NEW SYNTHESES OF FUROQUINOLINE DERIVATIVES

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Abstract: Fries rearrangement of 7-acyloxyquinolin-2-one and 7-acyloxy-2-chloroquinoline derivatives and their analogs provides useful intermediates for new ways of furoquinoline derivatives syntheses.

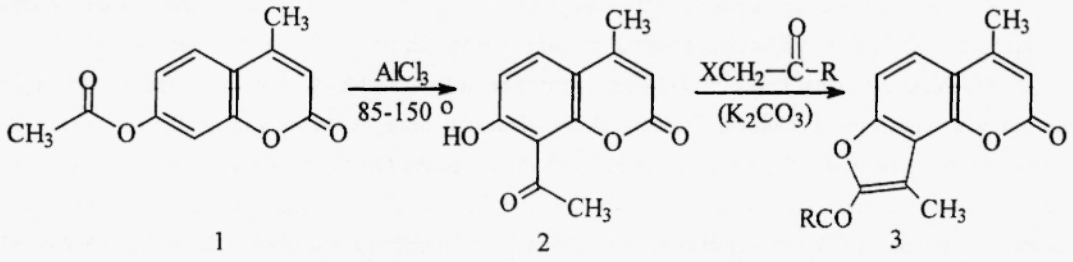
Introduction

Furocoumarins, psoralene and angelicine derivatives first of all, are known to possess a high photobiological activity [1]. However, they behave also some negative subside effects. For example, high activity of furocoumarins under UV-light provide DNA-crosslinking and thus possibility of cancer diseases. It has been found, that furocoumarin analogs which contain in lactone ring other heteroatoms, besides oxygen atom, are free of those subside effects [2-4]. Therefore, furoquinoline derivatives (particularily furoquinolin-2-one derivatives) are much of interest as furocoumarins analogs.

There are in literature some schemes of furoquinolin-2-one derivatives syntheses [5, 6]. While studying new ways of furocoumarins heteroanalogs preparation we have found the Fries rearrangement of acetoxyquinoline derivatives to be useful reaction to obtain key intermediates for the final furoquinolines.

We have earlier successfully used the Fries rearrangement in the syntheses of many furocoumarins [7-9]. For example, treatment of 7-acetoxy-4-methylcoumarin **1** with excess of aluminum chloride provides good yield of 8-acetyl-7-hydroxy-4-methylcoumarin **2** – key intermediate in the furocoumarin derivatives **3** syntheses (scheme 1).

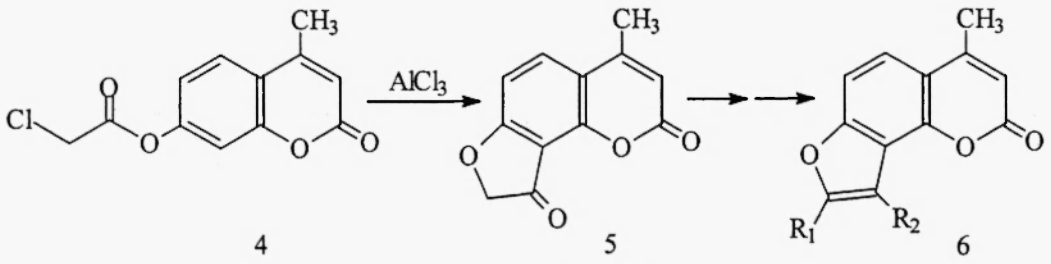
Scheme 1



1 2 3

Chloroacetate of 7-hydroxy-4-methylcoumarin **4** behaves under treatment with aluminum chloride unusual reactivity and transforms into dihydrofurocoumarinone **5** which is also useful intermediate in the preparation of angelicin **6** substituted in the furane ring (scheme 2).

