Methyl 2-Benzoylamino-3-dimethylaminopropenoate in the Synthesis of Fused Pyranones. The Synthesis of Derivatives of Tetrahydro-2*H*-1-benzopyran-2-one, Isomeric 2*H*-Naphtho[1,2-*b*]pyran-2-one and 3*H*-Naphtho[2,1-*b*]pyran-3-one, Pyrano[3,2-*c*]benzopyran-2,5-dione, and 7*H*-Pyrano[2,3-*d*]pyrimidin-7-one

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Dedicated to Professor Karl Gewald, Technical University of Dresden, on the occasion of his 60th birthday

Methyl 2-benzoylamino-3-dimethylaminopropenoate (**1**) reacts with carbocyclic and heterocyclic 1,3-diketones or potential 1,3-diketones, such as 1,3-cyclohexanediones **2-4**, and 4-hydroxy-2*H*-1-benzopyran-2-one derivative **17**, in acetic acid to afford the corresponding 3-benzoylamino substituted 5-oxo-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-ones **5-7**, and 2*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-2,5-dione derivative **18**. 1-Naphthol (**12**) and 2-naphthol (**13**) produce the isomeric 2*H*-naphtho[1,2-*b*]pyran-2-one (**14**) and 3*H*-naphtho[2,1-*b*]pyran-3-one (**15**) derivatives, respectively. Ethyl cyclopentanone-2-carboxylate (**8**) and ethyl cyclohexanone-2-carboxylate (**9**) do not react under these conditions, while in polyphosphoric acid the cyclization of the reagent **1** is taking place to give 4-dimethylaminomethylene-2-phenyl-5(4*H*)-oxazolone (**10**). 4,6-Dihydroxypyrimidine derivative **19** affords in acetic acid the noncyclized intermediate **20**, which can be further transformed in polyphosphoric acid into 7*H*-pyrano[2,3-*d*]pyrimidin-7-one derivative **21**.

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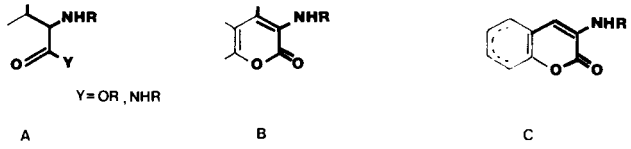
Dehydroamino acids are of major interest since many of them are found in the nature as secondary metabolites, components of polypeptides and pigments. Several reviews about α,β-dehydroamino acids and α,β-dehydropeptides containing the structural unit A have been published [1-3].

Recently, some new methods for the preparation of the α-heteroaryl substituted α-amino acids [4], β-heteroaryl-α,β-dehydro-α-amino acids [5], β-heteroarylamino-α,β-dehydro-α-amino acids [6-10], which cyclize under more severe reaction conditions into fused pyrimidones [11], have been developed in our laboratory. In this connection, we have introduced the preparation of β-heteroarylamino-α,β-dehydro-α-amino acids and dipeptides from primary or secondary amines and β-heteroaryl substituted-α,β-dehydro-α-amino acids and derivatives from heterocycles containing an active methylene group as a part of the cyclic system [12]. However, under the reaction conditions these latter compounds frequently cyclize to give pyranoazoles and pyranoazines [12], while aliphatic 1,3-dicarbonyl compounds, such as 1,3-diketones and β-keto esters, cyclize into 2*H*-pyran-2-ones having an α,β-dehydro-α-amino acid structural element partially incorporated into the cyclic system (type B) [5].

In this communication we report on some further applications of the reagent **1** for the synthesis of pyranones fused to either carbocyclic or heterocyclic ring (type C), such as 2*H*-1-benzopyran-2-ones, isomeric naphthopyranones, pyranobenzopyranones, and pyranopyrimidinones with the α,β-dehydro-α-amino acid structural element incorporated in the pyranone part of the bicyclic or polycyclic

Scheme 1



system. This method represents an alternative synthesis of the systems, frequently found in the naturally occuring compounds, in comparison to those described previously [12-15].

In this study, we selected 1,3-cyclohexanedione (**2**), 5-methyl-1,3-cyclohexanedione (**3**), 5,5-dimethyl-1,3-cyclohexanedione (**4**), ethyl cyclopentane-2-carboxylate (**8**) and ethyl cyclohexane-2-carboxylate (**9**). By treatment of the compounds **2-4** with an equimolar amount of the reagent **1** in acetic acid the corresponding 3-benzoylamino-5-oxo-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-ones **5-7**, identical with the compounds reported earlier [16-17], were formed in 81-83% yields. Ethyl carboxylates **8** and **9** do not react under these conditions and starting material was recovered unchanged. However, when polyphosphoric acid was employed for cyclization instead of acetic acid, the cyclization of the reagent took place to give 4-dimethylaminomethylene-2-phenyl-5(4*H*)-oxazolone (**10**), identical with

the compound prepared from hippuric acid (**11**), DMF and phosphorous oxychloride [10].

