THE FIRST PYRROLOFUROCOUMARINS

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Abstract: The first pyrrolo[2,3-f]furo[2,3-h]coumarins have been prepared from 4-methyldihydrofuro[2,3-h] coumarin-9-one via its 6-amino derivative, 6-amino-4-methylangelicin, 6-hydrazino-4-methylangelicin, HCl-salt and the appropriate hydrazones by the Fisher indole synthesis.

Introduction

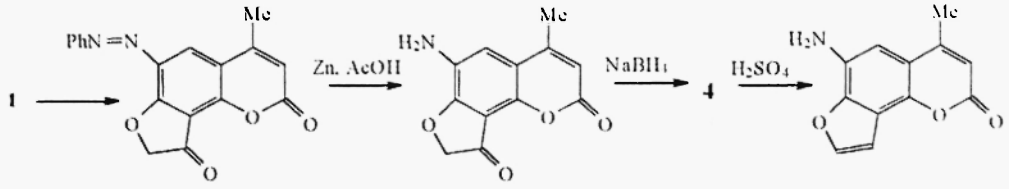
Furocoumarins, first of all angelicin and psoralen derivatives, show a great photosensitizing activity (1-4). Phototherapeutic effect of some heteroanalogs of furocoumarins (pyrrolo-, pyrido-, thienocoumarins) has been also studied (5). Strong antiproliferative effect of furocoumarins and pyrrolocoumarins are also well known (3-5). However, there are no synthetic paths and biological activity data for coumarins condensed with both furo- and pyrrolo- rings, even though pyrrolo(furo)coumarins of that kind might have ability to produce adducts with the pyrimidine bases of DNA via three potentially active sites.

We report in this paper the first pyrrolo[2,3-f]furo[2,3-h]coumarin synthesis based on dihydrofuro[2,3-h] coumarin-9-one reactivity (6-9).

Results and Discussion

Earlier we reported azocoupling reactions of 4-methyldihydrofuro[2,3-h]coumarin-9-one **1** and synthesis of 6-phenylazo-4-methyldihydrofuro[2,3-h]coumarin-9-one **2** (10). The azoketone **2** turned to be the most convenient starting compound for 6-amino-4-methyldihydrofuro[2,3-h] coumarin-9-one **3** preparation. When acetic acid and Zn have been used as reduction reagent, compound **3** was isolated as predominant reaction product. Reduction of the aminoketone **3** by $NaBH_4$ in methanol leads to the corresponding alcohol **4**, which provides 6-amino-4-methylangelicin **5** upon dehydration in H_2SO_4 (scheme 1).

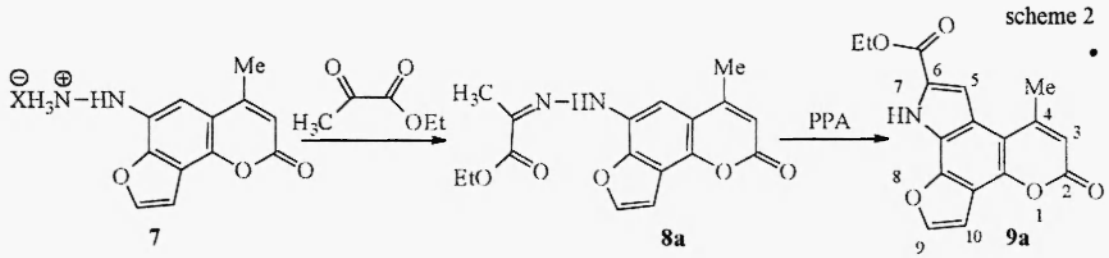
scheme 1



2 **3** **5**

4-Methylangelicin-6-diazonium chloride **6** has been prepared from 6-aminoangelicin **5** by usual procedure. Treatment of diazonium salt **6** by $SnCl_2$ in concentrated HCl at low temperature (-15 °C) leads to 4-methylangelicin-6-hydrazonium chloride **7** with a very good yield. However, reduction of diazonium salt **6** at higher temperature (0 °C) provides the amin **5** formation. The possible way of this reaction is the reduction of intermediate hydrazonium chloride **7**, because of treatment of the compound **7** by $SnCl_2$ in concentrated HCl at 0 °C also provides the amin **5** formation (11). We have also synthesized some angelicin **7** hydrazones **8a-c** by its reaction with the appropriate aliphatic aldehydes and ketones. These hydrazones **8** were used in further reactions immediately because of their unstability. However, we were successful in indole fragment cyclization from **8a-c** by the Fischer indole synthesis (12). The ease of cyclization depends on the nature of the substituents in the arylhydrazone, the acidic reagent, the solvent, the temperature and the type of carbonyl component of the hydrazone. As a rule, strong mineral acids in different solvents and polyphosphoric acid (PPA) were recommended for the Fisher indole method (13). We have used sulfuric acid in acetic acid, hydrogen chloride in acetic acid, tionyl chloride in ethanol and PPA for hydrazones **8** cyclization. PPA turned to be the best reagent for 6-carboethoxy-4-methylpyrrolo[2,3-f]furo[2,3-h]coumarin **9a** formation by the hydrazone **8a** cyclization (scheme 2). The lower yields have been achieved when mineral acids in acetic acid were used. No any product has been isolated when tionyl chloride in ethanol was used as acidic reagent in the Fisher synthesis.

