Chemistry of Heterocyclic Compounds, Vol. 37, No. 3, 2001

DIHYDROFURO[2,3-*h*]COUMARIN-9-ONE – SYNTHON IN THE SYNTHESIS OF 6-SUBSTITUTED ANGELICINS

V. F. Traven', I. I. Sakharuk, D. V. Kravchenko, and A. V. Ivashchenko

6-Aminocoumarin-9-one was obtained by the reduction of 6-phenylazo-4-methyldihydrofuro[2,3-h]-coumarin-9-one, and its diazotization, N-acylation, and N-formylation were realized. The diazo group at position 6 was substituted by chlorine atom and azide group and was reduced to hydrazino group. The synthesized 6-substituted 4-methyldihydrofuro[2,3-h]coumarin-9-ones were converted into the corresponding angelicins by reduction of the carbonyl group of the dihydrofuran ring and subsequent dehydration of the obtained alcohol and also by acylation with the fixed enolic form of the dihydrofuranone ring.

Keywords: dihydro[2,3-*h*]coumarin-9-one, 6-substituted angelicin, synthon, furocoumarin.

Furocoumarins represent a class of natural compounds traditionally employed for the treatment of a series of skin complaints (vitiligo, psoriasis, mycosis fungoides, alopecia areata) [1, 2] and effective for the treatment of such diseases as cutaneous lymphoma, progressive systematic sclerosis (scleroderma), red lupus, and rheumatoid arthritis by photophoresis [3]. Furocoumarins can act as mono- and bifunctional reagents toward the DNA of viruses and microorganisms.

During study of the photochemotherapeutic properties of substituted furocoumarins it was shown that monofunctional furocoumarins, such as certain methyl-substituted angelicins, are more active than the bifunctional compounds (including 8-methoxypsoralene) with their lower gene toxicity [2]. Study of a scheme for the synthesis of new angelicins and psoralenes is continuing in this connection [4-9].

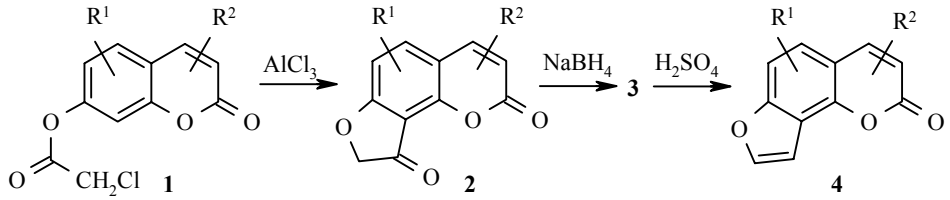
Earlier we established an unusual Fries rearrangement of chloroacetoxycoumarins to dihydrofurocoumarinones [5], which proved to be suitable synthons for the production of substituted furocoumarins. As a result of the clearly defined susceptibility to enolization they are capable of reacting at position 8 and of forming O-acetylenols in reaction with acetic anhydride. Substituted furocoumarins also proved accessible during the reduction of dihydrofurocoumarinones with sodium borohydride in dioxane and dehydration of the obtained alcohols (Scheme 1) [5, 6].

We reported on new reactions of 6-arylazo-4-methyldihydrofuro[2,3-*h*]coumarin-9-ones, obtained by azo coupling of the corresponding coumarinones [9]. Like other dihydrofurocoumarinones, compounds **5** and **11** readily undergo aromatization. Reduction of the carbonyl group of the dihydrofuranone ring followed by dehydration of alcohol **7** gave angelicin **8** (Scheme 2), while reduction of compound **5** with sodium borohydride gave 6-(*p*-dimethylaminophenylazo)-4-methyldihydrofuro[2,3-*h*]coumarin-9-ol (**7**) and coumarin **6** in a ratio of 9:1. The enolization of 6-arylazo-4-methyldihydrofuro[2,3-*h*]coumarin-9-ones by their conversion into the corresponding 9-enolacetates was reported earlier [9].

D. I. Mendeleev Russian Chemical Technology University, Moscow; e-mail: traven@main-gw.muctr.edu.ru.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 312-322, March, 2001. Original article submitted April 8, 1999.

