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FEATURES OF THE AMINOMETHYLATION OF 7-HYDROXY-4'-FLUOROISOFLAVONES WITH PRIMARY AMINES

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The behavior of 7-hydroxy-4'-fluoroisoflavones under the conditions of the Mannich reaction with primary amines was studied. New 9-alkyl-substituted 3-(4-fluorophenyl)-9,10-dihydro-4H,8H-chromeno-[8,7-e][1,3]oxazin-4-ones were synthesized. A method was developed for the synthesis of 8-amino- methyl derivatives of isoflavones.

Keywords: 8-aminomethylisoflavones, 3-(4-fluorophenyl)-9,10-dihydro-4H,8H-chromeno[8,7-*e*][1,3]oxazin-4-ones, aminomethylation, electrophilic substitution.

The derivatives of oxygen-containing heterocycles are some of the most widely distributed classes of natural compounds. An important position among them is occupied by isoflavones. The low toxicity of these compounds, together with their selective pharmacological action on the human organism, makes it possible to use them widely in the creation of medicines.

The derivatives of isoflavones substituted with fluorine in ring B exhibit various types of biological activity. Thus, derivatives of 4'- and 2'-fluoroisoflavones exhibit hypoglycemic and anabolic activity, while 4'-fluoroisoflavones in addition exhibit hypotensive, anti-inflammatory, hypolipidemic, hepatoprotective, and antioxidant activity [1].

It is well known that N-substituted aminomethyl derivatives of isoflavones and flavones are stimulants of the central nervous system, respiratory stimulants, are anesthetics, and also exhibit high anticonvulsive and antiallergic activity [2, 3]. The interest of investigators in the chemistry of Mannich bases is constantly increasing, and this is due not only to their valuable pharmacological characteristics but also to the possibility of the formation of water-soluble salts suitable for study of their biological activity.

The aim of our work was to develop the procedures and to synthesize new aminomethyl derivatives of 4'-fluoro-7-hydroxyisoflavone (**1a**) and its 2-methyl derivative **1b**. The choice of compounds **1a**,**b** was based on their pharmacological activity and also on the possibility of synthesizing tertiary amines by substitution of the fluorine atom as demonstrated for the case of 4'-fluoroflavones [4].

Earlier in the reaction of 3-hetaryl(aryl)-7-hydroxychromones with aminals (1,1'-methylenebisamines) we obtained their 8-dialkylaminomethyl and 8-(N-heteryl)methyl derivatives respectively [5-13].

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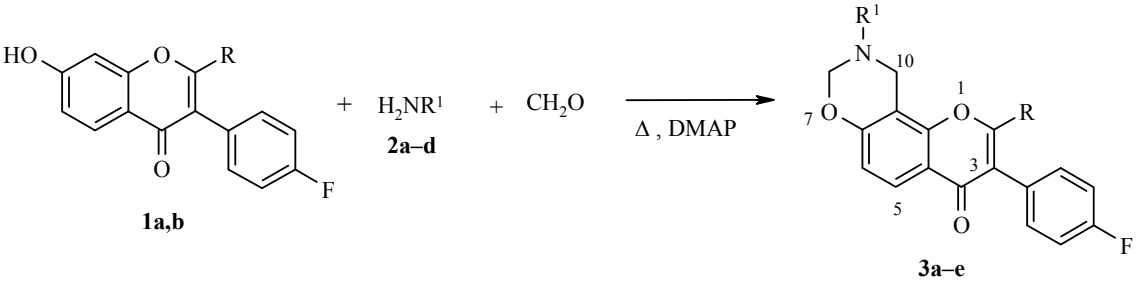
As known, under the conditions of the Mannich reaction with equivalent amounts of the substituted phenol and primary amine and also with a twofold excess of formalin in the presence of a catalyst [KOH or N,N-dimethylaminopyridine (DMAP)] derivatives of 3,4-dihydro-1,3-benzoxazine are formed as a result of electrophilic substitution (e.g., see [14, 15]).

Annelation of the oxazine ring to the coumarin ring by the reaction of 7-hydroxycoumarins and previously synthesized N,N-bis(hydroxymethyl)amines in the presence of DMAP leads to the formation of derivatives of 9,10-dihydro-2H,8H-chromeno[8,7-*e*][1,3]oxazin-2-one [16], while the isomeric derivatives of 9,10-dihydro-4H,8H-chromeno[8,7-*e*][1,3]oxazin-4-ones were obtained by the condensation of derivatives of isoflavones with the esters of α-amino acids and an excess of formalin [17].

