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N-(5-HYDROXY-3',4'-ETHYLENEDIOXY-7-ISOFLAVONYLOXYACETYL)-SUBSTITUTED AMINO ACIDS AND PEPTIDES

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A series of N-(5-hydroxy-3',4'-ethylenedioxy-7-isoflavonyloxyacetyl)-substituted amino acids and peptides were synthesized. Their structure was confirmed by data from the ^{1}H NMR spectra.

Keywords: N-(5-hydroxy-3',4'-ethylenedioxy-7-flavonyloxyacetyl)amino acids, peptides.

The synthesis of peptides modified by heterocycles is of interest in connection with the possibility of use as medicinal products of prolonged action, inhibitors of enzyme systems, etc. Natural and synthetic isoflavonoids, having a wide spectrum of biological activity, are promising from this standpoint [1]. In particular, 5,7-dihydroxy-3',4'-ethylenedioxyisoflavone (**1**), a synthetic homolog of the natural 5,7-dihydroxy-3',4'-methylenedioxyisoflavone [2], exhibits anabolic activity [3]. Earlier we modified compound **1** by the introduction of an OH group at position 7 with bromoacetic ester followed by hydrolysis. This made it possible to synthesize the succinimide ester of 5-hydroxy-3',4'-ethylenedioxy-7-isoflavonylacetic acid (**2**), which was subsequently used for the production of amino acid derivatives [4].

The aim of the present work was to modify compound **1** with substances of the peptide type, as described earlier [4]. For this purpose the succinimide ester **2** was brought into reaction with arginine (**3a**) and peptides based on it (**3b-e**), with prolinamide (**3f**) and a peptide based on it (**3g**), and with peptides based on glycinamide (**3h-j**) and phenylalaninamide (**3k**). The peptides were chosen so as to follow the variation of the biological activity of the synthesized compounds while gradually increasing the chain length and varying the *D*- and *L*-amino acids. It is known, for example, that a peptide chain based on glycinamide forms part of the natural hormone of the posterior lobe of the hypophysis – oxytocin, used to induce labor in childbirth and for the treatment of hypotonic uterine bleeding [5].

The reaction was conducted in dioxane or aqueous dioxane with agitation for 24 h at room temperature. As a result colorless crystalline substances **4** were isolated with satisfactory yields. They were purified by reprecipitation from their dimethylformamide solutions with diethyl ether (Scheme 1).

In the ^{1}H NMR spectra of compounds **4** there are signals for the protons characteristic of the chromone ring, the benzodioxane ring, the OH group at position 5 (11.39-12.91 ppm), the OCH_2 group at position 7 (4.56-4.96 ppm), and the amino acid residues. The structures of compounds **4** were confirmed by the data from elemental analysis.

Thus, new derivatives containing fragments of 5-hydroxy-7-methoxycarbonyl-3',4'-ethylenedioxyflavone and an amino acid or peptide were synthesized. They may prove useful for the development of new medicinal products.

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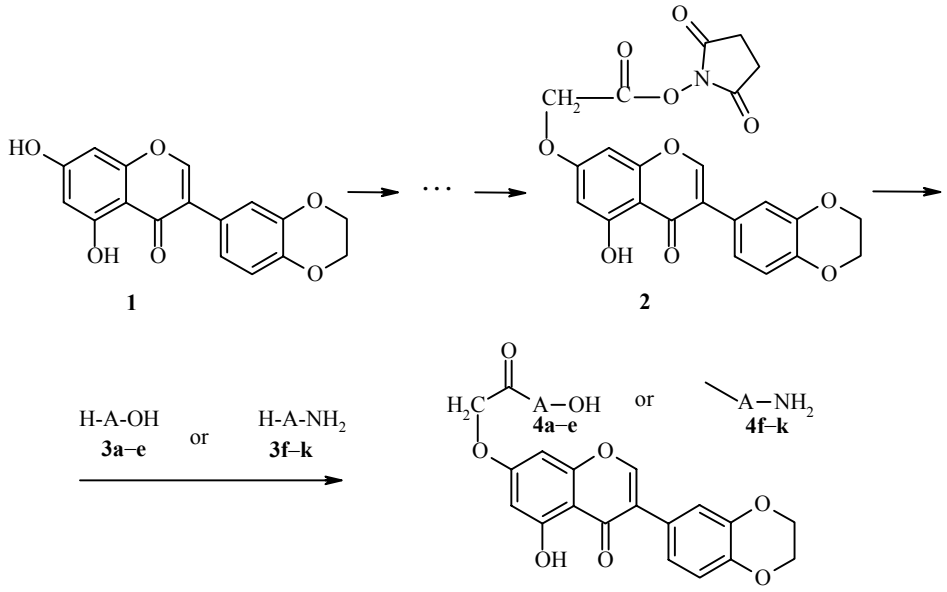
Scheme 1



