3-methylpyrrole was formed by intramolecular cyclization of the reagent [10].

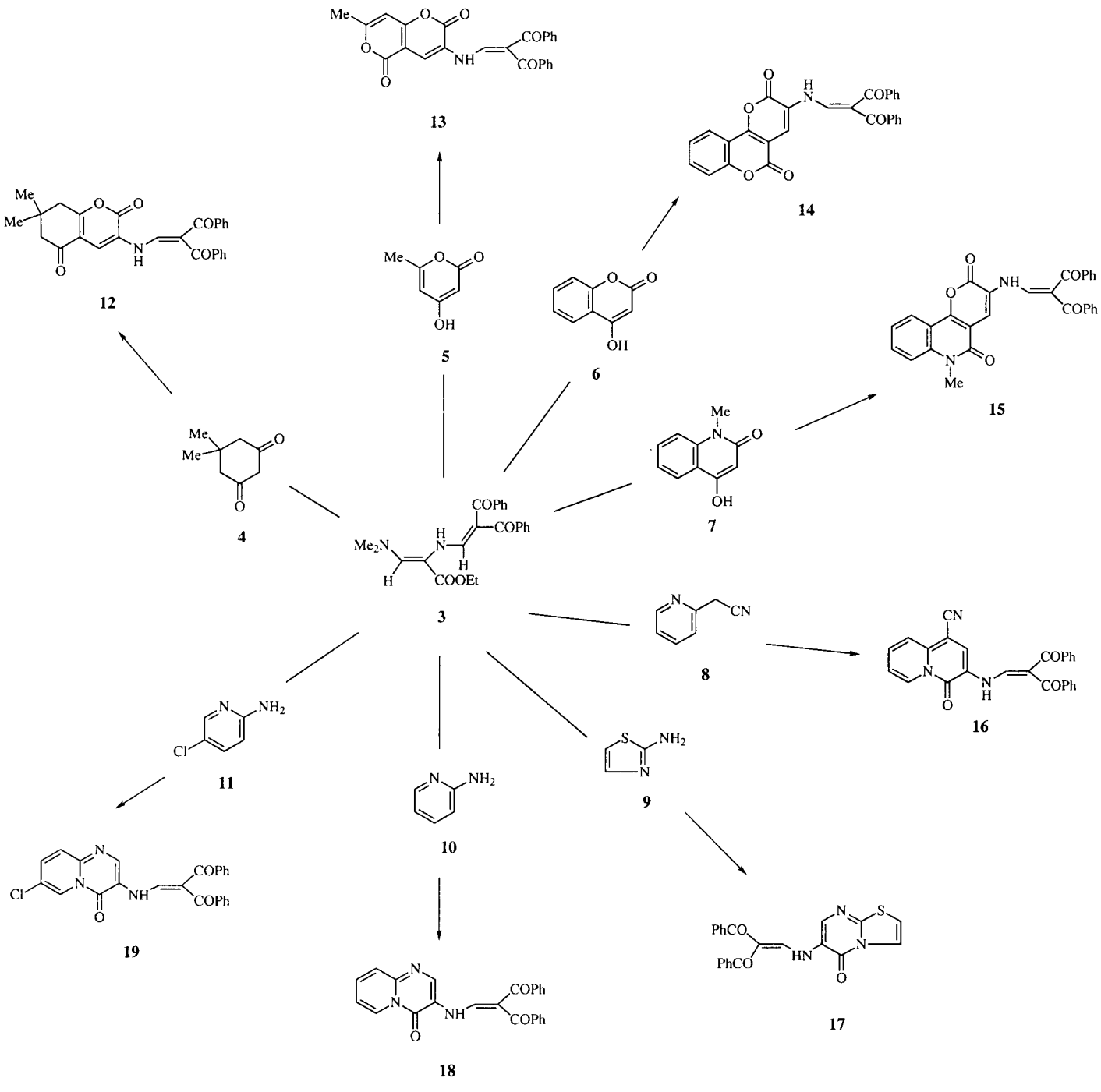
In continuation of our studies in this connection, ethyl 2-[(2,2-dibenzoyl)ethenyl]amino-3-dimethylaminopropenoate (**3**), a new reagent in this series, was prepared in the following manner. Dibenzoylmethane (**1**) was treated with *N*,*N*-dimethylformamide dimethyl acetal to give the corresponding dimethylaminomethylene derivative, which was without isolation converted with ethyl glycinate in acetic acid into ethyl *N*-[(2,2-dibenzoyl)-ethenyl]glycinate (**2**) in 94% yield. This was transformed with *N*,*N*-dimethylformamide diethyl acetal into **3** in 87% yield. (Scheme 1).