In the present work we showed that the reaction of 4'-fluoro-7-hydroxyisoflavones **1a**,**b** with primary aliphatic amines and formalin by boiling the reaction mixture in 2-propanol (3-5 h) in the presence of a catalytic amount of DMAP leads to derivatives of 3-(4-fluorophenyl)-9,10-dihydro-4H,8H-chromeno[8,7-*e*][1,3]oxazin-4-one **3a-e** (yields 68-84%).



1a,b **3a–e**

1a, 3a–c R = H, **1b, 3d,e** R = Me, **2a,3a** R^1 = Pr, **2b,3b** R^1 = *i*-Pr, **2c,3c,d** R^1 = $(CH_2)_3OMe$, **2d,3e** R^1 = CH_2CH_2OMe

TABLE 1. Characteristics of Compounds **3a-e** and **4a-f**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		N	F	Cl		
3a	$C_{20}H_{18}FNO_3$	4.27 / 4.13	5.58 / 5.60		116-117	68
3b	$C_{20}H_{18}FNO_3$	4.02 / 4.13	5.71 / 5.60		136-137	76
3c	$C_{21}H_{20}FNO_4$	4.02 / 3.79	5.01 / 5.14		108-109	80
3d	$C_{22}H_{22}FNO_4$	3.58 / 3.65	5.11 / 4.95		124-125	84
3e	$C_{21}H_{20}FNO_4$	3.67 / 3.79	5.10 / 5.14		142-143	78
4a	$C_{20}H_{20}FNO_4 \cdot HCl$	3.68 / 3.56	4.76 / 4.82	9.27 / 9.00	211-212	76
4b	$C_{20}H_{20}FNO_3 \cdot HCl$	3.68 / 3.71	4.95 / 5.03	9.20 / 9.38	194-195	65
4c	$C_{22}H_{22}FNO_3 \cdot HCl$	3.33 / 3.47	4.65 / 4.70	8.56 / 8.78	234-235	78
4d	$C_{23}H_{18}FNO_3 \cdot HCl$	3.47 / 3.40	4.82 / 4.61	8.78 / 8.61	181-182	82
4e	$C_{24}H_{19}ClFNO_3 \cdot HCl$	2.95 / 3.04	4.04 / 4.13	16.02 / 15.40	225-226	68
4f*	$C_{22}H_{18}FNO_3S \cdot HCl$	3.07 / 3.24	4.32 / 4.40	7.95 / 8.21	199-200	79

* Found, %: S 7.22. Calculated, %: S 7.42.

TABLE 2. The ^{1}H NMR Spectra of 9,10-Dihydro-4H,8H-chromeno[8,7-*e*][1,3]oxazin-4-ones **3a-e**

Compound	Chemical shifts($CDCl_3$), δ, ppm. (*J*, Hz)							
	Dihydrochromenooxazine fragment				2-R (s)	3-C_6H_4F-*p*		9-R^1
	(1H, d, ^3J = 8.8, H-5)	(1H, d, ^3J = 8.8, H-6)	(2H, s, H-8)	(2H, s, H-10)		(2H, m, H-2',6')	(2H, m, H-3',5')	
3a	8.06	6.87	4.98	4.18	7.93 (1H, H)	7.52	7.12	2.73 (2H, m, NCH_2); 1.62 (2H, m, $NCH_2C\underline{H_2}$); 0.96 (3H, m, CH_3)
3b	8.05	6.86	5.06	4.25	7.94 (1H, H)	7.52	7.12	3.14 (1H, m, NCH); 1.19 (6H, d, ^3J = 6.6, CH_3)
3c	8.07	6.87	4.97	4.18	7.92 (1H, H)	7.52	7.20	3.47 (2H, m, OCH_2); 3.34 (3H, s, OCH_3); 2.86 (2H, m, NCH_2); 1.87 (2H, m, $NCH_2C\underline{H_2}$)
3d	7.98	6.82	4.96	4.18	2.29 (3H, CH_3)	7.24	7.11	3.47 (2H, m, OCH_2); 3.34 (3H, s, OCH_3); 2.86 (2H, m, NCH_2); 1.87 (2H, m, $NCH_2C\underline{H_2}$)
3e	7.98	6.84	5.00	4.26	2.29 (3H, CH_3)	7.24	7.11	3.60 (2H, m, OCH_2); 3.40 (3H, s, OCH_3); 3.00 (2H, m, NCH_2)