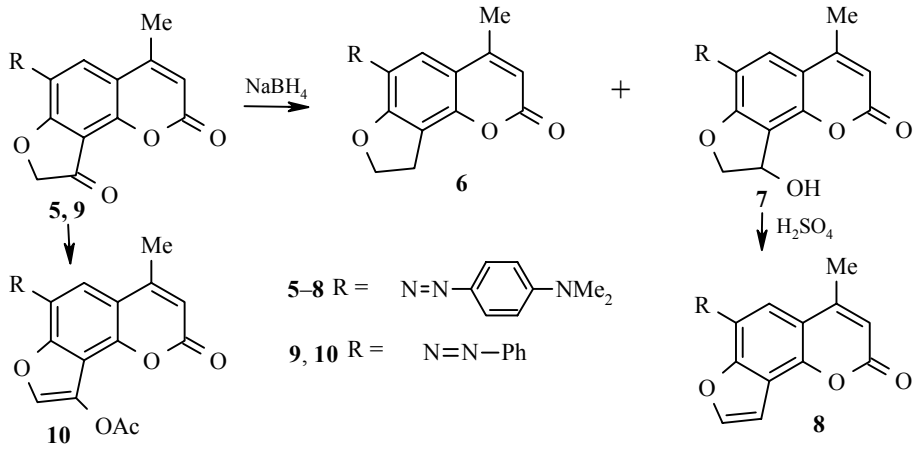
0009-3122/01/3703-0283$25.00

Scheme 1



R = Me, Et, Hal; R^1 = H, Me-4; R^2 = H, Et

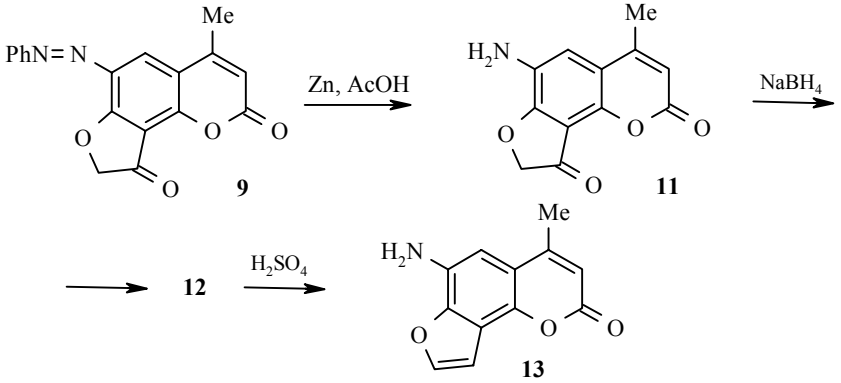
Scheme 2



By the transformations of the phenylazo group of the compound **9** it was possible to introduce new substituents at position 6 of dihydrofuro[2,3-*h*]coumarin-9-ones. Reduction of 6-phenylazocoumarin-9-one **9** with zinc in acetic acid took place not at the carbonyl group but at the azo group, leading to 6-aminocoumarin-9-one (**11**) (Scheme 3).

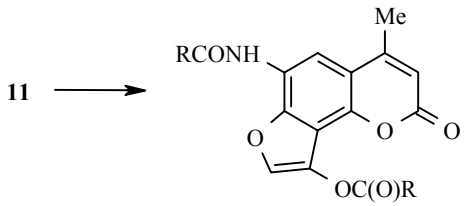
As expected, 6-amino-4-methyldihydrofuro[2,3-*h*]coumarin-9-one (**11**) has the characteristics typical of aromatic amines. On account of the presence of the fairly reactive methylene group of the dihydrofuranone ring and the tendency of the dihydrofuranone fragment to enolize it possesses characteristics typical of dihydrofurocoumarinones **2**.

Scheme 3



In particular, 6-aminocoumarin-9-one **11** is readily acetylated when heated with acetic anhydride, forming 6-acetamidocoumarin-9-one **14**. If pyridine is used as catalyst, amine **11** is acetylated both at the amino group and with simultaneous stabilization of the corresponding enolic form. 6-Acetamido-9-acetoxy-4-methylangelicin (**15**) was obtained in this way. The benzoylation of compound **11** by benzoyl chloride (Scheme 4) is similar and leads to 6-benzamido-9-benzoyloxy-4-methylangelicin (**16**).

Scheme 4



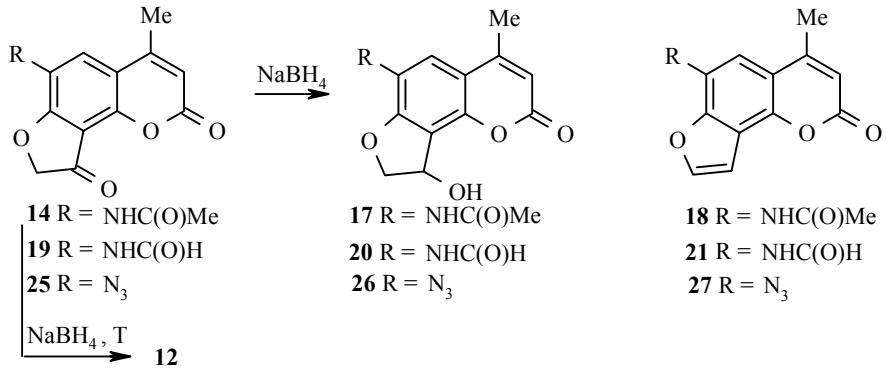
15 R = Me; **16** R = Ph

Like other compounds of this type [5, 6], 6-substituted furocoumarinones undergo aromatization by reduction of the carbonyl group of compound **11** with sodium borohydride and subsequent dehydration of the reduction product. 6-Amino-4-methylangelicin (**13**) was obtained in this way from the alcohol **12** (Scheme 3).

Acetamide **14** is reduced selectively by sodium borohydride at the carbonyl group of the dihydrofuranone ring. Retention or removal of the acetyl protection at the amino group depends on the temperature conditions. At 20°C reduction leads to formation of 6-acetamido-4-methyldihydrofuro[2,3-*h*]-coumarin-9-ol (**17**), while at 80°C 6-aminocoumarin-9-ol **12** is obtained. 6-Acetylamino-4-methylangelicin **18** was prepared by dehydration of alcohol **17** by heating in acetic acid (Scheme 5), the use of which makes it possible to avoid removing the acetyl protection.