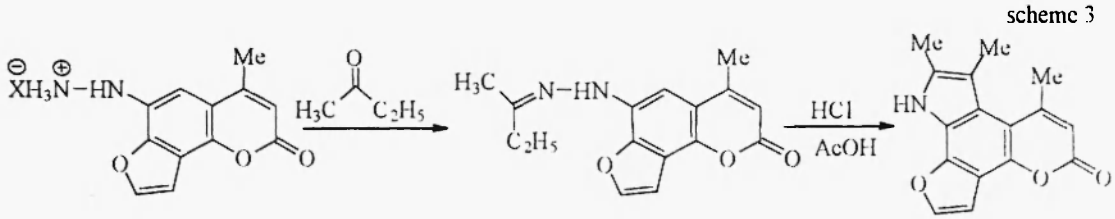
scheme 2



7 **8a** **9a**

Hydrazone of butanone **8b** reacts also with 4,5,6-trimethylpyrrolo[2,3-f]furo[2,3-h]coumarin **9b** formation (scheme 3). The best yield was achieved when hydrogen chloride in acetic acid was used.

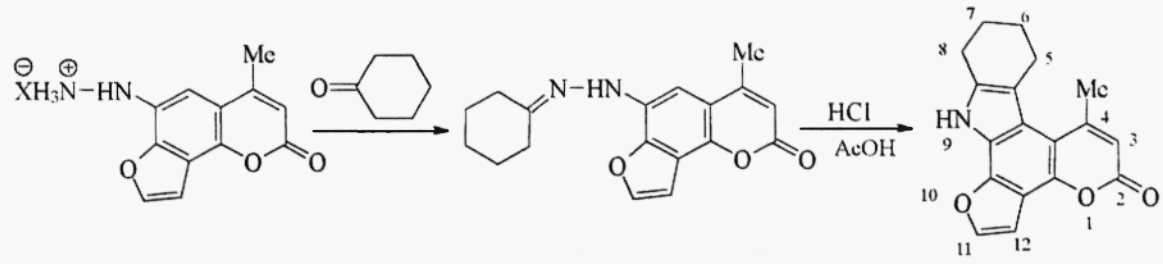
scheme 3



7 **8b** **9b**

4-Methyl-5,6,7,8-tetrahydroindolo[2,3-f]furo[2,3-h]coumarin **9c** has been synthesized by the cyclization of hydrazone **8c** in the presence of HCl in acetic acid (scheme 4).

scheme 4



7 **8c** **9c**

^{1}H-NMR and mass spectra

Mass spectra were scanned on a SSQ-710 (Finnigan MAT) spectrometer at the energy of ionising electrons equal to 70 ev.

^{1}H-NMR spectra were recorded on a Bruker-200 spectrometer at 200 MHz in DMSO-d_6 or $CDCl_3$ solutions using TMS as internal standard. Chemical shifts are given in ppm.

The most characteristic signal of hydrazones **8** is a singlet of NH group which appears at 8-10 ppm. The NH proton signal of the pyrrolo[2,3-f]furo[2,3-h]coumarins appears near 8.5 ppm in the ^{1}H NMR spectra of compounds **8b-c**. This signal shifts to the 13 ppm in the ^{1}H NMR spectra of **8a** because of strong intramolecular H-bond in it.

Experimental

6-Amino-4-methyldihydrofuro[2,3-h]coumarin-9-one 3

The mixture of the compound **2** (1g, 3 mmole), isopropanol (200 ml), glacial acetic acid (20 ml) and excess of Zn powder (0.98 g, 15 mmole) was stirred for 2 hours at 60 °C and poured then into water. The product was filtered off and recrystallized from DMFA.

3: yield 40%, yellow crystals, mp 280 °C (decomp):

^{1}H-NMR (DMSO-d_6, J/Hz), 2.36 (d, 3H, 4-Me, $J_{Me,3}$=1.1), 4.93 (s, 2H, CH_2), 5.42 (s, 2H, 6-NH_2), 6.25 (d, 1H, 3-H, $J_{3,Me}$=1.1), 7.16(s, 1H, 5-H).

MS: m/z (%) 231 (M^+, 100), 203 (-CO, 30), 202 (-HCO, 10), 175 (-2CO, 36), 146 (-2CO, -HCO, 6), 147 (-3CO, 4), 118 (-3CO, -HCO, 12).