Scheme 1



1 **2** **3**

Scheme 2



The structure of compound **3** was established by ^1H nmr spectra. Namely, the compound dissolved in dimethyl-d_6 sulfoxide shows one set of signals. Besides the multiplet at δ = 7.26-7.60 ppm for protons of benzoyl groups, and the triplet at δ = 1.22 ppm for methyl and the quartet at δ = 4.09 ppm for methylene group, it shows a singlet at δ = 3.05 ppm for NMe_2, and two doublets at δ = 7.54 ppm for CH and δ = 10.66 ppm for NH part of the CHNH structural element. The magnitude of the coupling constant, J_{CHNH} = 13.6 Hz, indicates the trans (antiperiplanar) orientation of both hydrogens in respect to each other. The H-C=C-^{13}C coupling constant, ^3J = 3.5 Hz, indicates the (*Z*)-orientation of H3 and ester group around the double bond. The orientation of groups around the C_2-C_3 double bond was established also by NOESY experiment, confirming the (*Z*)-orientation of both amino

groups around the double bond and free rotation around C_2-N single bond (Figures 1,2).

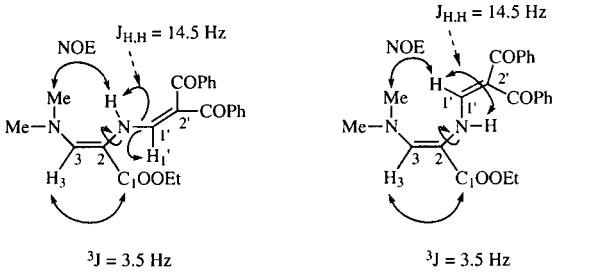


Figure 1.

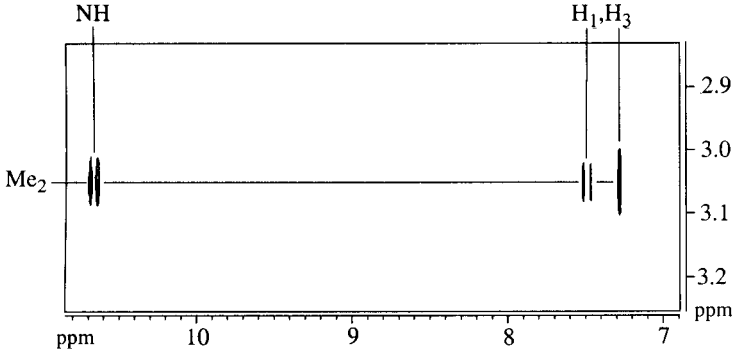


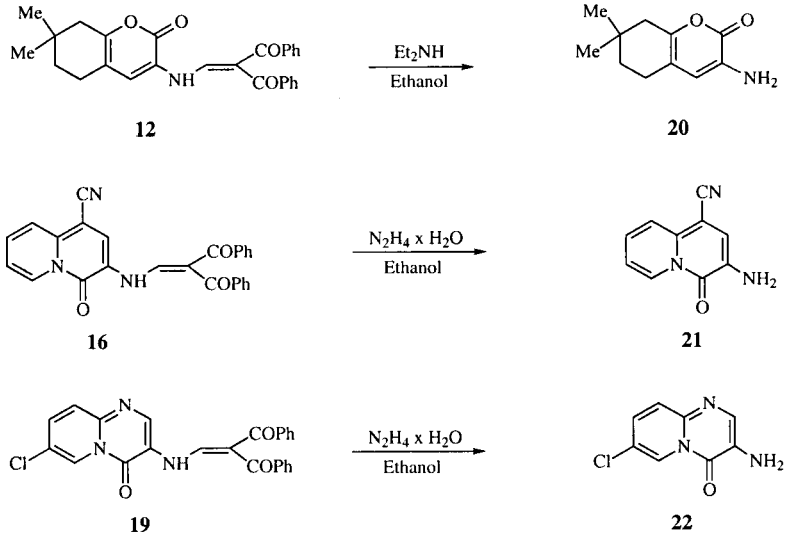
Figure 2. Partial NOESY spectrum of the compound **3** measured in dimethyl-d_6 sulfoxide at 302 K.

