A Novel and Direct Synthetic Route to Substituted 1,5-Dihydro-4*H*-[1]benzopyrano[4,3-*b*]pyridine-4,5-diones

Jan Světlík*

Department of Pharmaceutical Analysis and Nuclear Pharmacy, Faculty of Pharmacy, Odbojarov 10, SK-832 32 Bratislava, Slovak Republic

Nad'a Prónayová

NMR Laboratory, Slovak Technical University, Radlinskeho 9, SK-812 37 Bratislava, Slovak Republic

Vladimír Hanuš

The J. Heyrovsky Institute of Physical Chemistry, Dolejskova 3, CZ-182 23 Praha, Czech Republic

Received September 20, 1999

The condensation of 4-hydroxy-6-methyl-2*H*-pyran-2-one and substituted 2-hydroxybenzaldehydes with ammonium acetate gave the title heterocycles. Synthesis of 1,5-dihydro-2-methyl-4*H*-[1]naphtho-[1',2':5,6]pyrano[4,3-*b*]-pyridine-4,5-dione is also described. A reaction mechanism is discussed.

J. Heterocyclic Chem., **37**, 395 (2000).

The 2*H*-pyran-2-one structural unit appears frequently in naturally occurring products [1,2] that often exhibit remarkable biological profiles [1]. During the past few years our attention has been focused on simpler synthetic models due to the discovery of the antiviral properties of 4-hydroxypyranones and 4-hydroxycoumarins. Some of these compounds are believed to be promising drug candidates as non-peptidic HIV protease inhibitors [3]. Nevertheless, aspects other than medical use render this class of compounds an attractive target for chemists. There are several ring transformations that allow for conversion of the oxacyclic system into other types of heterocycles such as furanes [4], pyrazoles [5,6], pyridines [4,7], pyrimidines [4] and pyrano[2,3-*b*]pyridines [4].

Recently we have investigated hydrazinolysis of a 6,12-methanodipyrano[4,3-*b*;4,3-*f*][1,5]dioxocine-1,7-dione derivative yielding 3,4,6-trimethyl-1*H*-indazole-7-carboxylic acid [8]. Pursuing our current interests in the pyrane area we describe here a conceptually and experimentally simple approach to compounds with the [1]benzopyrano[4,3-*b*]pyridine framework **3** and its naphtho fused analogue **4**. This work is partly related to our studies on oxygen-bridged heterocycles [9] demonstrating the synthetic utility of salicylaldehyde as a valuable bifunctional building block.

The multicomponent condensation strategy is a tool for creating the target core structure in a single step operation [10]. Featuring this principle we have developed a one-flask synthesis of the title heterocycle starting from 4-hydroxy-6-methyl-2*H*-pyran-2-one (triacetic lactone, **1**), salicylaldehyde (**2a**) and ammonia. Thus, refluxing equimolar amounts of reactants **1** and **2a** with an excess of ammonium acetate in acetic acid for 15 hours afforded the tricyclic product **3a** in 33 % yield. Ammonium acetate serves simultaneously as a condensation reagent and a nitrogen source. Although the heterocyclization occurred also in warm dimethylformamide (DMF) or in boiling ethanol, attempts to improve the yield by changing the solvent or by allowing a longer reaction time have been fruitless. Other 2-hydroxybenzaldehydes **2b-f** reacted similarly to give substituted 1,5-dihydro-2-methyl-4*H*-[1]benzopyrano[4,3-*b*]pyridine-4,5-diones **3b-f**. It should be noted that these substances were the only isolated products. The yields ranged from 31 to 34 %, except for the nitro derivative **3f** (23 %). These results indicate that the yields are not influenced significantly by the nature of the salicylaldehyde substituent. Although the yields are scarcely satisfying, the low-cost materials make the present synthetic route for preparation of heterocycles **3** useful, in particular considering that compounds of this type are otherwise difficult to obtain directly. In spite of many members belonging to the benzopyrano[4,3-*b*]pyridine family, the diones **3** are previously unknown compounds.