Since we have observed earlier that 3-benzoylamino-2*H*-1-benzopyran-2-one is formed from resorcinol and **1** [12], we tried to extend this reaction to some other phenols. We found that phenol itself and 4-methylphenol do not react under these conditions, while 1-naphthol (**12**) and 2-naphthol (**13**) form the corresponding 2*H*-naphtho[1,2-*b*]pyran-2-one (**14**) and 3*H*-naphtho[2,1-*b*]pyran-3-one (**15**) derivatives, respectively.

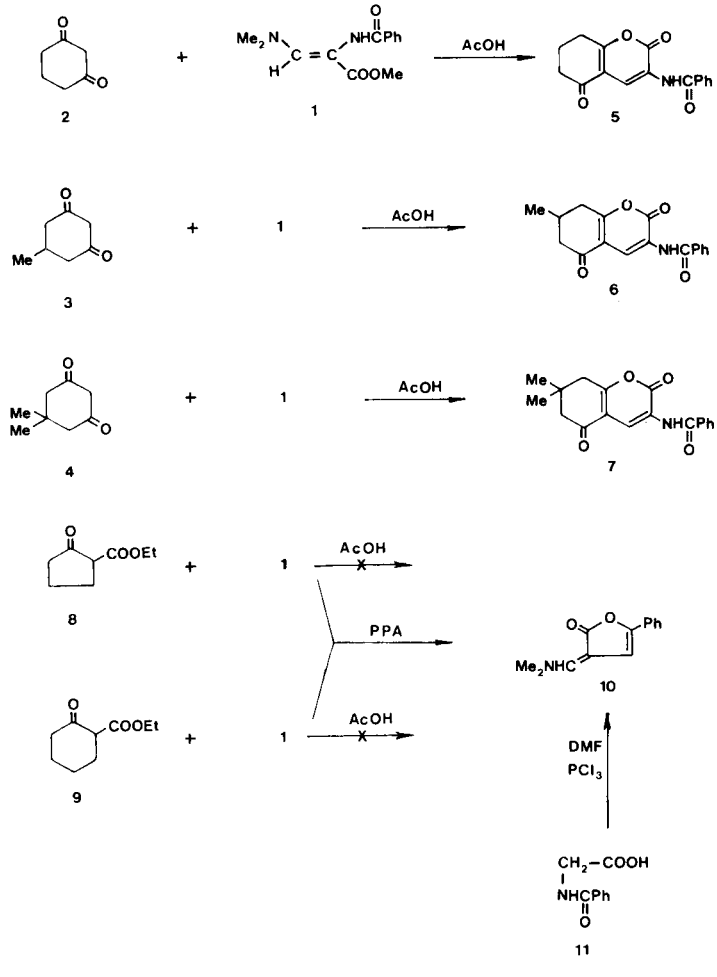
The structures of naphthopyranones **14** and **15** were determined on the basis of elemental analyses, ir and ^{1}H nmr spectra. In the ir spectra the carbonyl bands appear at ν = 1700 cm^{-1} and at ν = 1640-1660 cm^{-1} typical for 2-pyranones [5] and benzoyl group, respectively. Furthermore, in the ^{1}H nmr spectrum of **14** one of the naphthol protons disappears and a new singlet appears at δ = 8.8 ppm corresponding to H_4 in pyranone ring of the product. On the other hand, 2-naphthol can form two isomeric systems **15** or **16**. We observed in ^{1}H nmr spectrum a singlet at δ = 9.41 ppm for H_1 shifted downfield, due to the steric reasons. This is in agreement with the structure **15** and not with **16**.