4-ones. The following cyclic *C*-nucleophiles were selected: 5,5-dimethyl-1,3-cyclohexanedione (**4**), 4-hydroxy-6-methyl-2*H*-pyran-2-one (**5**), 4-hydroxy-2*H*-1-benzopyran-2-one (**6**), 4-hydroxy-1-methylquinolin-2(1*H*)-one (**7**). They were transformed by heating in acetic acid directly into the corresponding 3-[(2,2-dibenzoyl)ethenyl]amino derivatives of 7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-one (**12**), 7-methyl-5-oxo-2*H*,5*H*-pyrano[4,3-*b*]pyran-2-one (**13**), 5-oxo-2*H*,5*H*-pyrano[3,2-*c*]benzopyran-2-one (**14**), 6-methyl-5-oxo-5,6-dihydro-2*H*-pyrano[3,2-*c*]quinolin-2-one (**15**) in over 90% yields. 2-Pyridylacetonitrile (**8**) afforded 1-cyano-4*H*-quinolizin-4-one derivative **16** in 79% yield (Scheme 2).

Heterocyclic α-amino compounds yielded the corresponding [(2,2-dibenzoyl)ethenyl]aminoazolo- and -azinopyrimidin-4-one. In this manner, 2-aminothiazole (**9**), 2-aminopyridin-4-one (**10**) and its 5-chloro derivative **11** were transformed into 5*H*-thiazolo[3,2-*a*]pyrimidin-5-one **17**, 4*H*-pyrido[1,2-*a*]pyrimidin-4-one **18** and its 7-chloro derivative **19**, respectively, in 40-50% yields (Scheme 2).

The (2,2-dibenzoyl)ethenyl group can be easily removed from the protected amino group. Deprotection was achieved either with hydrazine hydrate or diethylamine by heating in ethanol for 1-2 hours. In this manner, compounds **12**, **16**, and **19** were converted into 3-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-2*H*-1-

Scheme 3



12 **20**

16 **21**

19 **22**

Compound **3** reacts with *C*- and *N*-nucleophiles. In this reaction, the *N*,*N*-dimethylamino group is formally substituted to give intermediates, which cyclise under the reaction conditions into fused pyran-2-ones or pyrimidin-

benzopyran-2-one (**20**), 3-amino-1-cyano-4*H*-quinolizin-4-one (**21**), and 3-amino-7-chloro-4*H*-pyrido-[1,2-*a*]pyrimidin-4-one (**22**) in 35%, 91%, and 71% yields, respectively. (Scheme 3).

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^{1}H nmr spectra were obtained on a Bruker Avance DPX 300 spectrometer, ir spectra on a Perkin-Elmer 1310 instrument, and microanalyses for C, H and N on a Perkin-Elmer Analyser 2400.

Ethyl *N*-[(2,2-Dibenzoyl)ethenyl]glycinate (**2**).

To a solution of dibenzoylmethane (**1**, 22.43 g, 0.10 mole) in *N,N*-dimethylformamide (70 ml), *N,N*-dimethylformamide dimethyl acetal (17.87 g, 0.15 mole) was added and the mixture was heated at 80° for 6 hours. After that the volatile components were evaporated *in vacuo*. Ethyl glycinate hydrochloride (13.96 g, 0.10 mole) and acetic acid (50 ml) as solvent were added. The mixture was heated for 2 hours under reflux. The volatile components were evaporated *in vacuo* and the solid residue was recrystallized from ethanol to give the compound **2** in 94% yield, mp 196-198°; ^{1}H nmr (deuteriochloroform): δ 1.22 (t, CH_2CH_3), 3.90 (d, CH_2NH), 4.10 (q, CH_2CH_3), 7.26-7.60 (m, 2 x COPh), 7.85 (d, C*H*NH), 9.22 (d, CHN*H*), J_{CHCH} = 7.0 Hz, J_{CHNH} = 14.5 Hz, J_{CH2NH} = 5.5 Hz.