The structures were established by analytical and spectral data. The mass spectra of **3a-f** exhibited correct molecular ions as confirmed by elemental compositions determined by high-resolution ms for selected compounds. In the ir spectrum of **3a** two stretching vibrations appeared at 1724 and 1660 cm^{-1} correspond to lactone and pyridone type of carbonyl function, respectively [11,12]. Diethylamino derivative **3b** also showed essentially identical frequencies of the C=O groups. Surprisingly, the ir spectra of the products **3c-f** revealed only one strong absorption band near 1690 cm^{-1}. The ^{1}H-nmr of the parent compound **3a** showed the peri-proton H-10 at the lower-field (δ_H 8.46). This down-field shift may be due to an anisotropy effect induced by the nearby pyridone ring. The ^{1}H-nmr also showed two singlets for the isolated olefinic proton H-3 (δ_H 6.88) and the methyl group (δ_H 2.57) and a broad signal for NH (δ_H 11.23). Substances **3b-f** also exhibited similar ^{1}H-nmr patterns.

The one-step procedure was also successfully applied to the synthesis of 1,5-dihydro-2-methyl-4*H*-[1]naphtho-[1',2':5,6]pyrano[4,3-*b*]pyridine-4,5-dione (**4**) employing 2-hydroxy-1-naphthaldehyde. As seen from the Dreiding model of **4**, the aromatic hydrogen H-12 is in close proximity of the nitrogen atom, so stronger deshielding effect was observed for H-12 (10.68 ppm). All six aromatic protons in **4** were unequivocally assigned by their multiplicity and using H,H-COSY and selective decoupling experiments. The only other example of this heterocyclic system has been reported by Lipschutz [13] who used intramolecular biaryl coupling *via* organocuprate intermediates to prepare an unsubstituted 5*H*-isomeric analogue.

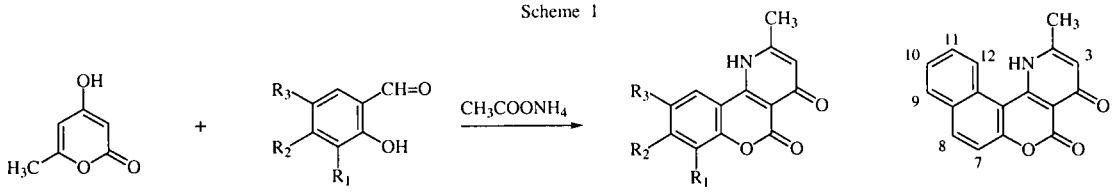
Similar short time (1 minute) reaction of salicylaldehydes (**2a-e**) with lactone **1** in ethanol gave 3-acetoacetylcoumarin **5a,d,e** or 3-(3-amino-2-butenoyl)coumarin **6b,c** as yellow crystals. The structure of **5a**, obtained from **2a**, was confirmed by comparing its melting point and mass spectrum with literature data [14,15]. A German patent [16] described a similar synthesis using triethylamine in refluxing toluene.

We have studied the keto-enol tautomerism in **5a**, and found that **5a** predominantly exists as tautomer **5'a** not **5''a**. This conclusion is based on a long-range H,C-correlation observed between the methyl protons and a ketone carbonyl carbon in 2D-nmr. The enol content was 81 % in dimethyl-d_6 sulfoxide, 93 % in deuteriochloroform, and almost 100 % in acetone-d_6.

The structure of **6b**, obtained from **2b**, was confirmed by nmr analyses. Its ^{1}H-nmr spectrum in dimethyl-d_6 sulfoxide showed enolic methine shifted upfield approximately by 1.0 ppm relative to that in **5'**. Of particular significance were two broad signals, each integrated for 1H, which disappeared upon addition of deuterium oxide (δ_H near 8.0 and 10.0). Apparently, these resonances belong to either an NH_2 or NH and OH functionalities which can be assigned to isomers **6** and **6'**, respectively. A cross peak between the signals of these protons in the COSY spectrum indicated a primary amine group and therefore the enaminoketone structure **6** rather than the imine form **6'**. Moreover, long-range H,C-correlations of both exchangeable protons with the methyl carbon atom gave additional evidence for isomer **6**. The different chemical shift values for the NH_2 protons pointed to a strong intramolecular hydrogen bonding between the acyclic carbonyl and one of the primary amine hydrogens. This could also be deduced from a broad ν_{NH} absorption band in the ir spectrum of **6b**. In addition, the resulting *Z* geometry at the C=C bond was confirmed by NOE experiments that showed a close proximity of the methine and terminal methyl protons. Undoubtedly, products **6b** and **6c** proved to be the key intermediates in the synthesis of benzopyranopyridines **3**.