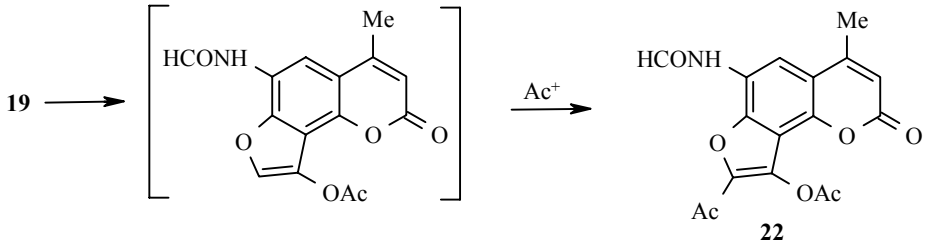
The formamide derivative **19** was obtained by heating of the compound **11** with formic acid. Like the acetamide derivative **14** the formamide derivative **19** is reduced by sodium borohydride in two directions, i.e., with the formation of 6-formamidocoumarin-9-ol (**20**) and (at a higher temperature) 6-aminocoumarin-9-ol (**12**). Formamide **20** was converted into 6-formamidoangelicin **21** by dehydration in formic acid (Scheme 5).

Scheme 5



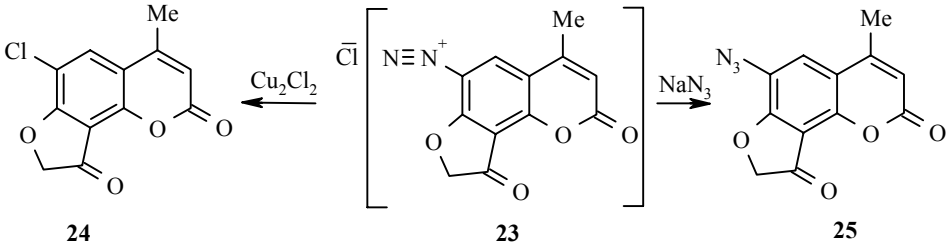
Enolization of the dihydrofuranone ring in compound **19** was realized by O-acetylation. However, with acetic anhydride in pyridine medium C-acetylation occurred simultaneously, 8-acetyl-9-acetoxyformamide (**22**) being formed (Scheme 6).

Scheme 6



The diazotization of 6-aminocoumarin-9-one **11** led to 4-methyldihydrofuro[2,3-*h*]coumarin-9-one-6-yldiazonium salts **23**. The diazo group at position 6 is substituted by chlorine atom in the Sandmeyer reaction and by azido group in reaction with sodium azide. In the last case 6-azido-4-methyldihydrofuro[2,3-*h*]coumarin-9-one (**25**) was obtained (Scheme 7).

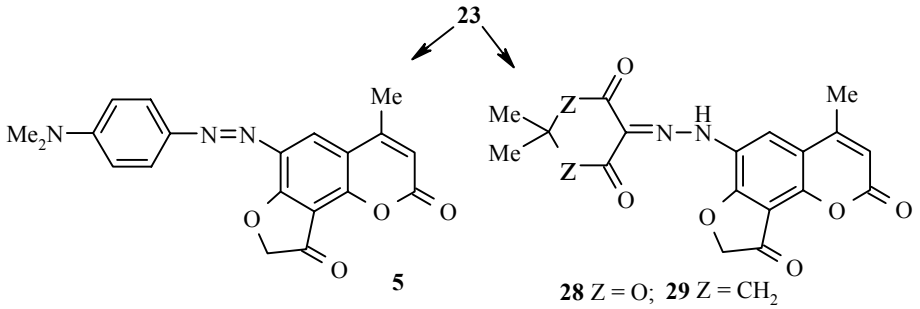
Scheme 7



Azide **25** is readily reduced by sodium borohydride in dioxane in two directions (Scheme 5). At 20°C reduction takes place regiospecifically at the carbonyl group of the dihydrofuranone ring, leading to 6-azidocoumarin-9-ol (**26**). At 60°C it takes place both at the carbonyl group and at the azide group with the formation of 6-aminocoumarin-9-ol **12**. Dehydration of alcohol **26** in sulfuric acid gave 6-azidoangelicin (**27**).

The diazo compound **23** enters readily into azo coupling with active substrates, in particular with N,N-dimethylaniline, Meldrum's acid, and dimedone (Scheme 8).

Scheme 8



According to data from the ^{1}H NMR spectrum, the azo coupling products **28** and **29** have the quinone–hydrazono–ketone form, which is probably more stable than the other possible tautomeric forms – azoenol or azoketone. The occurrence of the quinone–hydrazono–ketone form is confirmed by the characteristic signal of

TABLE 1. The Spectral Characteristics of 4-Methyldihydrofuro[2,3-*h*]coumarin-9-ones