6-Amino-4-methyldihydrofuro[2,3-h]coumarin-9-ol 4

The mixture of the compound **3** (0.23g, 1 mmole), $NaBH_4$ (0.038g, 1 mmole) and methanol (10 ml) was stirred for 2 hours at room temperature and poured then into water. The product was filtered off and recrystallized from ethanol.

4: yield 90%, light green crystals, mp 219-221 °C;

^{1}H-NMR (DMSO-d_6, J/Hz), 2.27 (d, 3H, 4-Me, $J_{Me,3}$=1.1), 4.37 (dd, 1H, 8a-H, J_{gem}=15.0, $J_{8a,9}$=2.0), 4.56 (dd, 1H, 8b-H, J_{gem}=15.0, $J_{8b,9}$=7.0), 4.83 (s, 2H, NH_2), 5.43 (dd, 1H, 9-H, $J_{9,8b}$=7.0, $J_{9,8a}$=2.0), 6.06 (d, 1H, 3-H, $J_{3,Me}$=1.1), 6.84 (s, 1H, 5-H).

MS: m/z (%) 233 (M^+, 100), 205 (-CO, 41), 187 (-CO, -H_2O, 53), 159 (-2CO, -H_2O, 21).

6-Amino-4-methylangelicin 5

Procedure 1. Compound **4** (0.94g, 4 mmole) was dissolved in excess of 20% sulfuric acid and refluxed for 1 hour. After cooling aqueous solution of Na_2CO_3 was added untill a solid formed. The product was filtered off and recrystallized from DMFA.

5: yield 70%, white crystals, mp 229-231 °C;

^{1}H-NMR (DMSO-d_6, J/Hz), 2.40 (d, 3H, 4-Me, $J_{Me,3}$=1.1), 5.43 (s, 2H, NH_2), 6.26 (d, 1H, 3-H, $J_{3,Me}$=1.1), 6.83 (s, 1H, 5-H), 7.15 (d, 1H, 9-H, $J_{9,8}$=2.1), 8,05 (d, 1H, 8-H, $J_{8,9}$=2.1).

MS: m/z (%) 215 (M^+, 100), 187 (-CO, 54), 158 (-CO, -HCO, 12), 130 (-2CO, -HCO, 27).

Procedure 2. Compound **5** has been synthesized following compound 7 preparation at 0 °C.

5: yield 60%, white crystals, mp 229-231 °C.

Procedure 3. Compound 7 (2.2 g, 8 mmole) was added to the solution of $SnCl_2$ (4 g, 21 mmole) in 5 ml concentrated HCl at 0 °C and stirred for 1 hour. The product was filtered off and recrystallized from DMFA.

5: yield 60%, white crystals, mp 229-231 °C.

6-Hydrazonium-4-methylangelicin chloride 7

Compound **5** (2.2 g, 10 mmole) was dissolved in 20 ml of concentrated HCl and was added under cooling to 3 ml of 30% aqueous $NaNO_2$ solution. The final diazonium salt **6** solution was added drop by drop to the solution of $SnCl_2$ (4 g, 21 mmole) in 5 ml concentrated HCl at -15 °C. Hydrazine salt was filtered off and dried. Yield 90%.

6-Hydrazono-4-methylangelicins (general procedure).

Compound 7 was dissolved in ethanol and the corresponding ketone was added to the solution at room temperature. The product was filtered off and used for compound **9** preparation.

Ethyl 6-(4-methylfuro[2,3-h]coumarinyl)hydrazone pyruvate 8a

8a: yield 80%, white crystals, mp 198-200 °C;

^{1}H-NMR (DMSO-d_6, J/Hz), 1.30 (t, 3H, $COOCH_2CH_3$), 2.18 (s, 3H, CH_3C=N), 2.48 (d, 3H, 4-Me, $J_{Me,3}$=1.1), 4.21 (q, 2H, $COOCH_2CH_3$), 6.39 (d, 1H, 3-H, $J_{3,Me}$=1.1), 7.29 (d, 1H, 9-H, $J_{9,8}$=2.1), 7.54 (s, 1H, 5-H), 8.20 (d, 1H, 8-H, $J_{8,9}$=2.1), 9.88 (s, 1H, NH).

MS: m/z (%) 328 (M^+, 67), 214 (-$CH_3CNCOOC_2H_5$, 100), 186 (-$CH_3CNCOOC_2H_5$, -CO, 92).

