Chemistry of Heterocyclic Compounds, Vol. 34, No. 4, 1998

N-(5-HYDROXY-3′,4′-ETHYLENEDIOXYISOFLAVONYL-7-OXYACETYL)AMINO ACIDS

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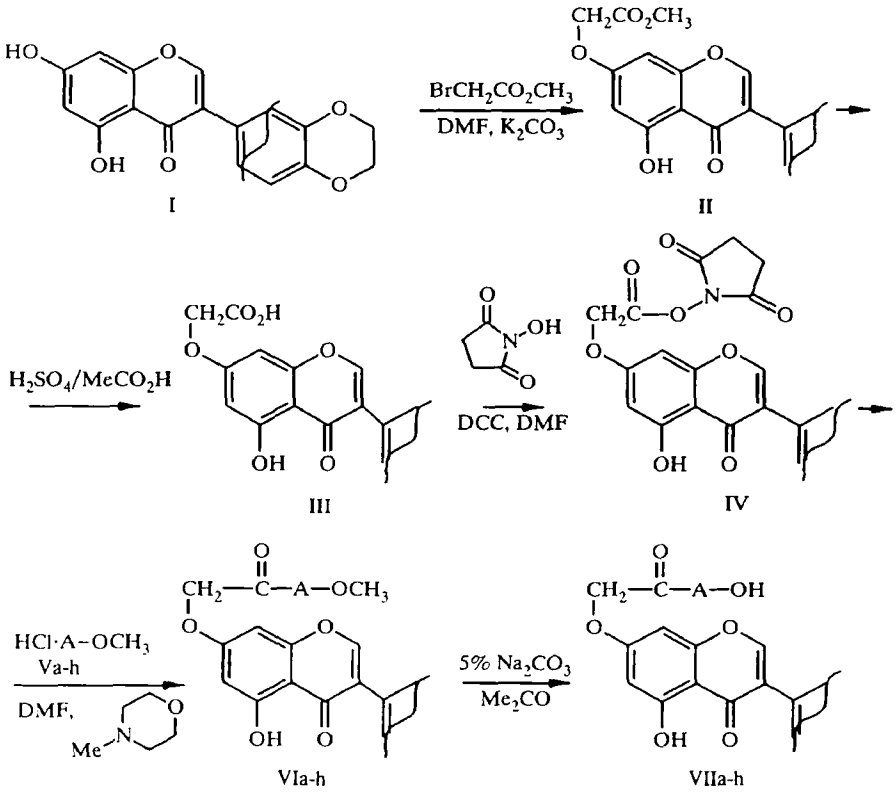
For the purpose of seeking new biologically active compounds in the flavonoid series, a series of N-(5-hydroxy-3′,4′-ethylenedioxyisoflavonyl-7-oxyacetyl)amino acids was synthesized; their structure was confirmed by PMR spectral data.

It is known that 5,7-dihydroxy-3′,4′-ethylenedioxyisoflavone (I), a synthetic homolog of the natural 5,7-dihydroxy-3′,4′-methylenedioxyisoflavone isolated from the roots of *Sophora japonica* [1], shows anabolic activity [2]. Modification of its structure by the introduction of a portion containing an amino acid residue will possibly allow the isolation of compounds with valuable biological properties.



V—VII a A = (D)-Ala, b A = (D)-Phe, c A = (D,L)-Tyr, d A = (D,L)-Trp, e A = (D)-Trp, f A = (D,L)-His, g A = (D)-Pro, h A = (D,L)-Pro

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0009-3122/98/3404-0427$20.00

TABLE 1. Characteristics of the Compounds (II)-(VII)