Scheme 2



4 5 6

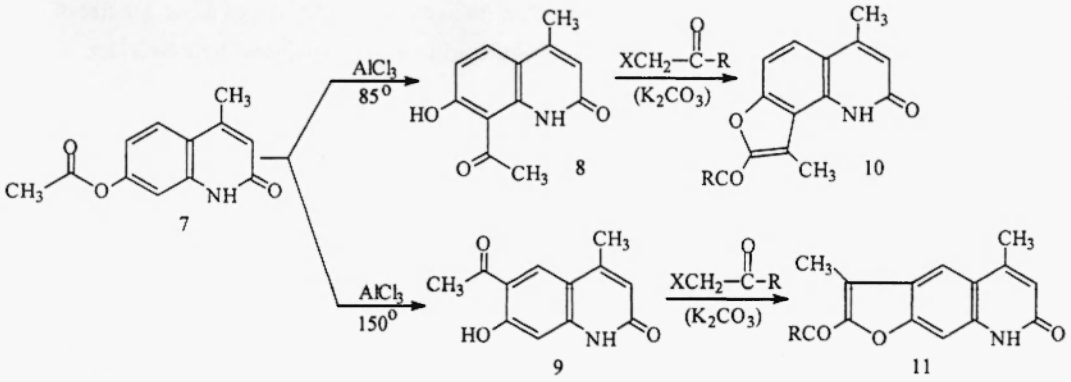
R_1 = H, Br, Cl, OH, OCH_3, $OCOCH_3$; R_2 = $OCOCH_3$, H.

Results and Discussions

Acetates of 7-hydroxyquinolin-2-ones undergo the Fries rearrangement in different way depending on temperature. This result is opposite to the Fries rearrangement of 7-acetoxycoumarins, which rearrange with equal regioselectivity at different temperatures.

8-Acetyl-7-hydroxy-4-methylquinolin-2-one **8** (yield is up to 50% comparing to 5% of the 6-acetyl-isomer) turns to be the predominant product of the rearrangement of 7-acetoxy-4-methylquinolin-2-one **7** at 85°C. However, 6-acetyl-7-hydroxy-4-methylquinolin-2-one **9** seems to be the only product (yield 94%) of the reaction at 150°C (scheme 3).

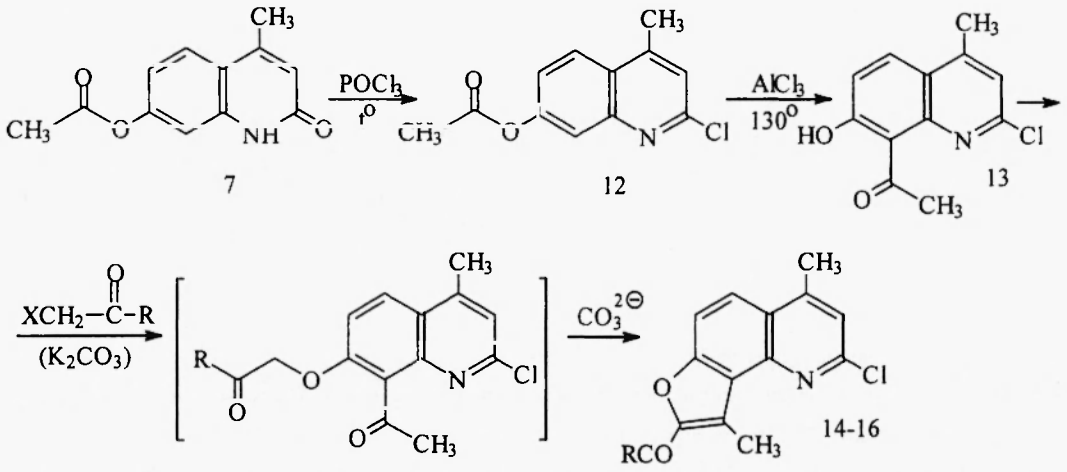
Scheme 3



Via base-catalyzed condensation with α-halogenoketones both isomers **8** and **9** are smoothly transformed into furoquinolin-2-ones of both linear and angular structure: compounds **10** and **11** respectively.

Nevertheless, angular furoquinolin-2-ones turned to be easier available by another way (scheme 4). Under treatment with phosphorous chloroxide 7-acetoxy-4-methylquinolin-2-one **7** transforms smoothly into 7-acetoxy-2-chloro-4-methylquinoline **12**. The Fries rearrangement of the compound **12** undergoes with exclusive formation of 8-acetyl-2-chloro-7-hydroxy-4-methylquinoline **13** and does not depend on the reaction temperature. Under treatment with α-halogenoketones (p-chlorophenacylbromide, chloroacetone and phenacylbromide) quinoline **13** transforms smoothly into 2-chlorofuroquinolines **14-16**.