6-(4-Methylfuro[2,3-h]coumarinyl)hydrazone of butanone 8b

8b: yield 80%, light green crystals, mp 144-146 °C (decomp);

^{1}H-NMR (acetone-d_6, J/Hz), 1.20 (t, 3H, CCH_2CH_3), 2.05 (s, 3H, CH_3C=N), 2.38 (q, 2H, $COOCH_2CH_3$), 2.51 (d, 3H, 4-Me, $J_{Me,3}$=1.1), 6.25 (d, 1H, 3-H, $J_{3,Me}$=1.1), 7.18 (d, 1H, 9-H, $J_{9,8}$=2.1), 7.53 (s, 1H, 5-H), 7.97 (d, 1H, 8-H, $J_{8,9}$=2.1), 8.00 (s, 1H, NH).

MS: m/z (%) 284 (M^+, 48), 214 (-$CH_3CNC_2H_5$, 94), 188 (-$CH_3CNC_2H_5$, -CO, 100).

6-(4-Methylfuro[2,3-h]coumarinyl)hydrazone of cyclohexanone 8c

8c: yield 80%, white crystals, mp 198-200 °C;

^{1}H-NMR ($CDCl_3$, J/Hz), 1.63 (s, 6H, 3'-CH_2, 4'-CH_2, 5'-CH_2), 2.48 (d, 3H, 4-Me, $J_{Me,3}$=1.1), 2.50 (m, 4H, 2'-CH_2, 6'-CH_2), 6.32 (d, 1H, 3-H, $J_{3,Me}$=1.1), 7.23 (d, 1H, 9-H, $J_{9,8}$=2.1), 7.37 (s, 1H, 5-H), 8.13 (d, 1H, 8-H, $J_{8,9}$=2.1), 8.87 (s, 1H, NH).

MS: m/z (%) 310 (M^+, 48), 214 (-$(CH_2)_5$=N-, 100), 186 (-$(CH_2)_5$=N,-CO, 94).

6-Carboethoxy-4-methylpyrrolo[2,3-f]furo[2,3-h]coumarin 9a

Compound 8a (0.33g, 1 mmole) was added to 10 ml of PPA, stirred for 15 min at 75 °C and poured then into ice water. The product was filtered off, washed by water and recrystallized from glacial acetic acid.

9a: yield 30%, white crystals, mp 280 °C (decomp.)

^{1}H-NMR (DMSO-d_6, J/Hz), 1.38 (t, 3H, $COOCH_2CH_3$),), 2.77 (d, 3H, 4-Me, $J_{Me,3}$=1.1), 4.39 (q, 2H, $COOCH_2CH_3$), 6.37 (d, 1H, 3-H, $J_{3,Me}$=1.1), 7.32 (d, 1H, 10-H, $J_{10,9}$=2.1), 7.82 (s, 1H, 5-H), 8.19 (d, 1H, 9-H, $J_{9,10}$=2.1), 13.17 (s, 1H, NH).

MS: m/z (%) 311 (M^+, 35), 265 (-C_2H_5OH, 80), 237 (-C_2H_5OH, -CO, 100).

4,5,6-Trimethylpyrrolo[2,3-f]furo[2,3-h]coumarin 9b

The mixture of the compound **8b** (0.28g, 1 mmole), glacial acetic acid (5 ml) and several drops of concentrated HCl was stirred for 3 hours at room temperature. The product was filtered off and recrystallized from DMFA.

9b: yield 85%, green crystals, mp 247 °C (decomp);

^{1}H-NMR ($CDCl_3$, J/Hz), 2.41 (s, 3H, 5-Me), 2.47 (s, 3H, 6-H), 2.73 (d, 3H, 4-Me, $J_{Me,3}$=1.1), 6.21 (d, 1H, 3-H, $J_{3,Me}$=1.1), 7.17 (d, 1H, 10-H, $J_{10,9}$=2.1), 7.55 (d, 1H, 9-H, $J_{9,10}$=2.1), 8.53 (s, 1H, NH).

MS: m/z (%) 267 (M^+, 100), 239 (-CO, 76), 225 (-CO, -CH_2, 33).

4-Methyl-5,6,7,8-tetrahydroindolo[2,3-f]furo[2,3-h]coumarin 9c

Solution of the compound 8c (0.31g, 1 mmole) in glacial acetic acid (5 ml) was refluxed for 1 hour and poured then into ice water. The product was filtered off and recrystallized from toluene.

9c: yield 90%, light green crystals, mp 253 °C (decomp);

^{1}H-NMR ($CDCl_3$, J/Hz), 2.87-2.93 (m, 8H, 5-CH_2, 6-CH_2, 7-CH_2, 8-CH_2), 2.74 (d, 3H, 4-Me, $J_{Me,3}$=1.1), 6.21 (d, 1H,

3-H, $J_{3,Me}$=1.1), 7.19 (d, 1H, 12-H, $J_{12,11}$=2.1), 7.37 (s, 1H, 5-H), 8.47 (d, 1H, 11-H, $J_{11,12}$=2.1), 8.47 (s, 1H, NH).

MS: m/z (%) 293 (M^+, 71), 265(-CO, 37), 237(-2CO, 100)

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