TABLE 3. Data from the ^{1}H NMR spectra of the Hydrochlorides of Substituted 2-R^1-8-Aminomethyl-4H-chromen-4-ones **4a-f**

Compound	Chemical shifts (DMSO-d_6), δ, ppm (*J*, Hz)							
	Chromone fragment		2-R (s)	3-C_6H_4F-*p* (4H, m)	7-OH (1H, s)	8-$CH_2N^+H_2R^1$		
	(1H, d, ^3J = 8.8, H-5)	(1H, d, ^3J = 8.8, H-6)				CH_2 (2H, s)	N^+H_2 (2H, s)	R^1
4a	7.98	7.33	7.25 (1H, H)	7.21-7.28	12.20	4.27	9.29	3.43 (2H, m, CH_2O); 3.28 (3H, s, OCH_3); 3.03 (2H, m, NCH_2); 1.99 (2H, m, $NCH_2C\underline{H_2}$)
4b	7.98	7.32	7.23 (1H, H)	7.21-7.28	12.17	4.26	9.29	2.95 (2H, m, NCH_2); 1.73 (2H, m, $NCH_2C\underline{H_2}$); 1.71 (2H, m, $C\underline{H_2}CH_3$), 0.94 (3H, m, CH_3)
4c	7.95	7.20	2.32 (3H, CH_3)	7.31	11.81	4.28	9.06	3.60 (1H, m, NCH); 2.06 and 1.56 (4H, 2m, β-CH_2); 1.76 (4H, m, γ-CH_2)
4d	7.96	7.32	7.38 (1H, H)	7.20-7.26	12.21	4.24	9.71	7.59 (2H, m, H Ph); 7.38 (3H, m, H Ph); 4.22 (2H, s, NCH_2)
4e	7.90	7.10	2.30 (3H, CH_3)	7.17-7.25	11.58	4.22	9.73	7.65 (2H, d, ^3J = 8.8, H Ph); 7.41 (2H, d, ^3J = 8.8, H Ph); 4.22 (2H, s, NCH_2)
4f	7.89	7.17	2.26 (3H, CH_3)	7.16-7.26	11.67	4.27	9.74	7.53, 7.45, 7.07 (3H, 3m, H thienyl); 4.44 (2H, s, NCH_2)

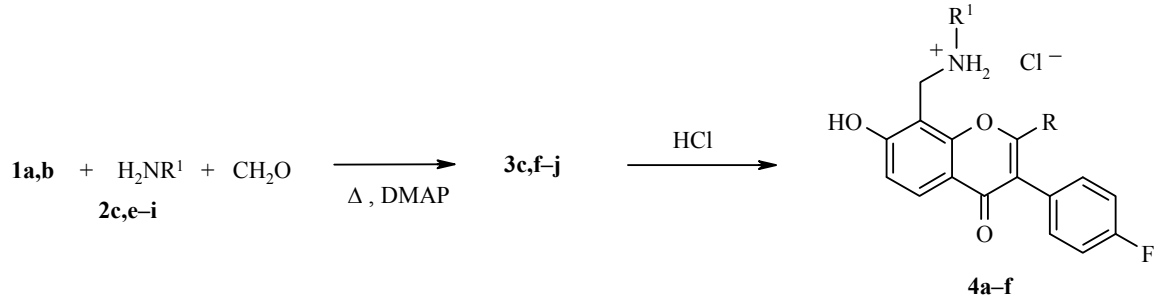
The structure of the obtained compounds **3a-e** is confirmed by the data from their ^{1}H NMR spectra: Compared with the spectra of the initial isoflavones **1a**,**b** the signal of the H-8 proton is absent, but there are signals for the protons of the C(10)H_2 and C(8)H_2 groups in the region of 4.18-4.26 and 4.96-5.06 ppm respectively and also the protons of the amine residue. The presence of a signal for the methylene group in the downfield region (4.96-5.06 ppm) indicates the formation of compounds of semiaminal structure, which is also confirmed by the structure of the synthesized compounds **3a-e**.

