Chemistry of Natural Compounds, Vol. 43, No. 2, 2007

AMINOMETHYLATION OF CYTISINE BY 3-HETARYL-7-HYDROXYCOUMARINS

M. S. Frasinyuk,[1] A. V. Turov,[2] V. I. Vinogradova,[3] and V. P. Khilya[2]

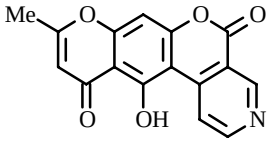
UDC 547.814.5

8-Aminomethyl derivatives of 7-hydroxycoumarins were prepared by reaction of methylene-bis-cytisine and substituted 7-hydroxycoumarins.

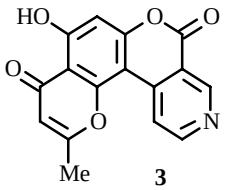
Key words: cytisine, alkylation, 3-hetaryl-7-hydroxycoumarins, aminomethylation.

Cytisine (**1**) is used in western countries as a diuretic [1] and in countries of the former Soviet Union as a respiratory analeptic and anti-smoking drug [2]. Such varied biological activity has generated great interest in cytisine derivatives. According to recent patents, cytisine and its *N*-methyl derivative exhibit hypolipidemic and anti-inflammatory activity [3, 4]. It has been found [5] that *N*-alkyl derivatives have the highest biological activity among the large number of synthetic cytisine derivatives. This is consistent pharmacologically with the similarity of cytisine and nicotine. Therefore, modification of cytisine, especially by alkylating reagents, and development of modern synthetic methods are interesting both from chemical and biologial viewpoints.

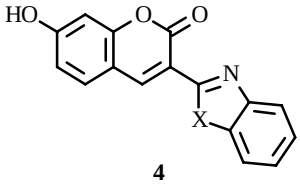
Addition to cytisine of a coumarin fragment, derivatives of which possess various types of biological activity and have pharmacological value that is hard to overestimate, is one of the interesting ways of modifying it. Coumarin derivatives containing a N atom are rarely encountered in the plant world. Condensed pyridocoumarins (**2** and **3**), which have been isolated [6, 7] from roots of *Schumanniophyton problematicum* and *S. magnificum*, are a minor group of tetracyclic alkaloids. Electron-accepting heterocyclic fragments in the 3-position of coumarin affect the physical and chemical properties of coumarins, in particular, anomalously large bathochromic shifts are observed in their UV spectra. As a result, absorption maxima of the coumarins shift into the visible region, especially if there are electron-donating hydroxyl or dialkylamino groups in the 7-position. Coumarins with aromatic heterocycles in the 3-position also have valuable fluorescent properties so that such compounds, namely 7-hydroxy-3-benzazolylcoumarin (**4**), can be used as fluorescent probes for biological investigations.



2



3



4

X = O, S, NH

Aminomethylation is a convenient method for modifying 7-hydroxycoumarins. Many Mannich bases in the coumarin series are CNS stimulants.

In continuation of research on modification of coumarins, we studied the addition of the natural alkaloid cytisine by aminomethylation of 7-hydroxy-3-hetarylcoumarins [8-10].

1) Institute of Bioorganic and Petroleum Chemistry, National Academy of Sciences of Ukraine, 02094, Ukraine, Kiev, ul. Murmanskaya, 1, e-mail: mfras@i.kiev.ua; 2) Taras Shevchenko Kiev National University, 01033, Ukraine, Kiev, ul. Vladimirskaya, 64; 3) S. Yu. Yunusov Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan, Tashkent, fax (99871) 120 64 75. Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 145-148, March-April, 2007. Original article submitted June 27, 2006.