Anal. Calcd. for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.05; H, 5.52; N, 4.06.

Ethyl 2-[(2,2-Dibenzoyl)ethenyl]amino-3-dimethylaminopropenoate (**3**).

To a solution of ethyl *N*-[(2,2-dibenzoyl)ethenyl]glycinate (**2**, 33.38 g, 0.10 mole) in *N,N*-dimethylformamide (80 ml) *N,N*-dimethylformamide diethyl acetal (20.61 g, 0.14 mole) was added and the mixture was heated for 5 hours at 80°. After the reaction was completed, the volatile components were evaporated *in vacuo* and the solid residue was crystalized from ethanol to give the compound **3** in 87% yield, mp 161-163°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.22 (t, CH_2CH_3), 3.05 (s, NMe_2), 4.09 (q, CH_2CH_3), 7.26-7.60 (m, 2 x COPh, C*H*NMe_2), 7.54 (d, C*H*NH), 10.66 (d, CHN*H*), J_{CHCH} = 7.2 Hz, J_{CHNH} = 13.6 Hz.

Anal. Calcd. for $C_{23}H_{24}N_2O_4$: C, 70.39; H, 6.16; N, 7.14. Found: C, 70.29; H, 6.27; N, 6.83.

The Reactions of *C*-Nucleophiles **4-8** and Heteroaryl Amines **9-11** with Ethyl 2-[(2,2-Dibenzoyl)ethenyl]amino-3-dimethylaminopropenoate (**3**).

General Procedure.

To a solution of *C*-nucleophile **4-8** (0.0015 mole) or heteroaryl amine **9-11** (0.0015 mole) in acetic acid (6 ml) the compound **3** (0.0015 mole) 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 solvent). After the reaction was completed, acetic acid was evaporated *in vacuo* and the solid residue recrystallized from an appropriate solvent to give compounds **12-19**.

The following compounds were prepared in this manner:

3-[(2,2-Dibenzoyl)ethenyl]amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-one (**12**).

This compound was prepared from 5,5-dimethyl-1,3-cyclohexanedione (**4**), 2 hours of reflux, in 95% yield, mp 223-224° (from acetic acid); ^{1}H nmr (deuteriochloroform): δ 1.20 (s, CMe_2), 2.45, 2.76 (2s, CH_2CMe_2 x 2), 7.16-8.14 (m, 2 x COPh, H_4), 8.14 (d, C*H*NH), 11.82 (d, CHN*H*), J_{CHNH} = 13.1 Hz.

Anal. Calcd. for $C_{27}H_{23}NO_5$: C, 73.46; H, 5.25; N, 3. 17. Found: C, 73.57; H, 5.28; N, 3.21.

3-[(2,2-Dibenzoyl)ethenyl]amino-7-methyl-5-oxo-2*H*,5*H*-pyrano[4,3-*b*]pyran-2-one (**13**).

This compound was prepared from 4-hydroxy-6-methyl-2*H*-pyran-2-one (**5**), 1/2 hour of reflux, in 96% yield, mp 291-293° (from acetic acid); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 2.38 (s, 7-Me), 6.71 (s, H_8), 7.28-7.55 (m, 2 x COPh), 7.93 (s, H_4), 8.37 (d, C*H*NH), 11.73 (d, CHN*H*), J_{CHNH} = 12.4 Hz.

Anal. Calcd. for $C_{25}H_{17}NO_6$: C, 70.25; H, 4.01; N, 3.28. Found: C, 70.37; H, 4.00; N, 3.22.

3-[(2,2-Dibenzoyl)ethenyl]amino-5-oxo-2*H*,5*H*-pyrano-[3,2-*c*]benzopyran-2-one (**14**).

This compound was prepared from 4-hydroxy-2*H*-1-benzopyran-2-one (**6**), 1/2 hour of reflux, in 93% yield, mp 298-299° (from acetic acid); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 7.33-8.03 (m, 2 x COPh, H_4, H_7, H_8, H_9, H_{10}), 8.45 (d, C*H*NH), 11.81 (d, CHN*H*), J_{CHNH} = 13.2 Hz.