On the basis of the derivatives **5** and **6** the following mechanistic pathway leading to the parent heterocycle **3a** can be formulated. It starts with the condensation of pyranone **1** with salicylaldehyde (**2a**) in the presence of ammonium acetate to give 3-salicylidenepyrane-2,4-dione **7**. This compound was already described to be produced from the same components and sodium amide in liquid ammonia [17]. The functional pyrone unit in **7** undergoes a ring opening reaction mediated by a nucleophilic attack of the phenolic group onto the lactone carbonyl yielding 3-acetoacetylcoumarin (**5a**) which is then converted into amine **6**. Subsequently, the nitrogen atom of **6** underwent a Michael type addition to the C-4 position of the benzo-

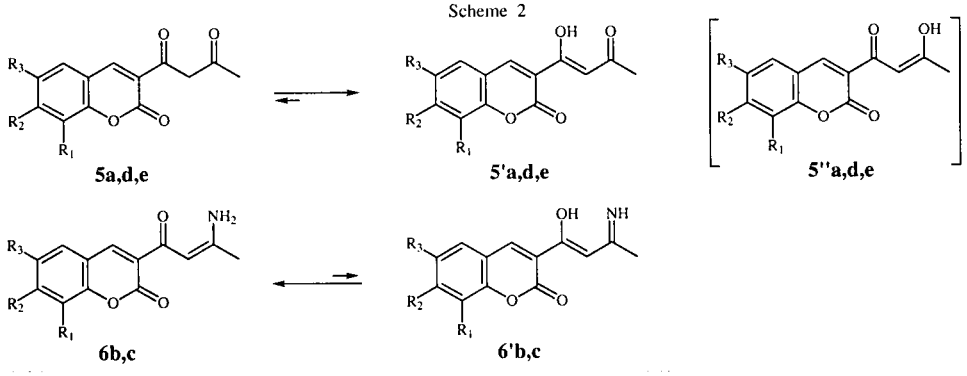
Scheme 1



1 **2a-f** **3a-f** **4**

a: R^1=R^2=R^3=H
b: R^2=NEt_2 R^1=R^3=H
c: R^1=R^3=Cl R^2=H
d: R^3=Br R^1=R^2=H
e: R^1=OMe R^2=R^3=H
f: R^3=NO_2 R^1=R^2=H

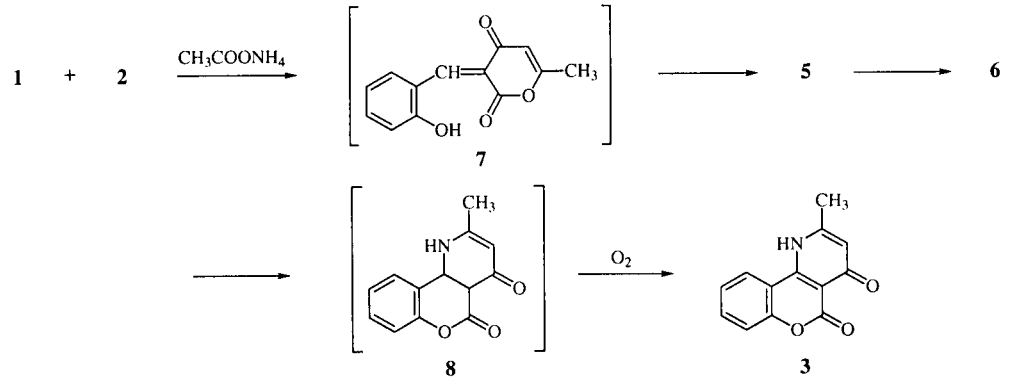
Scheme 2



5a,d,e **5'a,d,e** **5''a,d,e**

6b,c **6'b,c**

Scheme 3



pyranone moiety to form the dihydropyridone ring in **8**. Although the cyclization to **8** through a 6-endo-trig mode appears to be the most probable route, a ring closure of isomeric 1-azatriene **6'** by a 6π electrocyclic process may also be operative. In the final step, involving air oxidation of **8**, two hydrogens were eliminated to provide **3a**. To verify the whole reaction sequence, an independent experiment starting from 3-acetoacetylcoumarin (**5a**) and ammonium acetate was carried out. Indeed, this reaction provided the desired product **3a** which was formed in a slightly higher yield than by the three-component condensation described above.