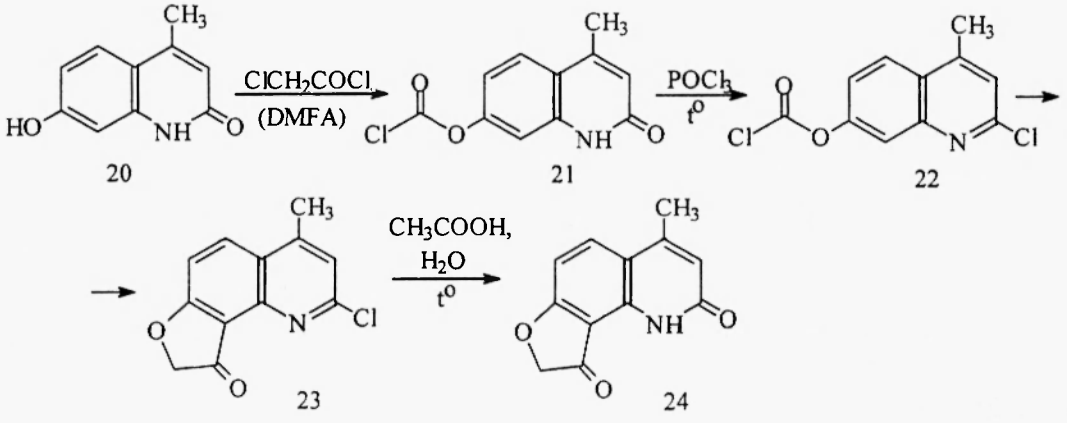
Scheme 4



By standard procedure (heating in the water - acetic acid mixture), furoquinolines **14-16** undergo quantitatively to furoquinolin-2-ones **17-19**. Furoquinolin-2-one derivatives turned thus to be available via two schemes: both from 7-acetoxyquinolin-2-ones and from 7-acetoxy-2-chloroquinolines.

The preliminary exchange of oxo-function for chloro atom in the quinoline ring seems to be useful also in the Fries rearrangement of 7-chloroacetoxyquinolines (scheme 5), since treatment of 7-chloroacetoxy-4-methylquinolin-2-one **16** with excess of $AlCl_3$ leads to complex mixture of reaction products.

Scheme 5

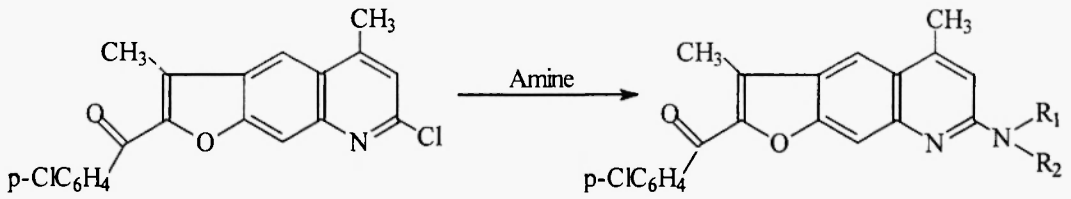


Nevertheless, analogous reaction of 7-chloroacetoxy-2-chloro-4-methylquinoline **22** provides 2-chloro-dihydrofuroquinolinone **23** as the exclusive product. By standard procedure, compound **23** has also be transformed into dihydrofuroquinolindione **24**.

Reasonable results of Fries rearrangement both quinolin-2-one derivatives and 2-chloroquinolines provides new ways in the preparation of furoquinoline derivatives. One of these ways consists of nucleophilic substitution of chlorine in quinoline ring of 2-chlorofuroquinolines. As example we have studied reactions of 2-chlorofuroquinolines with secondary amines (scheme **6**).

Amine	Diethylamine	4-(2-hydroxy-ethyl)piperazine	Pyrrolidine	Piperidine	Morpholine
Furoquinoline	**25**	**26**	**27**	**28**	**29**
Yield, %	75	72	78	81	85

Scheme 6



Experimental

7-Acetoxy-4-methylquinolin-2-one 7. 7-Hydroxy-4-methylquinolin-2-one (1g, 9,16 mmol) has been boiled in the excess of acetic anhydride until its dissolution and then for 1,5 hr. The resulted solution was cooled and poured into cold water. The precipitate was filtered off and washed by water. Yield 88%.

7: white crystals (from alcohol), mp 257-258°C; ^{1}H NMR (DMSO-d_6, δ, ppm; J, Hz): 2,30 (s,3H,CH_3CO-); 2,41 (d, 3H, 4-CH_3, $J_{CH3,3}$=0,82); 6,36 (q, 1H, H-3, $J_{3\,CH3}$=0,82); 6,96 (dd, 1H, H-6, $J_{6,5}$=8,6, $J_{6,8}$=2,2); 7,04 (d, 1H, H-8, $J_{8,6}$=2,2); 7,72 (d,1H, H-5, $J_{5,6}$=8,6); 11,57 (s, 1H,NH).