Compound	Empirical formula	Found, % / Calculated, %			^{1}H NMR spectrum, δ, ppm ($J_{Me,3}$ = 1.1 Hz)						M^+, *m/z* (*I*, %)
		C	H	N	3-H	4-Me	5-H	CH_2	6-R	solvent	
5*	$C_{20}H_{17}N_3O_4$	66.32 / 66.11	4.65 / 4.72	11.63 / 11.56	6.27	2.50	8.18	4.90	3.13 (NMe_2); 6.75 (3'-H, 5'-H); 7.91 (2'-H, 6'-H)	DMSO-d_6	363 (100)
9	$C_{18}H_{12}N_2O_4$	67.32 / 67.50	3.90 / 3.78	8.80 / 8.75	6.29	2.52	8.25	4.93	7.55-7.97 (Ph)	$CDCl_3$	320 (78)
11	$C_{12}H_9NO_4$	62.32 / 62.34	3.90 / 3.92	6.00 / 6.06	6.25	2.36	7.16	4.93	5.42 (NH_2)	DMSO-d_6	231 (100)
14	$C_{14}H_{11}NO_5$	61.50 / 61.54	4.15 / 4.06	5.19 / 5.13	6.33	2.38	8.52	4.98	2.13 (Ac); 9.99 (NH)	$CDCl_3$	273 (90)
19	$C_{13}H_9NO_5$	60.20 / 60.24	3.55 / 3.50	5.39 / 5.40	6.35	2.40	8.69	5.01	8.38 (CH); 10.32 (NH)	DMSO-d_6	259 (100)
25	$C_{12}H_7N_3O_4$	56.10 / 56.04	2.81 / 2.74	16.27 / 16.34	6.25	2.41	7.37	4.82	—	DMSO-d_6	257 (15)
26*[2]	$C_{12}H_7ClO_4$	57.43 / 57.51	2.71 / 2.82		6.25	2.41	7.81	4.82	—	$CDCl_3$	252/250 (100)
28	$C_{18}H_{14}N_2O_8$	55.73 / 55.96	3.41 / 3.65	7.49 / 7.25	6.28	2.51	8.29	4.88	1.16 (Me_2C); 15.45 (NH)	DMSO-d_6	386 (0.5)
29	$C_{20}H_{18}N_2O_6$	62.73 / 62.82	4.41 / 4.74	7.42 / 7.83	6.04	2.50	8.10	5.01	1.06 (Me_2C); 2.65 (CH_2); 15.15(NH)	DMSO-d_6	382 (68)
31*[3]	$C_{19}H_{13}FN_2O_4$	64.43 / 64.77	3.71 / 3.72	7.68 / 7.95	6.31	2.50	7.74	5.01	10.50 (NH); 7.26 (3'-H, 5'-H); 7.73 (2'-H, 6'-H)	DMSO-d_6	*[4]

* $J_{3',2'} = J_{5',6'} = 9.2$.

*[2] Found, %: Cl 14.36. Calculated, %: Cl 14.14.

*[3] Found, %: F 5.41. Calculated, %: F 5.39.

*[4] There is no peak for the molecular ion.

TABLE 2. The Spectral Characteristics of 8-Benzylidene-4-methyldihydrofuro[2,3-*h*]coumarin-9-ones

Compound	Empirical formula	Found, % / Calculated, %			^{1}H NMR spectrum (DMSO-d_6), δ, ppm ($J_{Me,3}$ = 1.1 Hz)					M^+, *m/z* (*I*, %)
		C	H	N	3-H	4-Me	5-H	6-R	8-R	
32*	$C_{26}H_{16}F_2N_2O_4$	68.43 / 68.12	3.71 / 3.52	6.28 / 6.11	6.34	2.48	8.27	7.82 (CH=N); 7.78 (3'-H, 5'-H); 8.21(2'-H, 6'-H); 10.49 (NH)	6.00 (CH=C); 7.27-7.28 (Ph)	458 (75)
33	$C_{19}H_{13}NO_4$	71.32 / 71.47	3.90 / 4.10	4.18 / 4.39	6.33	2.39	7.37	*[2]	6.99 (CH=C); 7.50-8.14 (Ph)	319 (100)
34*[3]	$C_{19}H_8F_5NO_4$	55.43 / 55.76	1.71 / 1.97	3.18 / 3.42	6.33	2.38	7.34	5.45 (NH_2)	6.78 (CH=C)	409 (100)
35	$C_{20}H_{13}NO_5$	63.73 / 69.16	4.31 / 3.77	3.18 / 4.03	6.42	2.45	8.71	8.54 (CHO); 10.49 (NH)	7.04 (CH=C); 7.52-8.12 (Ph)	347 (100)
36	$C_{21}H_{15}NO_5$	69.73 / 69.80	4.21 / 4.18	3.78 / 3.88	6.42	2.43	8.35	2.22 (OAc); 10.13 (NH)	7.04 (CH=C); 7.52-8.10 (Ph)	361 (98)

* Found, %: F 8.47. Calculated, %: F 8.29.

*[2] The signal is absent on account of deuteroexchange.

*[3] Found, %: F 23.41. Calculated, %: F 23.21.

TABLE 3. The Spectral Characteristics of 4-Methyldihydrofuro[2,3-*h*]coumarin-9-ols