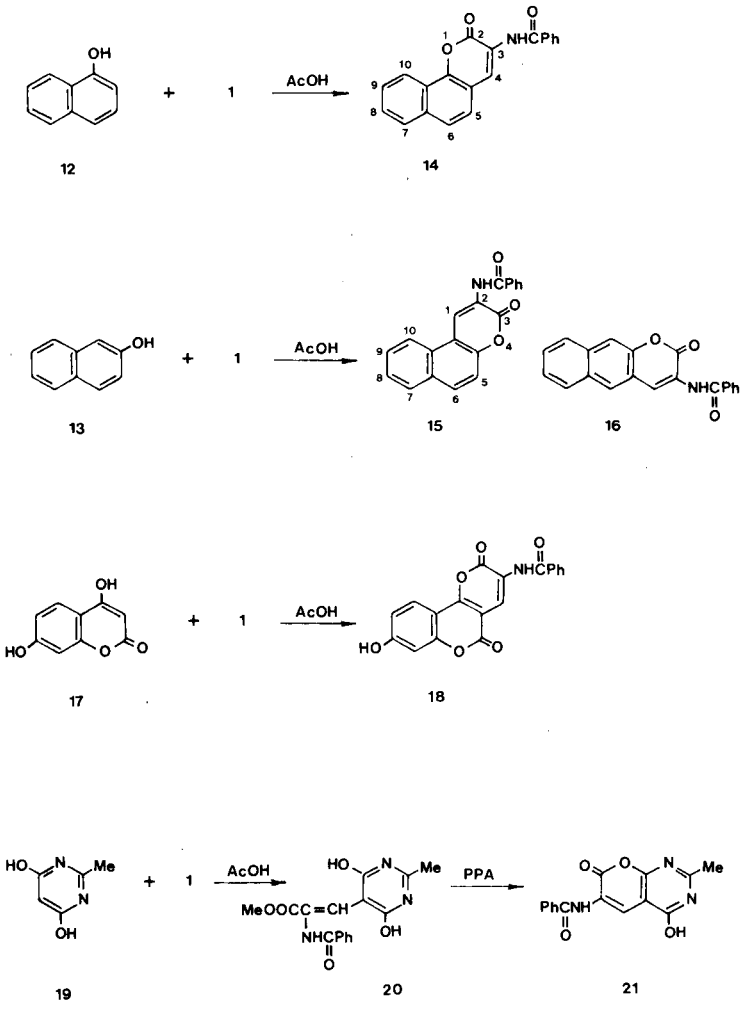
We extended this reaction also to 4,7-dihydroxy-2*H*-1-benzopyran-2-one (**17**) and 4,6-dihydroxy-2-methylpyrimidine (**19**) as potential 1,3-dicarbonyl heterocyclic compounds. With the compound **17** the corresponding pyrano-[3,2-*c*][1]benzopyran derivate **18** is formed, while with **19** the noncyclized intermediate **20** was isolated. Further treatment of **20** in polyphosphoric acid afforded the corresponding pyrano[2,3-*d*]pyrimidine derivative **21**. This experiment shows that 4,6-dihydroxypyrimidine derivative **19** is less reactive then barbituric or thiobarbituric acid and their derivatives, as we reported earlier [12].

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 with TMS as the internal standard, ir spectra on a Perkin-Elmer

Scheme 2





1310 spectrometer and elemental analyses for C, H, and N on a Perkin-Elmer CHN Analyser 240 C.

Methyl 2-benzoylamino-3-dimethylaminopropenoate (**1**) was prepared according to the procedure we have described previously [8].

3-Benzoylamino-5-oxo-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-ones.

General Procedure.

A mixture of 1,3-cyclohexanedione **2-4** (0.001 mole) and **1** (0.001 mole) in glacial acetic acid (5 ml) was heated under reflux for six hours. The solution was evaporated *in vacuo* to one-half, the precipitate was, after cooling, collected by filtration, washed with ethanol and recrystallized from an appropriate solvent.

The following compound were prepared in this manner:

3-Benzoylamino-5-oxo-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-one (**5**).

This compound was prepared from 1,3-cyclohexanedione (**2**, 112 mg, 0.001 mole) and **1** (248 mg, 0.001 mole) in 82% yield, mp 189°, lit [16] mp 189-190°, lit [18] mp 188-189°.

3-Benzoylamino-7-methyl-5-oxo-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-one (**6**).

This compound was prepared from 5-methyl-1,3-cyclohexanedione (**3**, 126 mg, 0.001 mole) and **1** (248 mg, 0.001 mole) in 81% yield, mp 192°, lit [18] mp 191-192°.

3-Benzoylamino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-one (**7**).

This compound was prepared from 5,5-dimethycyclohexanedione (**4**, 140 mg, 0.001 mole) and **1** (248 mg, 0.001 mole) in 83% yield, mp 180°, lit [18] mp 179-179.5°.

Reaction of **8** or **9** with **1**. Formation of 4-Dimethylaminomethylene-2-phenyl-5(4*H*)-oxazolone (**10**).

A mixture of **8** or **9** (0.001 mole) and **1** (248 mg, 0.001 mole) in PPA (10 g) was heated at 80° for two-and-a-half hours. The mixture was, after cooling, poured on crushed ice (20 g) and stirred for 20 minutes. The precipitate formed during this time was collected by filtration, washed with ice-cold water (5 ml) and recrystallized from methanol to give **10** in 54% yield, mp 157-160°; ^{1}H nmr (DMSO-d_6): δ 3.28 (s) and 3.32 (s) (NMe_2), 7.37 (s, CH=C), 7.46-7.55 (m) and 7.80-7.91 (m, 2-Ph).