3, **4** : **A = a** (L)-Arg, **b** (L)-Leu-(D)-Arg, **c** (L)-Phe-(L)-Leu-(D)-Arg, **d** (D)-Phe-(L)-Leu-(D)-Arg, **e** (L)-Phe-(L)-Leu-(L)-Arg, **f** (L)-Pro, **g** (L)-His-(L)-Pro, **h** (L)-Leu-(L)-Gly, **i** (L)-Pro-(L)-Leu-(L)-Gly, **j** (D)-Ala-(L)-Pro-(L)-Leu-(L)-Gly, **k** (L)-Pro-(L)-Phe

TABLE 1. The Characteristics of Compounds **4a-k**

Compound	Empirical formula	Found, % / Calculated, %	mp, °C*	Yield, %
4a	$C_{25}H_{26}N_4O_9$	10.68 / 10.64	228	57
4b	$C_{31}H_{37}N_5O_{10}$	10.66 / 10.95	128	62
4c	$C_{40}H_{47}N_6O_{11}$	10.47 / 10.67	206	72
4d	$C_{40}H_{47}N_6O_{11}$	10.88 / 10.67	144	67
4e	$C_{40}H_{47}N_6O_{11}$	10.78 / 10.67	174	61
4f	$C_{24}H_{22}N_2O_8$	6.16 / 6.01	210	71
4g	$C_{30}H_{29}N_5O_9$	11.85 / 11.60	158	66
4h	$C_{27}H_{29}N_3O_9$	7.49 / 7.79	dec.	63
4i	$C_{32}H_{36}N_4O_{10}$	8.90 / 8.80	198	79
4j	$C_{35}H_{41}N_5O_{11}$	9.76 / 9.90	dec.	72
4k	$C_{33}H_{31}N_3O_9$	6.72 / 6.85	135	68

*All the substances melt with decomposition.