Compound	Empirical formula	Found, % / Calculated, %			^{1}H NMR spectrum (DMSO-d_6), δ, ppm									M^+, *m/z* (*I*, %)
		C	H	N	3-H	4-Me	5-H	8a-H	8b-H	9-H	9-OH	6-R	*J*, Hz	
7	$C_{20}H_{19}N_3O_4$	65.32 / 65.74	5.45 / 5.24	11.63 / 11.50	6.23	2.48	7.95	4.83	4.86	5.86	*	3.10 (Me_2N); 6.74 (2'-H, 6'-H); 7.89 (3'-H, 5'-H)	$J_{Me,3}$ = 1.1; J_{gem} = 16.0; $J_{8a,9}$ = 3.0; $J_{8b,9}$ = 6.5; $J_{2',3'}$ = 9.2; $J_{6',5'}$ = 9.2	365 (16)
12	$C_{12}H_{11}NO_4$	61.84 / 61.80	4.82 / 4.75	6.06 / 6.01	6.06	2.27	6.84	4.37	4.56	5.43	*	4.83 (NH_2)	$J_{Me,3}$ = 1.1; J_{gem} = 15.0; $J_{8a,9}$ = 2.0; $J_{8b,9}$ = 7.0	233 (100)
17	$C_{14}H_{13}NO_5$	61.20 / 61.09	4.65 / 4.76	5.19 / 5.09	6.20	2.36	8.16	4.48	4.68	5.54	5.85	2.07 (Ac) 9.58 (NH)	$J_{Me,3}$ = 1.1; J_{gem} = 14.0; $J_{8a,9}$ = 2.2; $J_{8b,9}$ = 6.3; $J_{9,9\text{-}OH}$ = 6.2	275 (75)
20	$C_{13}H_{11}NO_5$	59.60 / 59.77	4.55 / 4.24	5.39 / 5.36	6.10	2.23	6.87	4.42	4.61	5.48	5.69	4.85 (CHO) 4.85 (NH)	$J_{Me,3}$ = 1.1; J_{gem} = 14.0; $J_{8a,9}$ = 2.2; $J_{8b,9}$ = 6.3; $J_{9,9\text{-}OH}$ = 6.2	261 (5)
25	$C_{12}H_9N_3O_4$	56.50 / 55.60	3.45 / 3.50	16.27 / 16.21	6.23	2.39	7.34	4.53	4.72	5.52	*	—	$J_{Me,3}$ = 1.1; J_{gem} = 15.0; $J_{8a,9}$ = 2.2; $J_{8b,9}$ = 7.0	259 (15)

* The signal is absent on account of deuteroexchange.

TABLE 4. The Spectral Characteristics of 6-Substituted 4-Methylangelicins

Compound	Empirical formula	Found, % / Calculated, %			^{1}H NMR spectrum (DMSO-d_6), δ, ppm							M^+, *m*/*z* (*I*, %)
		C	H	N	3-H	4-Me	5-H	8-H	9-H	6-R	*J*, Hz	
8	$C_{20}H_{17}N_3O_3$	69.25 / 69.15	4.73 / 4.93	12.18 / 12.10	6.63	2.57	7.90	7.82	7.22	3.12 (Me_2N); 6.79 (3'-H, 5'-H); 7.95 (2'-H, 6'-H)	$J_{Me,3}$ = 1.1; $J_{8,9}$ = 2.1; $J_{2',3'}$ = 9.1; $J_{6',5'}$ = 9.1	347 (32)
13	$C_{12}H_9NO_3$	66.84 / 66.97	4.42 / 4.22	6.16 / 6.51	6.26	2.40	6.83	8.05	7.15	5.43 (NH_2)	$J_{Me,3}$ = 1.1; $J_{8,9}$ = 2.1	215 (100)
18	$C_{14}H_{11}NO_4$	65.20 / 65.37	5.55 / 4.31	5.39 / 5.44	6.38	2.45	8.09	8.17	7.27	2.16 (NAc); 10.14 (NH)	$J_{Me,3}$ = 1.1; $J_{8,9}$ = 2.1	257 (47)
21	$C_{13}H_9NO_4$	64.60 / 64.20	3.55 / 3.73	5.69 / 5.76	6.32	2.50	8.11	8.41	7.23	8.35 (CHO); 10.51 (NH)	$J_{Me,3}$ = 1.1; $J_{8,9}$ = 2.1	243 (100)
27	$C_{12}H_7N_3O_3$	59.50 / 59.76	2.85 / 2.93	17.27 / 17.42	6.41	2.48	7.37	8.23	7.32	—	$J_{Me,3}$ = 1.1; $J_{8,9}$ = 2.1	241 (3)

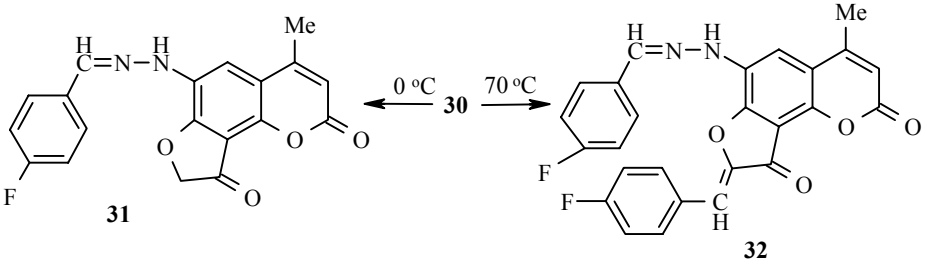
TABLE 5. The Spectral Characteristics of 6-Substituted 9-Acetoxy-4-methylangelicins

Compound	Empirical formula	Found, % / Calculated, %			^{1}H NMR spectrum (DMSO-d_6), δ, ppm ($J_{Me,3}$ = 1.1)						M^+, *m*/*z* (*I*, %)
		C	H	N	3-H	4-Me	5-H	8-R_1	9-OR	6-R	
15	$C_{16}H_{31}NO_6$	60.72 / 60.95	3.90 / 4.16	4.58 / 4.44	6.39	2.44	5.09	8.32 (H)	2.41 (OAc)	2.16 (NAc); 10.16 (NH)	315 (24)
16	$C_{26}H_{17}NO_6$	71.22 / 71.07	3.90 / 3.90	3.18 / 3.19	6.36	2.48	8.50	7.91 (H)	8.30-7.57 (Ph)	8.30-7.57 (Ph); 10.60 (NH)	439 (100)
22	$C_{17}H_{13}NO_7$	59.42 / 59.48	3.90 / 3.82	4.18 / 4.08	6.46	2.46	8.32	2.41 (Ac)	2.42 (OAc)	7.77 (CHO); 9.51 (NH)	343 (66)

the NH proton at 15 ppm in the ^{1}H NMR spectra of these compounds [9]; at the same time signals from the CH proton of the azoketone form and the OH proton of the azoenol form are not observed. Moreover, compounds **28** and **29** do not give a characteristic color with a solution of iron chloride, also indicating the absence of the azoenol form.