0009-3130/07/4302-0176

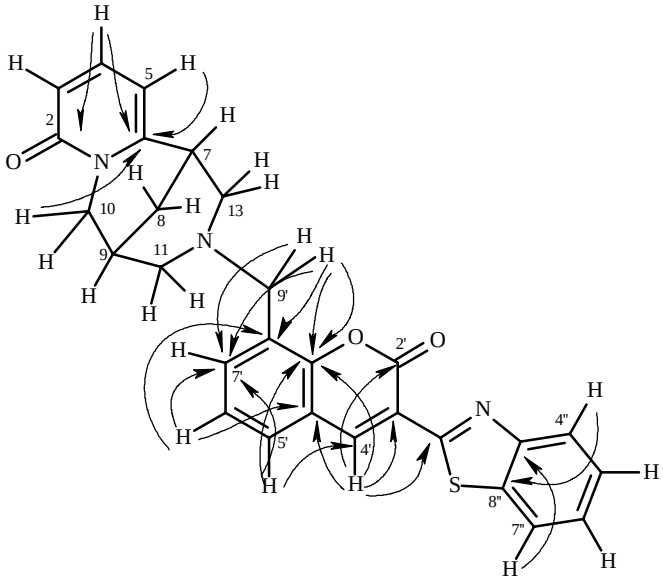
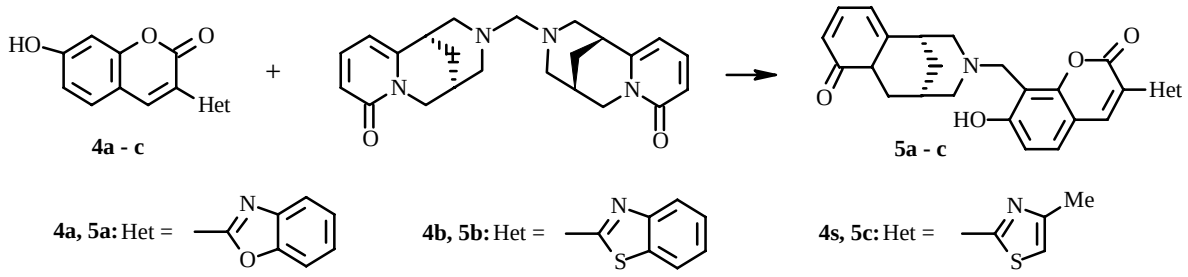


Fig. 1. HMBC correlations in **5b**.

Considering the reduced reactivity of 3-hetarylcoumarins in electrophilic substitution reactions, previous investigations [8, 9], and the possible mechanism of the Mannich reaction through the formation of aminals [11], aminomethylation of 7-hydroxy-3-hetarylcoumarins could be carried out only using methylene-*bis*-cytisine, which was prepared from cytisine (**1**) and diiodomethane [12] or formalin [13]. We used natural (-)-cytisine for the reaction.

PMR spectra of the synthesized Mannich bases **5a-c** contained signals of cytisine and the aromatic heterocycles. Bridging protons on C-8 appeared as two 1H doublets with SSCC ~15 Hz, consistent with the presence of diastereomers.



The structures of the Mannich adducts were established using PMR and ^{13}C NMR spectra, two-dimensional (2D) COSY and NOESY, and heteronuclear HMQC and HMBC correlations. Such varied methods were necessary because of the rather complicated proton and carbon spectra. Signals in the proton spectra could be assigned using COSY spectra. The assignments for protons located in close proximity to each other could be checked using NOESY spectra. HMQC spectra made it possible to assign signals for C atoms bonded directly to protons (correlations through one chemical bond) based on the assignments made in the proton spectra. Signals of quaternary C atoms could be assigned using HMBC based on correlations through 2-3 chemical bonds.

Chemical shifts of ^{1}H and ^{13}C in the amine and coumarin changed little in **5a-c** with the exception of C-3 of coumarin, to which the benzazole ring was bonded.