EXPERIMENTAL

The melting points (uncorrected) were determined with a Kofler hot stage microscope. The ir spectra were recorded on a Nicolet Impact 400 D spectrophotometer. The EI mass spectra were obtained on a Jeol JMS D-100 spectrometer operating at 75 eV. Peak matching with perfluorokerosene as the reference was utilized for hrms. The nmr spectra were measured on a Varian VXR-300 spectrometer equipped with a multinuclear broadband probe (299.943 MHz for ^1H; 75.429 MHz for ^{13}C). The DQ-COSY and HETCOR spectra were acquired using standard pulse sequences supplied by the producer. Long-range ^1H-^{13}C correlations were determined using INEPT with spin-selective proton pulses of 15 and 30 ms duration for 90° and 180° angles, respectively. The evolution interval for polarization transfer was set to 50 ms, the refocusing period was 40 ms.

General Procedure for the Preparation of 1,5-Dihydro-2-methyl-4*H*-[1]benzopyrano[4,3-*b*]pyridine-4,5-diones (**3a-f**).

To a solution of pyranone **1** (0.60 g, 4.75 mmoles) and 2-hydroxybenzaldehyde **2a-f** (4.75 mmoles) in acetic acid (15 ml) was added ammonium acetate (0.70 g, 9.0 mmoles) and the mixture was refluxed for 15 hours. After cooling, the crystallized products (**3d**, **3f**) were collected by suction, and the products (**3a-c**, **3e**) were collected by concentration of the mixture followed by crystallization in ethanol (**3a-c**) or acetonitrile (**3e**).

1,5-Dihydro-2-methyl-4*H*-[1]benzopyrano[4,3-*b*]pyridine-4,5-dione (**3a**).

This compound was obtained in 33 % yield (0.36 g), mp 208-210° (ethanol); ir (potassium bromide): ν 3280-2600 (NH), 1724, 1660 (C=O), 1617 (C=C-C=O), 1544 (C=C) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.56 (s, 3H, Me), 6.88 (s, 1H, H-3), 7.45 (dt, 2H, *J*=7.8 and 1.1 Hz, H-7 and H-9), 7.67 (dt, 1H, *J*=7.8 and 1.8 Hz, H-8), 8.46 (dd, 1H, *J*=7.9 and 1.7 Hz, H-10), 11.23 (br s, 1H, NH); ^{13}C nmr ($CDCl_3$-CD_3OD): δ 25.5 (Me), 102.2 (C-4a), 110.7 (CH-3), 117.2 (CH-7), 119.3 (C-10a), 125.4, 125.5 (CH-9/CH-10), 132.5 (CH-8), 152.2, 152.6 (C-6a/C-10b), 165.5, 167.7, 167.8 (C-2/C-4/C-5); ms: m/z (relative intensity) 228 (15), 227 ($C_{13}H_9NO_3$, M^+, 100), 199 ($C_{12}H_9NO_2$, 12), 198 ($C_{12}H_8NO_2$, 10), 170 ($C_{11}H_8NO$, 6) 143 ($C_{10}H_9N$, 3), 115 (C_9H_7, 4).

Anal. Calcd. for $C_{13}H_9NO_3$: C, 68.72; H, 3.99; N, 6.16. Found: C, 68.61; H, 3.94; N, 6.36.

8-Diethylamino-1,5-dihydro-2-methyl-4*H*-[1]benzopyrano[4,3-*b*]-pyridine-4,5-dione (**3b**).

This compound was obtained in 31 % yield (0.44 g), mp 231-233° (DMF); ir (potassium bromide): ν 3263 (NH), 1719, 1660 (C=O), 1617 (C=C-C=O), 1546 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$-CD_3OD): δ 1.26 (t, 6H, 2 x Me), 2.51 (s, 3H, Me-2), 3.51 (q, 4H, 2 x CH_2), 6.45 (s, 1H, H-3), 6.51 (d, 1H, *J*=2.4 Hz, H-7), 6.75 (d, 1H, *J*=6.4 Hz, H-9), 8.17 (d, 1H, *J*=8.8 Hz, H-10); ms: m/z (relative intensity) 299 (7), 298 (M^+, 36), 284 (18), 283 (100), 255 (33), 227 (7), 226 (7).