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.41; H, 5.82; N, 13.11.

3-Benzoylamino-2*H*-naphtho[1,2-*b*]pyran-2-one (**14**).

A mixture of α-naphthol (**12**, 2.88 g, 0.02 mole) and **1** (4.96 g, 0.02 mole) in glacial acetic acid (60 ml) was heated under reflux for two hours. The precipitate was, after cooling, collected by filtration and washed with ethanol to give 1.89 g (30%) of **14**, mp 215-219° (from a mixture of DMF and ethanol); ^{1}H nmr (DMSO-d_6): δ 7.53-8.43 (m, PhCO, H_5, H_6, H_7, H_8, H_9, H_{10}), 8.80 (s, H_4), 9.73 (br, s, NHCO).

Anal. Calcd. for $C_{20}H_{13}NO_3$: C, 76.42; H, 4.17; N, 4.46. Found: C, 76.49; H, 4.20; N, 4.40.

2-Benzoylamino-3*H*-naphtho[2,1-*b*]pyran-3-one (**15**).

A mixture of β-naphthol (**13**, 2.88 g, 0.02 mole) and **1** (4.96 g, 0.02 mole) in glacial acetic acid (60 ml) was heated under reflux for two hours. The precipitate was, after cooling, collected by filtration and washed with ethanol to give 1.83 g (29%) of **15**, mp 235-236° (from a mixture of DMF and ethanol); ^{1}H nmr (DMSO-d_6): δ 7.50-8.46 (m, PhCO, H_5, H_6, H_7, H_8, H_9, H_{10}), 9.33 (br, s, NHCO), 9.43 (s, H_1).

Anal. Calcd. for $C_{20}H_{13}NO_3$: C, 76.42; H, 4.17; N, 4.46. Found: C, 76.13; H, 4.16; N, 4.26.

3-Benzoylamino-8-hydroxy-2*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-2,5-dione (**18**).

A mixture of 4,7-dihydroxy-2*H*-1-benzopyran-2-one (**17**, 178 mg, 0.001 mole) and **1** (248 mg, 0.001 mole) in glacial acetic acid (5 ml) was heated under reflux for 40 minutes. The precipitate formed during heating was, after cooling, collected by filtration to give 252 mg (72%) of **18**, mp >320° (from a mixture of DMF and ethanol): ^{1}H nmr (DMSO-d_6): δ 6.83 (d, H_7), 7.0 (dd, H_9), 7.50-7.70 (m) and 7.83-8.10 (m) (PhCO), 7.82 (d, H_{10}), 8.57 (s, H_4), 9.83 (br s, NHCO), $J_{H_9,H_{10}}$ = 8.5 Hz, J_{H_7,H_9} = 1.5 Hz.

Anal. Calcd. for $C_{19}H_{11}NO_6$: C, 65.51; H, 3.18; N, 4.02. Found: C, 65.31; H, 3.29; N, 4.14.

Methyl 2-Benzoylamino-3-(4,6-dihydroxy-2-methylpyrimidinyl-5)-propenoate (**20**).

A suspension of 4,6-dihydroxy-2-methylpyrimidine (**19**, 126 mg, 0.001 mole) and **1** (248 mg, 0.001 mole) in glacial acetic acid (5 ml) was heated under reflux for 95 minutes. The crude product was, after cooling, collected by filtration to give 187 mg (57%) of **20**, mp >320° (from a mixture of DMF and ethanol); ^{1}H nmr (DMSO-d_6): δ 2.30 (s, 2-Me), 3.67 (s, OMe), 6.90 (s, CH=C), 7.43-7.67 (m) and 7.76-8.0 (m) (PhCO), 11.1 (br s, NHCO).

Anal. Calcd. for $C_{16}H_{15}N_3O_5$: C, 58.35; H, 4.59; N, 12.76. Found: C, 58.56; H, 4.60; N, 13.00.

6-Benzoylamino-4-hydroxy-2-methyl-7*H*-pyrano[2,3-*d*]pyrimidin-7-one (**21**).

A mixture of **20** (329 mg, 0.001 mole) and polyphosphoric acid (4 g) was heated at 170° for four hours. After cooling, water (7 ml) was added and the precipitate was collected by filtration to give 212 mg (71%) of **21**, mp >320° (from a mixture of DMF, ethanol and water); ^{1}H nmr (DMSO-d_6): δ 2.40 (s, 2-Me), 7.50-7.77 (m) and 7.97-8.10 (m) (PhCO), 8.53 (s, H_6), 9.73 (br s, NHCO).

Anal. Calcd. for $C_{15}H_{11}N_3O_4$: C, 60.61; H, 3.72; N, 14.14. Found: C, 60.26; H, 3.84; N, 14.06.

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