Figure 1 shows (arrows) those HMBC correlations that provided the basis for assigning the corresponding quaternary C atoms for **5b**. Protonated C atoms in **5a** were assigned based on their HMQC correlations. For example, the unprotonated atoms in the α-pyridone ring were C-6 and C-2. The assignment of the signal at 149.2 ppm to C-6 was based on correlations for it with signals of H-4 and H-5 with chemical shifts 7.37 and 6.05 ppm, respectively, and with the signal of the methylene protons with chemical shifts 3.9-4 ppm. The signal at 163.7 ppm could be assigned to C-2 based on its correlations with the proton signal at 7.37 ppm, corresponding to H-4 of the α-pyridone ring. Other assignments were made based on analogous arguments.

TABLE 1. NMR Spectra of **5a**

C atom	δ, ppm, J/Hz	HMQC	HMBC	COSY	NOESY
3	6.56 (d, J = 9)	118.0	105.5	7.37	7.37
4	7.37 (m)	139.1	163.7, 149.2	6.0.5, 6.56	6.05, 6.56
5	6.05 (d, J = 6.5)	105.5	149.2, 118.0	7.37	3.14, 7.37
7	3.14	35.2	25.8	2.01, 2.57	4.10, 4.20, 6.05
8a	2.01	25.8	-	1.94, 3.14	1.94, 2.58, 2.67, 3.14
8b	1.94	25.8	-	2.01	2.01, 2.58, 2.67, 3.14
9	2.58	27.8	49.7	3.14, 3.92	1.94, 2.01, 3.14, 3.92
10	4.20 (d, J = 15.6);	49.7	25.8, 27.8,	2.58, 3.92, 4.20	2.58, 3.14, 3.92
	3.92 (dd, J = 15.6, J = 6)		59.5, 149.2		
11	2.67; 3.14	59.5	27.8, 53.6, 49.7	2.67, 3.14	2.58, 3.14, 3.92
13	2.57; 3.14	61.1	35.2, 53.6	3.14	1.94, 2.01, 4.10
4′	8.65	146.2	130.1, 154.1, 157.1, 158.9	-	7.41
5′	7.41	130.1	146.1, 154.1, 165.8	6.75	6.75, 8.65
6′	6.75	115.3	107.4, 111.3, 164.8	7.41	7.41
9′	4.10	53.6	59.5, 61.1, 107.3, 154.1, 164.8	3.92	2.58, 3.14, 3.92
4″	7.85	120.7	125.8, 150.6	7.37	7.37
5″	7.37	125.0	110.8	7.37, 7.85	7.85
6″	7.37	125.8	120.7	7.60	7.60
7″	7.60	110.8	125.0, 142.1	7.37	7.37

TABLE 2. NMR Spectra of **5b** and **5c**

C atom	**5b**			**5c**		
	δ_H	HMQC	HMBC	δ_H	HMQC	HMBC
3	6.56	118.8	105.5	6.54	118.0	105.4
4	7.37	139.1	149.2; 163.7	7.34	139.1	149.3; 163.7
5	6.05	105.5	35.2; 118.0; 142.2	6.04	105.4	35.2; 118.0; 149.3
7	3.13	35.2		3.13	35.2	
8	1.94; 2.02	25.8		1.94; 2.01	25.8	
9	2.57	27.8		2.57	27.8	49.7
10	3.93; 4.20	49.7	25.8; 27.8; 59.6; 149.2	3.91; 4.19	49.7	149.3
11	2.57; 3.13	59.6		2.57; 3.13	59.6	49.7
13	2.65; 3.13	61.1	149.2	2.65; 3.09	61.1	149.3
4′	8.93	142.8	111.8; 115.5; 130.3;	8.71	140	115.8; 129.7; 152.7;
			153.3; 160.3; 160.7			159.2; 160.2
5′	7.45	130.3	142.8; 153.3; 164.2	7.40	129.7	140.1; 152.7; 163.3
6′	6.75	115.5	107.3; 111.8; 164.2	6.73	115.2	107.3; 111.9; 163.3
9′	3.93; 4.09	53.6	27.8; 59.6; 61.1;	3.91; 4.08	53.6	107.3; 152.7; 163.3
			107.3; 153.3; 164.2			
4″	7.94	122.7	126.6; 152.7			
5″	7.37	125.2	121.8	7.02	116.5	153.1; 159.2
6″	7.45	126.6	122.7; 152.7			
7″	8.03	121.8	125.2; 136.6			
CH_3-4				2.52	17.4	116.5; 153.1