Anal. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.69; H, 6.38; N, 9.64.

7,9-Dichloro-1,5-dihydro-2-methyl-4*H*-[1]benzopyrano-[4,3-*b*]pyridine-4,5-dione (**3c**).

This compound was obtained in 33 % yield (0.47 g), mp 194-196° (methanol); ir (potassium bromide): ν 3250-3120 (NH), 1695 (C=O), 1617 (C=C-C=O), 1560 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.66 (s, 3H, Me), 6.89 (s, 1H, H-3), 7.62 (d, 1H, *J*=2.4 Hz, H-8), 8.45 (d, 1H, *J*=2.4 Hz, H-10), 11.09 (br s, 1H, NH); ^{13}C nmr ($CDCl_3$): δ 25.6 (Me), 102.2 (C-4a), 111.5 (CH-3), 121.8, 123.1 (C-10a/C-7), 123.5 (CH-10), 130.9 (C-9), 132.3 (CH-8), 146.5, 150.9 (C-6a/C-10b), 163.9, 167.7, 168.3 (C-2/C-4/C-5); ms: m/z (relative intensity) 298 (10), 297 (M^+ for ^{37}Cl, 65), 296 (18), 295 ($C_{13}H_7NO_3Cl_2$, M^+ for ^{35}Cl, 100), 234 (7), 232 (19), 204 (7).

Anal. Calcd. for $C_{13}H_7NO_3Cl_2$: C, 52.73; H, 2.38; N, 4.73. Found: C, 52.61; H, 2.57; N, 4.91.

9-Bromo-1,5-dihydro-2-methyl-4*H*-[1]benzopyrano[4,3-*b*]pyridine-4,5-dione (**3d**).

This compound was obtained in 34 % yield (0.49 g), mp 271-272° (DMF); ir (potassium bromide): ν 3230-3130 (NH),

1683 (C=O), 1617 (C=C-C=O), 1562 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$-CD_3OD): δ 2.70 (s, 3H, Me), 6.92 (s, 1H, H-3), 7.31 (d, 1H, *J*=8.8 Hz, H-7), 7.72 (dd, 1H, *J*=8.9 and 2.4 Hz, H-8), 8.80 (d, 1H, *J*=2.5 Hz, H-10); ^{13}C nmr ($CDCl_3$-CD_3OD): δ 25.2 (Me), 102.3 (C-4a), 111.4 (CH-3), 118.6, 120.3 (C-10a/C-9), 118.9 (CH-7), 128.0 (CH-10), 135.4 (CH-8), 150.9, 151.0 (C-6a/C-10b), 164.5, 167.4, 167.9 (C-2/C-4/C-5); ms: m/z (relative intensity) 307 ($C_{13}H_8N_3OBr$, M^+ for ^{81}Br, 98), 305 (M^+ for ^{79}Br, 100), 226 ($C_{13}H_8N_3O$, 91), 198 ($C_{12}H_8NO_2$, 42), 170 ($C_{11}H_8NO$, 27), 158 ($C_9H_4NO_2$, 27), 130 (C_8H_4NO, 53), 102 (22), 85 (19), 51 (25), 39 (42).

Anal. Calcd. for $C_{13}H_8N_3OBr$: C, 51.01; H, 2.63; N, 4.58. Found: C, 50.88; H, 2.47; N, 4.79.

1,5-Dihydro-7-methoxy-2-methyl-4*H*-[1]benzopyrano-[4,3-*b*]pyridine-4,5-dione (**3e**).

This compound was obtained in 32 % yield (0.42 g), mp 207-208° (acetonitrile); ir (potassium bromide): ν 3230-3070 (NH), 1686 (C=O), 1618 (C=C-C=O), 1587, 1562 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.64 (s, 3H, Me), 4.00 (s, 3H, OMe), 6.82 (s, 1H, H-3), 7.13 (dd, 1H, *J*=8.1 and 1.5 Hz, H-8), 7.32 (t, 1H, *J*=8.1 Hz, H-9), 8.13 (dd, 1H, *J*=7.8 and 1.5 Hz, H-10), 11.35 (br s, 1H, NH); ^{13}C nmr ($CDCl_3$): δ 25.6 (Me), 56.3 (OMe), 102.1 (C-4a), 110.5 (CH-3), 114.1, 116.5 (CH-8/CH-9), 120.4 (C-10a), 125.0 (CH-9), 141.9, 147.6, 152.7 (C-7/C-6a/C-10b), 165.0, 167.7, 167.8 (C-2/C-4/C-5); ms: m/z (relative intensity) 258 (16), 257 ($C_{14}H_{11}NO_4$, M^+, 100), 242 (20), 214 (24), 186 (17), 173 (25), 158 (6).