MS (m/z, %): 217 (M+, 57).

Anal. Calc. for $C_{12}H_{11}NO_3$: C 66,35; H 5,10; N 6,45. Found: C 66,45; H 5,08; N 6,46.

8-Acetyl-4-methylquinolin-2-one 8. Mixture of the compound 7 (1g, 4,6 mmol) and $AlCl_3$ (2g, 15,2 mmol) has been heated at 80-85°C for 4 hr. The final reaction mixture was diluted by cold water; formed precipitate was filtered off and dried. Compound 8 was isolated by column chromatography (silicagel, eluent – ethyl acetate). Yield 15%.

8: white powder, mp 259-262°C; ^{1}H NMR (DMSO-d_6, δ, ppm; J, Hz): 2,35 (d, 3H, 4-CH_3, $J_{CH3,3}$=1,2); 2,65 (s, 3H, CH_3CO); 6,24 (q,1H, H-3, $J_{3,CH3}$=1,2); 6,84 (d, 1H, H-6, $J_{6,5}$=8,0); 7,78 (d, 1H, H-5, $J_{5,6}$=8,0); 12,10 (s, 1H, NH).

MS (m/z, %): 217 (M+,61).

Anal. Calc. for $C_{12}H_{11}NO_3$: C 66,35; H 5,10; N 6,45. Found: C 66,15; H 5,06; N 6,42.

6-Acetyl-4-methylquinolin-2-one 9. Mixture of the compound 7 (1g, 4,6 mmol) and $AlCl_3$ (2g, 15,2 mmol) has been heated at 145-155°C for 4 hr. The final reaction mixture was diluted by cold water; formed precipitate was filtered off and dried. Compound **8** was isolated by recrystalization. Yield 68%.

9: white powder (from ethanol), mp 191-194°C; ^{1}H NMR (DMSO-d_6, δ, ppm; J, Hz): 2,44 (d, 3H, 4-CH_3, $J_{CH3,3}$=0,8); 2,69 (s, 3H, CH_3CO); 6,24 (q,1H, H-3, $J_{3,CH3}$=0,8); 6,71 (d, 1H, H-8); 8,15 (s, 1H, H-5); 11,67 (s, 1H, OH); 12,21 (s,1H, NH).

MS (m/z, %): 217 (M+, 63).

Anal. Calc. for $C_{12}H_{11}NO_3$: C 66,35; H 5,10; N 6,45. Found: C 66,18; H 5,11; N 6,40.

8-(4'-Chlorobenzoyl)-4,9-dimethylfuro[2,3-h]quinolin-2-one 10. Compound 8 (1g, 2,84 mmol) was dissolved in minimal amount of DMSO and mixed then with p-chlorophenacylbromide (0,66g, 2,84 mmol) and K_2CO_3 (1g). The mixture has been stirred then for 7 hr. The final reaction mixture poured into water, precipitate was filtered off. Compound **10** was purified by recrystalization. Yield 72%.

10: yellow crystals (from acetic acid), mp 283-286°C (decomp.). ^{1}H NMR (DMSO-d_6, δ, ppm; J, Hz): 2,55 (d, 3H, 4-CH_3, $J_{CH3,3}$=1,0); 3,02 (s, 3H, 9-CH_3); 6,99 (d, 1H, H-3, $J_{3,CH3}$=1,0); 7,38 (d, 2H, H-2', $J_{2',3'}$=9,0); 7,51 (d, 2H, H-5, $J_{5,6}$=8,7); 7,78 (d, 2H, H-3', $J_{3',2'}$=9,0); 8,03 (d, 2H, 6-H, $J_{6,5}$=8,7).

MS (m/z, %): 351 (M+, 100).

Anal. Calc. for $C_{20}H_{14}ClNO_3$: C 68,29; H 4.01; N 3,98; Cl 10,08. Found: C 68,03; H 3,95; N 3,71; Cl 10,21..

2-(4'-Chlorobenzoyl)-3,5-dimethylfuro[3,2-g]quinolin-7(1H)-one 11. Compound **11** has been prepared by the procedure similar to that of the compound **10**.Yield 84%.

11: green-yellow crystals (from acetic acid), mp 309-312°C (decomp.). ^{1}H NMR (DMSO-d_6, δ, ppm; J, Hz): 2,62 (s, 3H, 5-CH_3); 2,71 (s, 3H, 3-CH_3); 6,58 (s, 1H, H-6); 7,44 (s,1H,H-9); 7,49 (d, 2H, H-2', $J_{2',3'}$=7,9); 7,97 (s, 1H, H-4); 8,11 (d, 2H, H-3', $J_{3',2'}$=7,9); 11,07 (s, 1H, NH).