The correlations completely confirmed the structure of the compound. Significantly fewer correlations were found for the aliphatic protons than for the aromatic protons. This was due to the smaller SSCC in the saturated compounds. However, the correlations found were entirely sufficient to assign reliably the signals.

Table 1 contains a complete list of the correlations found for **5a**; Table 2, for **5b** and **5c**.

Correlations observed in 2D spectra were also practically identical for all studied compounds. Thus, cross-peaks in COSY and NOESY spectra were found for **5b** and **5c**. However, we did not give them in the Tables because they were identical to those observed for **5a**.

The synthesized compounds were crystalline and readily soluble in dilute mineral acids and most organic solvents.

Thus, the developed methods of aminomethylation could be used to synthesize compounds containing cytisine that may be useful for biological investigations, opened new possibilities for chemical modification of cytisine, and expanded knowledge of its reactivity.

EXPERIMENTAL

The course of reactions and purity of products were monitored by TLC on Merck plates (Germany) with elution by $CHCl_3$:CH_3OH:Et_2NH (88:10:2). ^{13}C NMR COSY, NOESY, HMQC, and HMBC spectra in DMSO-d_6 relative to TMS (internal standard) were recorded on the δ-scale on a Mercury M 400 instrument (Varian, 400 MHz). Elemental analyses of all compounds agreed with those calculated.

General Method of Preparing 3-(2-Hetaryl)-7-hydroxy-8-(cytisyl-12)aminocoumarins 5a-5c. A boiling solution of the appropriate 3-(2-hetaryl)-7-hydroxycoumarin (**4a-4c**, 2 mmol) in absolute dioxane (20 mL) was treated with aminal (2.5 mmol). The mixture was boiled for 1 h (end of reaction determined by TLC) and cooled. Dioxane was evaporated in vacuo. The solid was crystallized from propan-2-ol.

3-{[3-(1,3-Benzoxazol-2-yl)-7-hydroxy-2-oxo-2*H*-chromen-8-yl]methyl}-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (5a), $C_{28}H_{23}N_3O_5$, yield 52%, mp 206-207°C (propan-2-ol). Table 1 gives the ^{13}C NMR spectrum.

^{13}C NMR spectrum (100 MHz, DMSO-d_6, δ, ppm): cytisine: 163.7 (C-2), 118.0 (C-3), 139.1 (C-4), 105.5 (C-5), 149.2 (C-6), 35.2 (C-7), 25.8 (C-8), 27.8 (C-9), 49.7 (C-10), 59.5 (C-11), 61.1 (C-13); coumarin: 158.9 (C-2), 109.9 (C-3), 146.2 (C-4), 130.1 (C-5), 111.3 (C-5a), 115.3 (C-6), 164.8 (C-7), 107.4 (C-8), 154.1 (C-8a), 53.6 (C-8-CH_2N); benzoxazole: 157.1 (C-2), 120.7 (C-4), 142.1 (C-4a), 125.0 (C-5), 125.8 (C-6), 110.8 (C-7), 150.6 (C-7a).

3-{[3-(1,3-Benzothiazol-2-yl)-7-hydroxy-2-oxo-2*H*-chromen-8-yl]methyl}-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (5b), $C_{28}H_{23}N_3O_4S$, yield 74%, mp 226-227°C (propan-2-ol).

Table 2 gives the ^{13}C NMR spectrum.