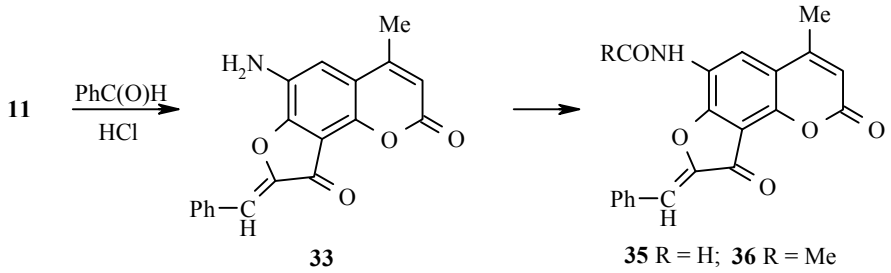
The diazonium salt **23** is reduced with the formation of hydrazino derivative **30**. Hydrazones are not produced in a well-defined manner by reaction with benzaldehydes owing to the presence of the active methylene group in the dihydrofuranone ring. For example, hydrazone **31** could be obtained only at 0°C. At higher temperatures the benzylidene derivative **32** is formed at the same time. Thus, the hydrazine fragment occurs to be more nucleophilic than the methylene group of the dihydrofuranone ring (Scheme 9).

Scheme 9



The obtained data can be compared with the results of the condensation of amine **11** with benzaldehydes. During an attempt to produce Schiff base in an acidic medium the benzylidene derivative **33**, analogous with the previously obtained product [6], was detected (Scheme 10).

Scheme 10



The C–H bond at position 8 of compound **11** is probably more nucleophilic than the amino group at position 6 of coumarin on account, possibly, of protonation of the latter. Even in the case of the active pentafluorobenzaldehyde the reaction takes place exclusively at position 8 of the dihydrofuranone ring with the formation of the pentafluorobenzylidene derivative **34**. Formylation and acetylation at the amino group of the benzylidene derivative **33** under standard conditions gave the corresponding derivatives **35** and **36** (Scheme 10).

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker WP-200 instrument with DMSO-d_6 or chloroform as solvent and TMS as internal standard. The mass spectra were recorded on a Finnegan MAT SSQ-710 instrument at 70 eV.

The spectral characteristics of the synthesized compounds are given in Tables 1-5.

6-(*p*-Dimethylaminophenylazo)-4-methyldihydrofuro[2,3-*h*]coumarin-9-one (5). The compound was obtained by the method [9] with a yield of 80%; mp 190°C (chloroform).

4-Methyl-6-phenylazodihydrofuro[2,3-*h*]coumarin-9-one (9). The compound was obtained by the method [9]. The yield was 90%; mp 248-250°C (DMSO).

6-Amino-4-methyldihydrofuro[2,3-*h*]coumarin-9-one (11). Mixture of compound **9** (1 g, 3 mmol), isopropyl alcohol (200 ml), and glacial acetic acid (20 ml) was stirred with an excess of zinc (15 mmol) for 2 h at 60°C and was then poured into water. The formed precipitate was filtered off. Yield 0.03 g (40%); decomp. 280°C (DMF).

6-Acetamido-4-methyldihydrofuro[2,3-*h*]coumarin-9-one (14). Mixture of compound **11** (0.1 g, 0.4 mmol) and acetic anhydride (5 ml) was heated for 10 min and cooled until precipitation occurred. The precipitate separated was recrystallized from acetic acid. Yield 0.1 g (90%); mp 279-281°C.

6-Formamido-4-methyldihydrofuro[2,3-*h*]coumarin-9-one (19). Compound **11** (0.1g, 0.4 mmol) was dissolved in formic acid (5 ml). The precipitate that separated after 2 days was filtered off and recrystallized from acetic acid. Yield 0.1 g (90%); mp 279-281°C.

4-Methyldihydrofuro[2,3-*h*]coumarin-9-one-6-yldiazonium Chloride (23). 6-Aminocoumarin-9-one **11** (2.31 g, 10.0 mmol) was dissolved by heating in concentrated hydrochloric acid (20 ml). The solution was cooled to 0-2°C, and sodium nitrite (0.77 g, 12.0 mmol) was added in the form of 30% solution. The mixture was stirred for 30 min and filtered, and the solution was used for the further reactions.

6-Azido-4-methyldihydrofuro[2,3-*h*]coumarin-9-one (25). To the solution of diazonium chloride **23** we added sodium azide (0.72 g, 11 mmol) in the form of 30% solution. The precipitate was filtered off, washed several times with water, dried, and recrystallized from DMF. Yield 0.3 g (40%); decomp. 204°C.