MS (m/z, %): 351 (M+, 100).

Anal. Calc. for $C_{20}H_{14}ClNO_3$: C 68,29; H 4,01; N 3,98; Cl 10,08. Found: C 68,13; H 3,99; N 3,62; Cl 10,09.

7-Acetoxy-2-chloro-4-methylquinoline 12. Mixture of the compound **7** (1g, 4,6 mmol) and phosphorous oxide (0,85 g, 5,5 mmol) was heated at 80-85°C for 1 hr. and poured then into cold water. The precipitate was filtered off and purified by recrystallization. Yield 76%.

12: white crystals (from ethanol); mp 115-117°C; ^{1}H NMR ($CDCl_3$, δ, ppm, J, Hz): 2,37 (s, 3H, CH_3COO); 2,68 (d, 3H, 4-CH_3, $J_{CH3,3}$=0,9); 7,25 (d, 1H, H-3, $J_{3,CH3}$=0,9), 7,40 (dd, 1H, H-6, J_{65}=9,0, J_{68}=2,3); 7,78 (d, 1H, H-8, J_{86}=2,3); 8,0 (d, 1H, H-5, J_{56}=9,0).

MS, m/z(%): 235 (70) M

Anal. calc. for $C_{12}H_{10}ClNO_2$: C 61,16; H 4,28; N 5,94; Cl 15,04. Found: C 61,07; H 4,29; N 5,91; Cl 15,04.

1-(2-Chloro-7-hydroxy-4-methylquinolin-8-yl)-1-ethanone 13. Mixture of the compound **8** (1g, 4,2 mmol) and aluminum chloride (1,9 g, 14,0 mmol) was heated at 125-130°C for 3 hr., cooled and mixed then with cold water. The precipitate was filtered off and purified by recrystallization. Yield 68%.

13: white powder (from ethanol); mp 115-117°C; ^{1}H NMR ($CDCl_3$, δ, ppm, J, Hz): 2,71 (s, 3H, CH_3CO); 2,94 (d, 3H, 4-CH_3, $J_{CH3,3}$=0,9); 7,25 (d, 1H, H-3, $J_{3,CH3}$=0,9), 7,40 (dd, 1H, H-6, J_{65}=9,0, J_{68}=2,3); 7,78 (d, 1H, H-8, J_{86}=2,3); 8,0 (d, 1H, H-5, J_{56}=9,0).

MS, m/z(%): 235 (M+, 70).

Anal. calc. for $C_{12}H_{10}ClNO_2$: C 61,16; H 4,28; N 5,94; Cl 15,04. Found: C 61,07; H 4,29; N 5,91; Cl 15,04.

Compounds 14-16 have been synthesized by similar procedure. It is given below for the compound **14** as example. Solution of the compound **13** (0,5g, 2,1 mmol), p-chlorophenacylbromide (0,49g, 2,1 mmol) and K_2CO_3 (0,5g) in DMSO was heated for 7 hrs., cooled and mixed then with cold water. The precipitate was filtered off and purified by recrystallization. Yield 67%.

(2-chloro-4,9-dimethylfuro[2,3-h]quinolin-8-yl)(4-chlorophenyl)methanone 14: yellow powder (from ethanol);yield 67%; mp 262-264°C; ^{1}H NMR (DMSO-d_6, δ, ppm, J, Hz): 2,88 (s, 3H, 9-CH_3), 2,97 (s, 3H, 4-CH_3); 7,28 (s, 1H, H-3); 7,44 (d, 1H,H-2, J_{23}=8,9); 7,57 (d, 1H, H-6, J_{65}=8,7); 7,85 (d, 2H, H-3, J_{32}=8,9); 8,13 (d, 1H, H-5, J_{56}=8,7).

MS, m/z(%): 370 (M+, 100).

Anal. calc. for $C_{20}H_{14}Cl_2NO_2$: C 64,88; H 3,54; N 3,78; Cl 19,15. Found: C 64,69; H 3,51; N 3,79; Cl 19,24.

Compounds 17-19 have been synthesized by similar procedure. It is given below for the compound **17** as example. Compound **14** has been boiled in 10% CH_3COOH for 1 hr., cooled. The precipitate was filtered off and purified by recrystallization. Yield 88%.