Anal. Calcd. for $C_{14}H_{11}NO_4$: C, 65.37; H, 4.31; N, 5.44. Found: C, 65.58; H, 4.19; N, 5.58.

1,5-Dihydro-2-methyl-9-nitro-4*H*-[1]benzopyrano[4,3-*b*]pyridine-4,5-dione (**3f**).

This compound was obtained in 23 % yield (0.30 g), mp 260-262° (acetic acid); ir (potassium bromide): ν 3201 (NH), 1697 (C=O), 1622 (C=C-C=O), 1563 (C=C), 1532, 1335 (NO_2) cm^{-1}; ^1H nmr ($CDCl_3$-CD_3OD): δ 2.72 (s, 3H, Me), 6.97 (s, 1H, H-3), 7.58 (d, 1H, *J*=9.1 Hz, H-7), 8.48 (dd, 1H, *J*=9.1 and 2.7 Hz, H-8), 9.49 (d, 1H, *J*=2.8 Hz, H-10); ms: m/z (relative intensity) 272 ($C_{13}H_8N_2O_5$, M^+, 100), 242 (27), 226 ($C_{13}H_8NO_3$, 75), 214 ($C_{12}H_8NO_3$, 26), 170 (13), 158 (31), 141 (14), 130 (C_8H_4NO, 90), 115 (23), 102 (14), 75 (27), 51 (39).

Anal. Calcd. for $C_{13}H_8N_2O_5$: C, 57.36; H, 2.96; N, 10.29. Found: C, 57.64; H, 3.25; N, 10.65.

1,5-Dihydro-2-methyl-4*H*-[1]naphtho[1',2':5,6]pyrano[4,3-*b*]-pyridine-4,5-dione (**4**).

This compound was prepared from pyranone **1**, 2-hydroxy-1-naphthaldehyde and ammonium acetate according to the general procedure described above for **3a-f**. The product precipitated from the reaction mixture after cooling to room temperature. Yield 0.26 g (20 %), mp 240-241° (acetic acid); ir (potassium bromide): ν 3352 (NH), 1681 (C=O), 1561 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$-CD_3OD): δ 2.78 (s, 3H, Me), 6.89 (s, 1H, H-3), 7.52 (d, 1H, *J*=9.0 Hz, H-7), 7.62 (t, 1H, *J*=7.3 Hz, H-10), 7.76 (dt, 1H, *J*=7.9 and 1.5 Hz, H-11), 7.93 (d, 1H, *J*=8.1 Hz, H-9), 8.05 (d, 1H, *J*=9.0 Hz, H-8), 10.68 (d, 1H, *J*=8.8 Hz, H-12); ms: m/z (relative intensity) 277 ($C_{17}H_{11}NO_3$, M^+, 100), 276 (71), 249 ($C_{16}H_{11}NO_2$, 19), 220 ($C_{15}H_{10}NO$, 13), 165 (9), 152 (13), 77 (11), 63 (13), 51 (20).

Anal. Calcd. for $C_{17}H_{11}NO_3$: C, 73.64; H, 4.00; N, 5.05. Found: C, 73.44; H, 4.40; N, 5.25.

Similar Reaction of Pyranone **1** with 2-Hydroxybenzaldehydes **2a-e** in Ethanol.

To a solution of pyranone **1** (0.60 g, 4.75 mmoles) and a 2-hydroxybenzaldehyde (4.75 mmoles) in ethanol (15 ml) was added ammonium acetate (0.70 g, 9.0 mmoles) and the reaction mixture was refluxed under stirring for 1 minute. On cooling to room temperature the precipitated product was collected by suction filtration and recrystallized. Compound **6a** needs several days for the precipitation.