Anal. Calcd. for $C_{28}H_{17}NO_6$: C, 72.57; H, 3.70; N, 3.02. Found: C, 72.37; H, 3.84; N, 3.09.

3-[(2,2-Dibenzoyl)ethenyl]amino-6-methyl-5-oxo-5,6-dihydro-2*H*-pyrano[3,2-*c*]quinolin-2-one (**15**).

This compound was prepared from 4-hydroxy-1-methylquinolin-2(1*H*)-one (**7**), 1/2 hour of reflux, in 91% yield, mp 270-272° (from acetic acid); ^{1}H nmr (deuteriochloroform): δ 3.80 (s, 6-Me), 7.20-8.24 (m, 2 x COPh, H_7, H_8, H_9, H_{10}), 7.91 (s, H_4), 8.23 (d, C*H*NH), 12.00 (d, CHN*H*), J_{CHNH} = 13.2 Hz.

Anal. Calcd. for $C_{29}H_{20}N_2O_5$: C, 73.10; H, 4.23; N, 5.88. Found: C, 72.97; H, 4.23; N, 5.88.

3-[(2,2-Dibenzoyl)ethenyl]amino-1-cyano-4*H*-quinolizin-4-one (**16**).

This compound was prepared from 2-pyridylacetonitrile (**8**), 1 hour of reflux, in 79% yield, mp 275-277° (from acetic acid); ^{1}H nmr (deuteriochloroform): δ 7.18-8.27 (m, 2 x COPh, H_7, H_8, H_9) 7.98 (s, H_2), 9.20 (d, C*H*NH), 9.22 (m, H_6), 12.34 (d, CHN*H*), J_{CHNH} = 13.8 Hz.

Anal. Calcd. for $C_{26}H_{17}N_3O_3$: C, 74.45; H, 4.09; N, 10.02. Found: C, 74.81; H, 4.09; N, 9.98.

6-[(2,2-Dibenzoyl)ethenyl]amino-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**17**).

This compound was prepared from 2-aminothiazole (**9**), 1 hour of reflux, in 41% yield, mp 219-220° (from a mixture of ethanol and acetic acid); ^{1}H nmr (deuteriochloroform): δ 7.25-7.47 (m, 2 x COPh), 7.67 (d, H_2), 8.14 (d, H_3), 8.43 (d, C*H*NH), 8.46 (m, H_7), 11.80 (d, CHN*H*), J_{CHNH} = 13.2 Hz.

Anal. Calcd. for $C_{22}H_{15}N_3O_3S$: C, 65.82; H, 3.77; N, 10.47. Found: C, 65.91; H, 3.70; N, 10.50.

3-[(2,2-Dibenzoyl)ethenyl]amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**18**).

This compound was prepared from 2-aminopyridine (**10**), 6 hours of reflux, in 39% yield, mp 276-277° (from ethanol); ^{1}H nmr (deuteriochloroform): δ 7.22-8.11 (m, 2 x COPh, H_7, H_8, H_9, H_{10}), 7.75 (d, C*H*NH), 8.55 (s, H_2), 10.2 (br. s, CHN*H*), J_{CHNH} = 14.6 Hz.

Anal. Calcd. for $C_{24}H_{17}N_3O_3$: C, 72.90; H, 4.29; N, 10.83. Found: C, 72.51; H, 4.33; N, 10.63.

3-[(2,2-Dibenzoyl)ethenyl]amino-7-chloro-4*H*-pyrido-[1,2-*a*]pyrimidin-4-one (**19**).

This compound was prepared from 2-amino-5-chloropyridine (**11**), 7 hours of reflux, in 45% yield, mp 265-266° (from ethanol); ^{1}H nmr (deuteriochloroform): δ 7.16-7.69 (m, 2 x COPh, H_8, H_9), 8.43 (s, H_2), 8.52 (d, C*H*NH), 9.08 (s, H_6), 12.20 (d, CHN*H*). J_{CHNH} = 15.1 Hz. The compound was transformed into 3-amino-7-chloro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**22**).

N-Deprotection with Diethylamine.

3-Amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-2*H*-1-benzo-pyran-2-one (**20**).