TABLE 2. The ^{1}H NMR Spectra of Compounds **4**

Com-pound	Protons of chromone ring, δ, ppm, SSCC (*J*, Hz)					Protons of benzodioxane ring, δ, ppm (*J*, Hz)				Protons of amino acid and peptide residues (A), δ, ppm
	2H, s, C(7)OCH$_2$	1H, d, C(6)H, J = 2.3	1H, d, C(8)H, J = 2.3	1H, s, C(2)H	1H, s, C(5)OH	4H, s, (CH$_2$)$_2$,	1H, d, C(8)H, J = 8.0	1H, dd, C(7)H, $J_{7,5}$ = 2.0, $J_{7,8}$ = 8.0	1H, d, C(5)H, J = 2.0	
1	2	3	4	5	6	7	8	9	10	11
4a	4.64	6.40	6.62	8.39	12.86	4.26	6.89	7.04	7.08	1.58 (4H, m, 2CH$_2$); 3.05 (2H, m, CH$_2$NH); 4.04 (1H, m, CH); 7.60 (2H, br. s, NH$_2$); 7.92 (1H, s, =NH); 7.97 (1H, d, NHCO); 9.26 (1H, br. s, NH)
4b	4.70	6.40	6.61	8.41	11.39	4.27	6.89	7.04	7.08	0.82 (6H, dist. t, 2CH$_3$); 1.50 (6H, m, CH$_{2Leu}$ + 2CH$_{2Arg}$); 2.15 (1H, m, CH(CH$_3$)$_2$); 3.04 (2H, m, CH$_2$NH); 3.98 (1H, m, CH); 4.40 (1H, m, CH); 7.55 (2H, br. s, NH$_2$); 7.79 (1H, d, NHCO); 7.95 (1H, s, =NH); 8.38 (1H, d, NHCO); 9.30 (1H, br. m, NHCH$_2$)
4c	4.56	6.31	6.43	8.42	11.45	4.26	6.89	7.04	7.09	0.84 (6H, dist. t, 2CH$_3$); 1.51 (6H, m, CH$_{2Leu}$ + 2CH$_{2Arg}$); 2.15 (1H, m, CH(CH$_3$)$_2$); 2.98 (4H, m, CH$_{2Phe}$ + CH$_2$NH); 3.56 (1H, m, CH); 3.98 (1H, m, CH); 4.38 (1H, m, CH); 7.21 (5H, s, C$_6$H$_5$); 7.55 (3H, br. m, NHCO + NH$_2$); 7.96 (1H, s, =NH); 8.39 (1H, d, NHCO); 8.70 (1H, d, NHCO); 9.05 (1H, br. m, NHCH$_2$)
4d	4.61	6.37	6.50	8.43	11.40	4.27	6.89	7.06	7.11	0.79 (6H, dist. t, 2CH$_3$); 1.44 (6H, m, CH$_{2Leu}$ + 2CH$_{2Arg}$); 2.05 (1H, m, CH(CH$_3$)$_2$); 2.98 (4H, m, CH$_{2Phe}$ + CH$_2$NH); 3.58 (1H, m, CH); 4.04 (1H, m, CH); 4.42 (1H, m, CH); 7.21 (5H, s, C$_6$H$_5$); 7.59 (3H, br. s, NHCO + NH$_2$); 7.95 (1H, s, =NH); 8.39 (1H, d, NHCO); 8.56 (1H, d, NHCO); 8.98 (1H, br. m, NHCH$_2$)

TABLE 2 (continued)

1	2	3	4	5	6	7	8	9	10	11
4e	4.56	6.35	6.47	8.45	11.40	4.27	6.91	7.07	7.10	0.83 (6H, dist. t, $2CH_3$); 1.51 (6H, m, CH_{2Leu} + $2CH_{2Arg}$); 2.05 (1H, m, $\underline{CH}(CH_3)_2$); 2.98 (4H, m, CH_{2Phe} + $\underline{CH_2}NH$); 3.60 (1H, m, CH); 3.98 (1H, m, CH); 4.43 (1H, m, CH); 7.19 (5H, s, C_6H_5); 7.60 (3H, br. s, NHCO + NH_2); 7.94 (1H, s, =NH); 8.42 (1H, d, NHCO); 8.56 (1H, d, NHCO); 9.23 (1H, br. m, $\underline{NH}CH_2$)
4f	4.94	6.44	6.67	8.43	11.50	4.26	6.90	7.06	7.10	1.90 (4H, m, $2CH_2$); 3.39 (2H, m, CH_2); 4.46 (1H, d, CH); 7.35 (2H, br. s, NH_2)
4g	4.83	6.42	6.63	8.45	12.91	4.27	6.91	7.07	7.11	1.85 (4H, m, $2CH_{2Pro}$); 3.12 (2H, d, CH_{2His}); 3.48 (2H, m, CH_{2Pro}); 3.75 (1H, d, CH_{Pro}); 4.72 (1H, t, $\underline{CH}NH$); 7.50 (2H, br. s, NH_2); 7.96 (2H, br. s, H_{arom} + NHCO); 8.40 (1H, s, H_{arom}); 8.74 (1H, br. s, NH_{His})
4h	4.72	6.44	6.65	8.45	12.89	4.27	6.89	7.04	7.09	0.84 (6H, dist. t, $2CH_3$); 1.51 (2H, dd,, CH_2); 2.16 (1H, m, CH); 3.60 (2H, s, CH_2); 4.36 (1H, m, CH); 7.18 (2H, br. s, NH_2); 8.28 (2H, dist. t, 2NHCO)
4i	4.96	6.44	6.65	8.45	12.90	4.27	6.91	7.07	7.11	0.81 (6H, dist. t, $2CH_3$); 1.50 (2H, m, CH_2); 1.92 (4H, m, $2CH_2$); 2.05 (1H, m, $\underline{CH}(CH_3)_2$); 3.36 (2H, m, CH_2); 3.56 (2H, m, CH_2); 4.36 (1H, m, CH); 4.65 (1H, m, CH); 7.18 (2H, br. s, NH_2); 8.12 (1H, d, NHCO); 8.39 (1H, t, NHCO)
4j	4.69	6.44	6.64	8.45	12.88	4.27	6.90	7.06	7.10	0.82 (6H, dist. t, $2CH_3$); 1.29 (3H, d, CH_3); 1.51 (2H, m, CH_2); 1.89 (4H, m, $2CH_2$); 2.05 (1H, m, $\underline{CH}(CH_3)_2$); 3.36 (2H, m, CH_2); 3.61 (2H, d, CH_{2Gly}); 4.18 (1H, m, CH); 4.40 (1H, m, CH); 4.55 (1H, m, CH); 7.18 (2H, br. s, NH_2); 7.75 (1H, t, NHCO); 7.98 (1H, d, NHCO); 8.21 (1H, d, NHCO)
4k	4.70	6.42	6.66	8.42	12.87	4.26	6.89	7.04	7.10	1.66 (4H, m, $2CH_{2Pro}$); 3.04 (2H, m, CH_{2Phe}); 3.82 (2H, m, CH_{2Pro}); 4.34 (1H, m, CH); 4.58 (1H, dd, CH); 7.21 (5H, s, C_6H_5); 7.60 (2H, br. s, NH_2); 7.91 (1H, d, NHCO)