3-Acetoacetyl-2*H*-[1]benzopyran-2-one (3-acetoacetylcoumarin) (**5a**).

This compound was obtained in 74 % yield (0.81 g), mp 148-150° (ethanol) (lit. [14] 152-153°); ir (potassium bromide): ν 3440 (OH), 1729 (C=O), 1607, 1583 (C=C-C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.23 (s, Me enol + oxo), 4.17 (s, CH_2 oxo), 6.90 (s, CH= enol), 7.46 (m, H-6 and H-8 enol + oxo), 7.74 (m, H-7 enol + oxo), 7.98 (m, H-5 enol + oxo), 7.98 (m, H-5 enol + oxo), 8.76 (s, H-4 oxo), 8.82 (s, H-4, enol), 16.0 (s, OH enol).

Anal. Calcd. for $C_{13}H_{10}O_4$: C, 67.82; H, 4.38. Found: 67.55; H, 4.62.

Compound **3a** was also obtained by refluxing of 3-acetoacetylcoumarin **5a** (1.08 g, 4.75 mmoles) with ammonium acetate (0.70 g, 9.0 mmoles) in acetic acid (20 ml) for 15 hours. Yield 0.40 g (37 %).

3-Acetoacetyl-6-bromo-2*H*-[1]benzopyran-2-one (**5d**).

This compound was obtained in 80 % yield (1.18 g), mp 213-214° (DMF); ir (potassium bromide): ν 3450 (OH), 1736 (C=O), 1609, 1581 (C=C-C=O); ^1H nmr ($CDCl_3$-CD_3OD): δ 2.29 (s, 3H, Me), 7.01 (s, 1H, CH=), 7.27 (d, 2H, *J*=8.8 Hz, H-8), 7.73 (dd, 1H, *J*=8.8 and 2.3 Hz, H-7), 7.80 (d, 1H, *J*=2.3 Hz, H-5), 8.57 (s, 1H, H-4). None of the oxo-form was observed.

Anal. Calcd. for $C_{13}H_9O_4Br$: C, 50.51; H, 2.93. Found: C, 50.41; H, 3.08.

3-Acetoacetyl-8-methoxy-2*H*-[1]benzopyran-2-one (**5e**).

This compound was obtained in 75 % yield (0.93 g), mp 172-173° (methanol); ir (potassium bromide): ν 3441 (OH), 1741 (C=O), 1604 (C=C-C=O); ^1H nmr ($CDCl_3$): δ 2.27 (s, 3H, Me), 3.99 (s, 3H, OMe), 7.05 (s, 1H, CH=), 7.20 (m, 3H, H-8, H-9, H-10), 8.63 (s, 1H, H-4), 15.88 (s, 1H, OH). None of the oxo-form was observed.

Anal. Calcd. for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65. Found: C, 64.80; H, 4.52.

3-(3-Amino-1-oxo-2-butenyl)-7-diethylamino-2*H*-[1]benzopyran-2-one (**6b**).

This compound was obtained in 59 % yield (0.84 g), mp 195-197° (ethanol); ir (potassium bromide): ν 3500-3100 (NH), 1732, 1719 (C=O), 1616 (C=C-C=O); ^1H nmr (DMSO-d_6): δ 1.11 (t, 6H, 2 x Me), 1.96 (s, 3H, Me), 3.43 (q, 4H, 2 x CH_2), 6.15 (d, 1H, *J*=1.5 Hz, CH=), 6.51 (d, 1H, *J*=2.2 Hz, H-8), 6.70 (dd, 1H, *J*=9.0 and 2.2 Hz, H-6), 7.58 (d, 1H, *J*=9.0 Hz, H-5), 7.86 (d, 1H, *J*=4.1 Hz, NH), 8.45 (s, 1H, H-4), 10.10 (d, 1H, *J*=4.8 Hz, NH); ^{13}C nmr (DMSO-d_6): δ 12.3 (Me of NEt_2), 21.9 (Me), 44.2 (CH_2 of NEt_2), 93.7

(CH=), 95.7 (CH-8), 107.8 (C-4a), 109.4 (CH-6), 117.5 (C-3), 131.1 (CH-5), 145.5 (CH-4), 151.7 (C-7), 157.1 (C-8a), 159.6 (C-2), 164.5 (=C(NH_2)-Me), 181.5 (C=O).