6-Chloro-4-methyldihydrofuro[2,3-*h*]coumarin-9-one (24). To a solution of diazonium chloride **23** (~10 mmol) under stirring we slowly added solution of cuprous chloride (2 g, 10.0 mmol). The precipitate was filtered off and dried. Yield 0.5 g (20%); mp 258-260°C (chloroform).

Reduction of Dihydrofuro[2,3-*h*]coumarin-9-ones (General Procedure). To suspension of the respective dihydrofuro[2,3-*h*]coumarin-9-one (10 mmol) in methanol (200 ml) we added sodium borohydride (0.74 g, 20 mmol). The mixture was stirred at room temperature for 2 h, after which it was poured into water. The precipitate was filtered off and recrystallized.

6-(*p*-Dimethylaminophenylazo)-4-methyldihydrofuro[2,3-*h*]coumarin-9-ol (7). Yield 80%; decomp. 200°C (alcohol).

6-(*p*-Dimethylaminophenylazo)-4-methyldihydrofuro[2,3-*h*]coumarin (6). This compound was obtained simultaneously with compound **7** and isolated by column chromatography on aluminum oxide with chloroform as eluent. Yield 10%; decomp. 230°C (alcohol). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 1.45 (2H, m, 9-CH_2); 2.47 (3H, d, 4-Me, $J_{Me,3}$ = 1.1); 3.13 (6H, s, Me_2N); 2.52 (2H, m, 8-CH_2); 6.18 (1H, d, 3-H, $J_{3,Me}$ = 1.1); 6.75 (2H, d, 2'-H, 6'-H, $J_{2',3'} = J_{6',5'}$ = 9.2); 7.78 (2H, d, 3'-H, 5'-H, $J_{3',2'} = J_{5',6'}$ = 9.2); 8.05 (1H, s, 5-H). Found, %: C 68.70; H 5.40; N 12.00. M^+ 349 (45%). $C_{20}H_{19}N_3O_3$. Calculated, %: C 68.75; H 5.48; N 12.03.

6-Amino-4-methyldihydrofuro[2,3-*h*]coumarin-9-ol (12). Yield 90%; decomp. 219-221°C (alcohol).

6-Acetamido-4-methyldihydrofuro[2,3-*h*]coumarin-9-ol (17). Yield 60%; mp 238-240°C (alcohol).

6-Formamido-4-methyldihydrofuro[2,3-*h*]coumarin-9-ol (20). Yield 55%; mp 207-210°C (alcohol).

6-Azido-4-methyldihydrofuro[2,3-*h*]coumarin-9-ol (26). Yield 70%; decomp. 205°C (alcohol).

6-(*p*-Dimethylaminophenylazo)-4-methylangelicin (8). To solution of compound **7** (0.5 g, 1.37 mmol) in dioxane (10 ml) we added excess of 20% sulfuric acid. The mixture was heated for 1 h, and the solution was poured into water. The formed precipitate was filtered off. Yield 0.31 g (65%); mp 230-232°C (chloroform).

6-Amino-4-methylangelicin (13). Solution of compound **12** (2.33 g, 1 mmol) in excess of 20% sulfuric acid was heated for 1 h, and solution of sodium carbonate was added until a precipitate separated. The precipitate was filtered off and recrystallized from DMF. Yield 1.54 g (70%); mp 229-231°C.

6-Acetamido-4-methylangelicin (18). A solution of compound **17** (0.5 g, 1.8 mmol) in excess of acetic acid was heated for 1 h and poured into cold water. The precipitate was filtered off and recrystallized from DMF. Yield 0.33 g (70%); mp 276-278°C.

6-Formamido-4-methylangelicin (21). Solution of compound **20** (0.5 g, 1.9 mmol) in excess of formic acid was heated for 1 h and poured into cold water. The formed precipitate was filtered off and recrystallized from DMF. Yield 0.3 g (65%); mp 238-240°C.

6-Azido-4-methylangelicin (27). To solution of compound **26** (2.6 g, 10 mmol) in dioxane (20 ml) we added excess of acetic acid. The mixture was heated for 1 h, and the solution was poured into water. The formed precipitate was filtered off and recrystallized from DMF. Yield 1.45 g (60%); decomp. 205°C.

9-Acetoxy-6-acetamido-4-methylangelicin (15). Mixture of compound **11** (0.1 g, 0.4 mmol), acetic anhydride (10 ml), and pyridine (5 ml) was heated for 20 min. It was then cooled until a precipitate separated. The precipitate was recrystallized from acetic anhydride. Yield 0.1 g (80%); mp 228-230°C.

9-Benzoyloxy-6-benzamido-4-methylangelicin (16). Mixture of compound **11** (6.93 g, 3 mmol), benzoyl chloride (1 g, 7 mmol), pyridine (0.5 ml), and chloroform (8 ml) was heated with a reflux condenser for 1 h. The crystals that separated on cooling were filtered off and dried. Yield 2.0 g (75%); mp 208-210°C (chloroform).

9-Acetoxy-8-acetyl-6-formamido-4-methylangelicin (22). Mixture of compound **19** (0.5 g, 1.9 mmol), acetic anhydride (30 ml), and pyridine (5 ml) was heated for 20 min and was then cooled until a precipitate separated. The product was recrystallized from acetic anhydride. Yield 0.5 g (75%); mp 184-186°C.