As known, compounds with acetal, semiaminal, and aminal structures are unstable toward acids. Thus, we obtained the hydrochloride of the Mannich base **4a** by heating compound **3c** in a 10% alcohol solution of HCl. As expected, the ^{1}H NMR spectrum of **4a** did not contain a two-proton singlet at 4.95-5.06 ppm, confirming the opening of the 1,3-oxazine ring in compound **3c**.

The instability of the derivatives of 3,4-dihydro-1,3-benzoxazine **3** in an acidic medium made it possible to develop a simple preparative method for the synthesis of Mannich bases of a series of isoflavones.

Thus, compounds **3c**,**f-j** with a 3,4-dihydro-1,3-benzoxazine ring were synthesized by boiling 7-hydroxyisoflavones **1a**,**b** with primary amines **2c**,**e-i** and an excess of formalin in the presence of a catalytic amount of DMAP. A 36% aqueous solution of HCl was then added to the reaction mixture, and further boiling led to formation of 65-82% yields of the hydrochlorides of 8-aminomethyl-4'-fluoro-7-hydroxyisoflavones (**4a-f**) containing the residues of primary aliphatic amines, cyclopentylamine, arylmethylamines, and 2-thienylmethyl-amine. The process was monitored by TLC.

The structure of the synthesized compounds **4a-f** was confirmed by the data from the ^{1}H NMR spectra. They do not contain the signal of the H-8 proton of the chromones ring, whereas signals for the 8-CH_2 group are observed in the region of 4.22-4.28 ppm and also for the protons of the amine residue characteristic for aminomethyl derivatives. The signal of the 7-OH group has the form of a narrow singlet at 11.58-12.21 ppm, while the signal for the protons of the ammonium group is a broad two-proton singlet in the region of 9.06-9.74 ppm since the fast exchange processes lead to disappearance of the spin–spin coupling with the protons of the aliphatic methylene and methine groups.



4a–f

4 a,b,d R = H, **c,e,f** R = Me; **4a** R^1 = $(CH_2)_3OMe$; **2e**,**3f,4b** R^1 = Bu;
2f,**3g,4c** R^1 = cyclopentyl; **2g,3h,4d** R^1 = CH_2Ph; **2h**,**3i,4e** R^1 = $CH_2C_6H_4Cl$-*p*;
2i,3j,4f R^1 = 2-thienylmethyl

Thus, we have synthesized new substituted 9,10-dihydro-4H,8H-chromeno[8,7-*e*][1,3]oxazin-4-ones containing alkyl substituents at position 9. We also developed a simple and effective method for the synthesis of 8-aminomethyl derivatives of isoflavones with various substituents at the amino group.

EXPERIMENTAL

The progress of the reactions and the purity of the obtained compounds were monitored by TLC on Sorbfil UV-254 (Russia) and Merck (Germany) plates. As eluant we used 9:1 and 19:1 mixtures of toluene and ethanol. The ^{1}H NMR spectra were recorded on Varian VXR-300 and Mercury M-400 instruments (300 and 400 MHz respectively) with TMS as internal standard.

The initial 7-hydroxyisoflavones (**1a,b**) were obtained as described earlier [17, 18].

2-R-9-R1-3-(4-Fluorophenyl)-9,10-dihydro-4H,8H-chromeno[8,7-e][1,3]oxazin-4-ones 3a-e (General Method). To a hot solution of 7-hydroxyisoflavone **1a**,**b** (2 mmol) in 2-propanol (20 ml), the primary amine (2.2 mmol), 37% solution of formalin (1.2 ml), and DMAP (5 mg) were added. The reaction mixture was boiled for 3-5 h and was then cooled, and the solvent was evaporated under vacuum. The residue was crystallized from a mixture of 2-propanol and hexane.

Hydrochlorides of 2-R-8-(R^1-Aminomethyl)-3-(4-fluorophenyl)-7-hydroxy-4H-chromen-4-ones 4a-f (General Method). The reaction mixture obtained as described above was boiled for 2-8 h, after which 36% aqueous solution of HCl (0.5 ml) was added to it, and the boiling was continued for a further 1-2 h. After cooling the solvent was evaporated under vacuum. The residue was crystallized from acetone or 2-propanol.

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