EXPERIMENTAL

The purity of the obtained compounds was monitored by TLC (Silufol UV-254, 16:4:1 chloroform–methanol–conc. ammonia). The ^{1}H NMR spectra were recorded in DMSO-d_6 on a Bruker WP-100 SY instrument.

The succinimide ester **2** was obtained by the method in [4].

The characteristics of compounds **4** are given in Table 1. The data from the ^{1}H NMR spectra are given in Table 2.

N-(5-Hydroxy-3',4'-ethylenedioxy-7-isoflavonyloxyacetyl)arginine (4a), N-(5-Hydroxy-3',4'-ethylenedioxy-7-isoflavonyloxyacetyl)prolinamide (4f), and Peptides (4b-e, g-k). To a solution of the ester **2** (1.4 g, 3 mmol) in dioxane (30 ml) we added a solution of arginine (**3a**) or peptide **3b-e**,**j** (3 mmol) in water (30 ml). The same amount of prolinamide (**3f**) or peptide **3h**,**i**,**k** was dissolved in the smallest amount of dioxane (5-30 ml). In the case of histidineprolinamide dihydrochloride (**3g**) its solution in 30 ml of water was neutralized with an equivalent amount of N-methylmorpholine (0.33 ml, 3 mmol). The obtained reaction mixtures were stirred with a magnetic stirrer for 24 h, and the precipitate was filtered off. Compounds **4a-g**,**i** were purified by reprecipitation from dimethylformamide solution with diethyl ether. Compound **4h** was precipitated from dimethylformamide solution with water. The obtained precipitates, including the precipitate of compound **4k** that separated after evaporation of the dioxane were washed with 1 N sulfuric acid, and the precipitate was filtered off. The oily product **4j** was rubbed in diethyl ether and recrystallized from isopropyl alcohol.

REFERENCES

1. A. L. Kazakov, V. P. Khilya, V. V. Mezheritskii, and Yu. Litkei, *Natural and Modified Isoflavonoids* [in Russian], Izd. Rost. Un-ta (1985), 184 pp.
2. M. Komatsu, I. Yokol, and V. Shirataki, *Yakugaku Zasshi*, **96**, 254 (1976); *Chem. Abs.*, **84**, 147717 (1976).
3. V. P. Khilya and A. Aitmambekov, *Khim. Prirod. Soedin.*, 343 (1994).
4. T. V. Shokol, A. S. Ogorodniichuk, V. V. Shilin, V. B. Milevskaya, and V. P. Khilya, *Khim. Geterotsikl. Soedin.*, 482 (1998).
5. M. D. Mashkovskii, *Drugs* [in Russian], Vol. 1 (1987), p. 539.