^{13}C NMR spectrum (100 MHz, DMSO-d_6, δ, ppm): cytisine: 163.7 (C-2), 118.0 (C-3), 139.1 (C-4), 105.5 (C-5), 149.2 (C-6), 35.2 (C-7), 25.8 (C-8), 27.8 (C-9), 49.7 (C-10), 59.6 (C-11), 61.1 (C-13); coumarin: 160.0 (C-2), 115.5 (C-3), 142.8 (C-4), 130.3 (C-5), 111.8 (C-5a), 115.5 (C-6), 164.2 (C-7), 107.3 (C-8), 153.3 (C-8a), 53.6 (C-8-CH_2N); benzothiazole: 160.3 (C-2), 122.7 (C-4), 136.6 (C-4a), 125.2 (C-5), 126.6 (C-6), 121.8 (C-7), 152.7 (C-7a).

3-{[7-hydroxy-3-(4-methyl-1,3-thiazol-2-yl)-2-oxo-2*H*-chromen-8-yl]methyl}-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (5c), $C_{25}H_{23}N_3O_4S$, yield 52%, mp 163-165°C (propan-2-ol:hexane).

Table 2 gives the ^{13}C NMR spectrum.

^{13}C NMR spectrum (100 MHz, DMSO-d_6, δ, ppm): cytisine: 163.7 (C-2), 118.0 (C-3), 139.1 (C-4), 105.4 (C-5), 149.3 (C-6), 35.2 (C-7), 25.8 (C-8), 27.8 (C-9), 49.7 (C-10), 59.5 (C-11), 61.1 (C-13); coumarin: 160.2 (C-2), 115.8 (C-3), 140.1 (C-4), 129.7 (C-5), 111.9 (C-5a), 115.2 (C-6), 163.3 (C-7), 107.3 (C-8), 152.7 (C-8a), 53.6 (C-8-CH_2N); thiazole: 159.2 (C-2), 153.1 (C-4), 116.5 (C-5), 17.41 (Me-4).

REFERENCES

1. P. Lebeau and M. M. Janot, *Traite de Pharmacie Chimique*, Vol. IV, Masson, Paris, 2859 (1955).
2. M. D. Mashkovskii, *Medicinal Preparations* [in Russian], Vol. 1, Torsing, Khar′kov (1997).
3. I. Murkhoshi, Y. Fujii, S. Takedo, and I. Arai, Jpn. Kokai Tokkyo Koho, Jpn. Pat. No. 04-295480, Oct. 20, 1992; *Chem. Abstr.*, **118**, 45733 (1993).
4. I. Murakhoshi, Y. Fujii, and H. Kawamura, and H. Maruyama, Jpn. Kokai Tokkyo Koho, Jpn. Pat. No. 04-295479, Oct. 20, 1992; *Chem. Abstr.*, **118**, 45734 (1993).

5. C. C. Boido, B. Tasso, V. Boido, and F. Sparatore, *Farmaco*, **58**, 3, 265 (2003).
6. E. Schlittler and U. Spitaler, *Tetrahedron Lett.*, **32**, 2911 (1978).
7. P. J. Houghton and H. Yang, *Planta Med.*, 23 (1985).
8. H. A. Naik and S. Seshadri, *Indian J. Chem., Sect. B*, **15**, 6, 506 (1977).
9. O. V. Khilya, M. S. Frasinyuk, A. V. Turov, and V. P. Khilya, *Khim. Geterotsikl. Soedin.*, No. 8, 1120 (2001).
10. O. V. Khilya, O. V. Shablykina, M. S. Frasinyuk, A. V. Turov, V. V. Ishchenko, and V. P. Khilya, *Khim. Prir. Soedin.*, No. 11, 1632 (2004).
11. M. Tramontini, *Synthesis*, **12**, 703 (1973).
12. Z. P. Pakudina and S. Yu. Yunusov, *Izv. Akad. Nauk Uzb. SSR*, 2, 69 (1957).
13. H. Auterhoff and F. Moll, *Arch. Pharm. Ber. Dtsch. Pharm. Ges.*, **293**, 132 (1960).