To a starting compound 3-[(2,2-dibenzoyl)ethenyl]amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-one (**12**, 0.441 g, 0.001 mole) 4 ml of 0.5*M* solution of diethylamine in ethanol was added. The mixture was heated under reflux for 1 hour. After that the volatile components were evaporated *in vacuo*. The solid residue was collected by filtration to give **20** in 35% yield, mp 190-191° (from ethanol, [11]: 195.5-196.5, [7]: 186-189); ^{1}H nmr (deuteriochloroform): δ 1.13 (s, 2 x 7-Me), 2.38, 2.67 (2 s, 2 x CH_2), 4.07 (s, NH_2), 6.78 (s, H_4).

N-Deprotection with Hydrazine Hydrate.

General Procedure.

To compound **16** or **19** (0.001 mole) 80% hydrazine hydrate (0.005 mole) in ethanol (5 ml) was added. The mixture was heated under reflux for 2 hours. After the reaction was completed the volatile components were evaporated *in vacuo*. The solid residue was collected by filtration and recrystallized from an appropriate solvent to give compounds **21** or **22**, respectively.

The following compounds were prepared in this manner:

3-Amino-1-cyano-4*H*-quinolizin-4-one (**21**).

This compound was prepared from 3-[(2,2-dibenzoyl)-ethenyl]amino-1-cyano-4*H*-quinolizin-4-one (**16**), 2 hours of reflux, in 91% yield, mp 206-208° (from methanol); ^{1}H nmr (deuteriochloroform): δ 4.40 (br s, NH_2), 7.01, 7.28 (2ddd, H_7, H_8), 7.28 (s,H_2), 7.78 (d, H_9), 8.95 (d, H_6), J_{H6-H7} = 7.2 Hz, J_{H8-H9} = 8.2 Hz, J_{H6-H8} = 1.1 Hz.

Anal. Calcd. for $C_{10}H_7N_3O_4$: C, 64.86; H, 3.81; N, 22.69. Found: C, 64.81; H, 4.00; N, 22.53.

3-Amino-7-chloro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**22**).

This compound was prepared from 3-[(2,2-dibenzoyl)-ethenyl]amino-7-chloro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**19**), 2 hours of reflux, in 71% yield, mp 188-190° (from methanol; [12]: 189-190, [7]: 192-193), ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 5.40 (s, NH_2), 7.41 (dd, H_8), 7.49 (dd, H_9), 7.89 (s, H_2), 8.75 (dd, H_6), $J_{H8,H9}$ = 9.5 Hz, $J_{H8,H6}$ = 2.0 Hz, $J_{H6,H9}$ = 1.0 Hz.

Acknowledgement.

The authors wish to express their gratitude to the Ministry of Science and Technology, Slovenia, for financial support.

REFERENCES AND NOTES

[1] G. Soršak, A. Sinur, L. Golič and B. Stanovnik, *J. Heterocyclic Chem.*, **32**, 921 (1995).

[2] R. Toplak, L. Selič, G. Soršak and B. Stanovnik, *Heterocycles*, **45**, 555 (1997).

[3] S. Strah, B. Stanovnik and S. Golič Grdadolnik, *J. Heterocyclic Chem.*, **34**, 263 (1997).

[4] S. Strah, A. Golobič, L. Golič and B. Stanovnik, *J. Heterocyclic Chem.*, **34**, 1511 (1997).

[5] S. Strah and B. Stanovnik, *J. Heterocyclic Chem.*, **34**, 1629 (1997).

[6] L. Selič and B. Stanovnik, *J. Heterocyclic Chem.*, **34**, 813 (1997).

[7] L. Selič, S. Golič Grdadolnik and B. Stanovnik, *Helv. Chim. Acta*, **80**, 2418 (1997).

[8] L. Selič, S. Golič Grdadolnik and B. Stanovnik, *Heterocycles*, **45**, 2349 (1997).

[9] L. Pizzioli, B. Ornik, J. Svete and B. Stanovnik, *Helv. Chim. Acta*, **81**, 231, (1998).

[10] M. Malešič, A. Krbavčič, A. Golobič, L. Golič and B. Stanovnik, *J. Heterocyclic Chem.*, **34**, 1757 (1997).

[11] M. Kočevar, S. Polanc, M. Tišler and B. Verček, *Heterocycles*, **30**, 227 (1990).

[12] J. Parrick and H. K. Rami, *J. Chem. Res. (M)*, 2411 (1990).