8-Acetyl-4,9-dimethylfuro[2,3-h]quinolin-2(1H)-one 17: white powder (from ethanol); mp 266-268°C; ^{1}H NMR (DMSO-d_6, δ, ppm, J, Hz): 2,48 (d, 3H, 4-CH_3, J_{43}=0,9); 2,57 (s, 3H, 9-CH_3), 2,71 (s, 3H, CH_3CO); 6,63 (d, 1H, H-3, J_{34}=0,9), 7,31 (d, 1H, H-6, J_{65}=8,9); 7,86 (d, 1H, H-5, J_{56}=8,9).

MS, m/z(%): 255 (M+, 100).

Anal. calc. for $C_{15}H_{13}NO_3$: C 70,58; H 5,13; N 5,49. Found: C 70,74; H 5,09; N 5,44.

4-Methyl-2-chlorofuro[2,3-h]quinolin-9(8H)-one 23 has been prepared by procedure similar to that of **9**. Yield 65%.

White powder, mp 226-228°C; ^{1}H NMR ($CDCl_3$, δ, ppm, J, Hz): 2,89 (s, 3H, 4-CH_3); 4,80 (s, 2H, 8-CH_2); 7,26 (s,1H, H-3); 7,37 (d, 1H, H-6, J_{65}=9,2); 8,23 (d, 1H, H-5, J_{56}=9,2).

MS, m/z(%): 233 (100) M.

Anal. calc. for $C_{12}H_8ClNO_2$: C 61,69; H 3,45; N 5,99; Cl 15,17. Found: C 61,87; H 3,48; N 5,91; Cl 15,08.

4-Methylfuro[2,3-h]quinolin-2,9(1H,8H)-dione 24 has been prepared by procedure similar to that of **17**. Yield 82%.

White powder, mp 285-287°C; ^{1}H NMR ($CDCl_3$, δ, ppm, J, Hz): 2,89 (s, 3H, **4**-CH_3); 4,80 (s, 2H, 8-CH_2); 7,26 (s,1H, H-3); 7,37 (d, 1H, H-6, J_{65}=9,2); 8,23 (d, 1H, H-5, J_{56}=9,2).

MS, m/z(%): 233 (100) M.

Anal. calc. for $C_{12}H_8ClNO_2$: C 61,69; H 3,45; N 5,99; Cl 15,17. Found: C 61,87; H 3,48; N 5,91; Cl 15,08.

Compounds **25-29** have been synthesized by similar procedure. It is given below for the compound **25** as example. Solution of the compound **14** (1 mmol) and diethylamine in $CHCl_3$ has been boiled for 2 hrs. $CHCl_3$ has been evaporated, compound was purified by chromatography (eluent – ethylacetate). Yield 75%.

(4-chlorophenyl)[7-(Diethylamino)-3,5-dimethylfuro[3,2-g]quinolin-2-yl]methanone 25: yellow powder; mp 211-213°C; ^{1}H NMR ($CDCl_3$, δ, ppm, J, Hz): 1,42 (t, 6H, 2CH_3); 2,15 (s, 3H, 5-CH_3); 2,72 (s, 3H, 3-CH_3); 3,00 (q, 4H, 2CH_2); 7,21 (s, 1H, H-6); 7,53 (d, 2H, H-3, J_{32}=8,5); 8,10 (d, 2H, H-2, J_{23}=8,5); 8,12 (s, 1H, H-9); 8,25 (s,1H,H-4).

MS, m/z(%): 406 (100) M.

References

1. R.D.H. Murray, The Natural Coumarins. Occurrence, chemistry and biochemistry, Wiley-Interscience, New York, 1982.
2. E. Fahr, Pharmazeutische Zeitung 127, 163 (1982).
3. R.L. Edelson, J. Photochem. Photobiol., B: Biol. 10, 165 (1991).
4. A. Guiotto, A. Chilin, P. Manzini, F. DallÁqua, F. Bordin, P. Rodighiero, IL Farmaco 50, 479 (1995).
5. E. Bisagni, J. Photochem. Photobiol., B: Bioligy, 14, 23 (1992).
6. A. Guiotto, A. Chilin, G. Pastorini, J. Heterocyclic Chem., 26, 917 (1989).
7. V.F. Traven, T.A. Chibisova, Mendeleev Commun., 1, 25 (1995).
8. V.F. Traven, T.A. Chibisova, Mendeleev Commun., 3, 249 (1997).
9. V.F. Traven, T.A. Chibisova, S.V. Shorshnev, R. Eliason, D.H. Wakefield, Heterocyclic Commun., 2, 345 (1996).

Received on February 13, 2004.