Anal. Calcd. for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 68.21; H, 6.93; N, 9.30.

3-(3-Amino-1-oxo-2-butenyl)-6,8-dichloro-2*H*-[1]benzopyran-2-one (**6c**).

This compound was obtained in 13 % yield (0.18 g), mp 191-193° (ethanol); ir (potassium bromide): ν 3360 (NH), 1715 (C=O), 1600 (C=C-C=O); ^{1}H nmr (DMSO-d_6): δ 2.01 (s, 3H, Me), 5.95 (s, 1H, CH=), 8.00 (m, 1H, H-5/H-7), 8.04 (m, 1H, H-7/H-5), 8.30 (br s, 1H, NH), 8.54 (s, 1H, H-4), 10.20 (br s, 1H, NH).

Anal. Calcd. for $C_{13}H_9NO_3Cl_2$: C, 52.37; H, 3.04; N, 4.70. Found: C, 52.12; H, 3.31; N, 4.53.

Acknowledgements.

This work was supported by the Grant Agency of the Slovak Republic (# 1/5201/98).

REFERENCES AND NOTES

[1] J. D. Hepworth, Comprehensive Heterocyclic Chemistry, Vol. **3**, Part **2B**, A. R. Katritzky and C. W. Rees, eds, Pergamon Press, Oxford, 1984, pp. 874-883.

[2] J. M. Dickinson, *Nat. Prod. Rep.*, **10**, 71 (1993).

[3] S. Thaisrivongs, M. N. Janakiraman, K.-T. Chong, P. K. Tomich, L. A. Dolak, S. R. Turner, J. W. Strohbach, J. C. Lynn, M.-M. Horng, R. R. Hinshaw, and K. D. Watenpaugh, *J. Med. Chem.*, **39**, 2400 (1996).

[4] G. P. Ellis, Comprehensive Heterocyclic Chemistry, Vol. **3**, Part **2B**, A. R. Katritzky and C. W. Rees, eds, Pergamon Press, Oxford, 1984, pp 675-689.

[5] C. Ainsworth and R. G. Jones, *J. Am. Chem. Soc.*, **76**, 3172 (1954).

[6] A. Brbot-Saranovic, B. Katusin-Razem, and I. Vickovic, *Heterocycles*, **34**, 1547 (1992).

[7] M. Cervera, M. Moreno-Manas, and R. Pleixats, *Tetrahedron*, **46**, 7885 (1990).

[8] J. Svetlik, V. Hanus, I. M. Lagoja, and J. G. Schantl, *Heterocycles*, **45**, 1833 (1997).

[9a] J. Svetlik, F. Turecek, and V. Hanus, *J. Chem. Soc., Perkin Trans. 1*, 563 (1987); [b] J. Svetlik, F. Turecek, and V. Hanus, *J. Chem. Soc., Perkin Trans. 1*, 2053 (1988); [c] J. Svetlik, V. Hanus, and J. Bella, *Justus Liebigs Ann. Chem.*, 91 (1989); [d] J. Svetlik, I. Goljer, and F. Turecek, *J. Chem. Soc., Perkin Trans. 1*, 1315 (1990); [e] J. Svetlik, V. Hanus, and J. Bella, *J. Chem. Res. (S)*, 4 (1991).

[10] I. Ugi, A. Doemling, and W. Hoerl, *Endeavour*, **18**, 115 (1994).

[11] M. A. Khan and A. L. Gemal, *J. Heterocyclic Chem.*, **14**, 1009 (1977).

[12] H. W. Schmidt, R. Schipfer, and H. Junek, *Justus Liebigs Ann. Chem.*, 695 (1983).

[13] B. H. Lipshutz, F. Kayser, and N. Maullin, *Tetrahedron Lett.*, **35**, 815 (1994).

[14] F. M. Dean, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 895 (1950).

[15] R. A. W. Johnstone, B. J. Millard, F. M. Dean, and A. W. Hill, *J. Chem. Soc. C*, 1712 (1966).

[16] B. Hirsch and N. Hoefgen, German Patent (East) DD 218,892 (1985); *Chem. Abstr.*, **103**, 123357z (1985).

[17] A. I. Scott, H. Guilford, J. J. Ryan, and D. Skingle, *Tetrahedron*, **27**, 3025 (1971).