Azo Coupling of 4-Methyldihydrofuro[2,3-*h*]coumarin-9-one-6-yldiazonium Chloride (23) (General Procedure). We added the respective azo component (10 mmol) to solution of diazonium chloride **23** and stirred the mixture at 0°C for 10 h. The formed precipitate was filtered off, washed several times with water, dried, and recrystallized.

6-(*p*-Dimethylaminophenylazo)-4-methyldihydrofuro[2,3-*h*]coumarin-9-one (5). Yield 80%; mp 190°C (chloroform).

Hydrazone (29). Yield 72%; mp 228-230°C (chloroform).

Hydrazone (23). Yield 70%; mp 263-265°C (chloroform).

6-Hydrazino-4-methyldihydrofuro[2,3-*h*]coumarin-9-one (30). To solution of tin dichloride (2.9 g, 15.0 mmol) in concentrated hydrochloric acid (15 ml), cooled to -15°C, we slowly added with stirring solution of diazonium chloride **23** in such a way that the temperature did not rise above -10°C. The precipitated hydrazine salt was filtered off and dried. Yield 2.84 g (70%).

6-(*p*-Fluorophenylhydrazono)-4-methyldihydrofuro[2,3-*h*]coumarin-9-one (31). Hydrazine **30** (0.5 g, 0.61 mmol) was dissolved at room temperature in acetic acid (10 ml), and *p*-fluorophenylbenzaldehyde (0.077 g, 0.61 mmol) was added with stirring. The reaction mixture was stirred at 0°C for 2 h, after which the precipitate was filtered off, washed with water, and dried. Yield 0.17 g (80%); mp 233-245°C (acetic acid).

8-*p*-Fluorobenzylidene-6-(*p*-fluorophenylhydrazono)-4-methyldihydrofuro[2,3-*h*]coumarin-9-one (32). To solution of hydrazine **30** (0.5 g, 0.62 mmol) in acetic acid (10 ml) we added under stirring *p*-fluorophenylbenzaldehyde (0.15 g, 1.24 mmol). The reaction mixture was heated with a reflux condenser for 1.5 h. The precipitate was filtered off, washed with water, and dried. Yield 0.24 g (85%); mp 272-273°C (acetic acid).

Synthesis of 6-Amino-8-benzylidene-4-methyldihydrofuro[2,3-*h*]coumarin-9-ones (General Procedure). Mixture of compound **11** (0.2 g, 0.87 mmol), the respective aromatic aldehyde (0.87 mmol), acetic acid (10 ml), and concentrated hydrochloric acid (10 ml) was heated for 40 min, after which it was cooled until the product separated.

6-Amino-8-benzylidene-4-methyldihydrofuro[2,3-*h*]coumarin-9-one (33). Yield 70%; decomp. 300°C (acetone).

6-Amino-8-pentafluorobenzylidene-4-methyldihydrofuro[2,3-*h*]coumarin-9-one (34). Yield 60%; decomp. 190°C (acetone).

8-Benzylidene-6-formamido-4-methyldihydrofuro[2,3-*h*]coumarin-9-one (35). We added compound **33** (0.5 g, 1.57 mmol) to formic acid (10 ml) and heated the mixture until dissolution. The precipitate that separated on cooling was filtered off and recrystallized from acetic acid. Yield 0.41 g (70%); decomp. 280°C.

6-Acetamido-8-benzylidene-4-methyldihydrofuro[2,3-*h*]coumarin-9-one (36). Mixture of compound **33** (0.5 g, 1.57 mmol) and acetic anhydride (10 ml) was heated for 20 min and cooled until a precipitate separated. The product was filtered off and recrystallized from acetic anhydride. Yield 0.29 g (80%); decomp. 283-285°C.

REFERENCES

1. F. Dall'Acqua, D. Vedaldi, S. Caffieri, A. Guiotto, P. Rodighiero, F. Carlassare, and F. Bordin, *J. Med. Chem.*, **24**, 178 (1981).
2. A. Guiotto, P. Rodighiero, P. Manzini, G. Pfstorini, F. Carlassare, D. Vedaldi, F. Dall'Acqua, M. Tamaro, G. Recchia, and M. Cristofolini, *J. Med. Chem.*, **27**, 959 (1984).
3. R. L. Edelson, *J. Photochem. Photobiol. B: Biology*, **10**, 165 (1991).
4. V. F. Traven, D. V. Kravtchenko, and T. A. Chibisova, *Mendeleev Commun.*, No. 1, 21 (1995).
5. V. F. Traven, D. V. Kravtchenko, T. A. Chibisova, S. V. Shorshnev, R. Eliason, and D. H. Wakefield, *Heterocycl. Commun.*, **2**, 345 (1996).
6. V. F. Traven, D. V. Kravtchenko, and T. A. Chibisova, *Mendeleev Commun.*, 249 (1997).
7. D. V. Kravtchenko, V. F. Traven, and T. A. Chibisova, *Heterocycl. Commun.*, **3**, 331 (1997).
8. V. F. Traven, R. V. Rozhkov, A. Y. Tolmachev, N. F. Kuznezova, N. Y. Podhaluzina, and E. A. Carberry, *Heterocycl. Commun.*, **3**, 4 (1997).
9. V. F. Traven, I. I. Saharuk, and D. V. Kravtchenko, *Heterocycl. Commun.*, **4**, 429 (1998).