Compound	mp, °C	Found, % N	Empirical formula	Calculated, % N	Yield, %
II	201	62,78* 4.39†	$C_{20}H_{16}O_8$	62,50* 4.20†	94
III	268	61,37* 4.93†	$C_{19}H_{14}O_8$	61,62* 3.81†	92
IV	156	3,31	$C_{23}H_{17}NO_{10}$	2,91	93
VIa	166	3,18	$C_{23}H_{21}NO_9$	3,08	49
VIb	145	2,64	$C_{29}H_{25}NO_9$	2,64	60
VIc	204	2,45	$C_{29}H_{25}NO_{10}$	2,56	75
VId	193	4,85	$C_{31}H_{26}N_2O_9$	4,91	85
VIe	193	4,86	$C_{31}H_{26}N_2O_9$	4,91	81
VIf	109	8,16	$C_{26}H_{23}N_3O_9$	8,06	75
VIg	145	2,64	$C_{25}H_{23}NO_9$	2,91	82
VIh	154	3,04	$C_{25}H_{23}NO_9$	2,91	81
VIIa	221	2,87	$C_{22}H_{19}NO_9$	3,17	90
VIIb	212	2,71	$C_{28}H_{23}NO_9$	2,71	95
VIIc	214	2,39	$C_{28}H_{23}NO_{10}$	2,62	96
VIId	194	5,16	$C_{30}H_{24}N_2O_9$	5,03	92
VIIe	197	4,75	$C_{30}H_{24}N_2O_9$	5,03	92
VIIf	208	8,58	$C_{25}H_{21}N_3O_9$	8,28	90
VIIg	183	2,91	$C_{24}H_{21}NO_9$	3,00	90

*C, %.
†H, %.

In order to synthesize the indicated derivatives of the isoflavone (I), we first accomplished its alkylation at the 7-OH group with methyl bromoacetate, and then hydrolyzed the resulting ester (II) to the acid (III). It should be noted that the hydrolysis of compound (II) was conducted in an acidic medium, which enabled us to avoid the possible breakdown of the chromone ring, occurring in an alkaline medium [3], and obtain the acid (III) with a high yield and in a chromatographically pure form.

The PMR spectrum of the ester (II) shows two singlets at 3.73 and 4.94 ppm corresponding with protons of the methyl and methylene groups of the methyl ester of the oxyacetic acid at the position 7 of the chromone nucleus, together with proton signals of the chromone and benzodioxane rings, as well as the low-field singlet of the 5-OH group at 12.90 ppm characteristic of the initial isoflavone (I) [2]. After the hydrolysis of the ester, the signal of the methyl group disappears from the spectrum, and that of the methylene group is shifted by 0.12 ppm to high field.

The method of activated N-hydroxysuccinimide esters was utilized for the synthesis of amino acid derivatives of the isoflavone (III) at the carboxyl group [4]. The reaction of the acid (III) with N-hydroxysuccinimide in dimethylformamide in the presence of dicyclohexylcarbodiimide in the cold afforded the activated ester (IV), which was condensed with methyl esters of hydrochlorides of amino acids (Va-h) in dimethylformamide in the presence of N-methylmorpholine at room temperature. This resulted in good yields of the methyl esters (VIa-h) containing the amino acid residue (A). Alkaline hydrolysis of the compounds (VIa-g) gave the corresponding acids (VIIa-g).

The synthesized derivatives (VI) and (VII) are colorless crystalline products. Their structure was confirmed by results of the elemental analysis and PMR data. The PMR spectra of the compounds (VI) and (VII) contain signals of protons characteristic of the chromone and benzodioxane rings, the 5-OH group (12.84-12.91 ppm), the 7-OCH_2 group (4.62-4.97 ppm), and the amino acid residue. The spectra of the methyl esters (VI) contain a three-proton singlet of the methoxyl group at 3.61-3.64 ppm, which is absent from the products (VII). The broadened doublet of the proton of the CONH group in the esters (VIa-f) appears at 8.46-8.74 ppm; it is shifted by 0.14-0.52 ppm to high field in the acids (VIIa-f).

Therefore, derivatives containing the amino acid residue, which may present practical interest in the development of new medicinals, were synthesized on the basis of 5-hydroxy-7-carbomethoxy-3',4'-ethylenedioxyisoflavone.

TABLE 2. Characteristics of the PMR Spectra of the Compounds (II)-(VII) [δ, ppm, SSCC (J, Hz)]

Compound	Protons of the chromone ring					Protons of the benzodioxane ring			
	7-OCH_2, s, 2H	5-OH, s, 1H	2-H, s, 1H	6-H, d, 1H, J = 2,3	8-H, d, 1H, J = 2,3	$(CH_2)_2$, s, 4H	6-H, d, 1H, J = 2,0	7-H, d, 1H, J = 8,0	8-H, d.d, 1H, J = 2,0; 8,0
II	4,96	12,90	8,44	6,45	6,69	4,27	7,11	6,90	7,07
III	4,84	12,88	8,43	6,41	6,65	4,27	7,10	6,90	7,06
IV	4,85	12,89	8,44	6,36	6,55	4,27	7,10	6,89	7,06
VIa	4,69	12,91	8,46	6,46	6,66	4,27	7,11	6,94	7,02
VIb	4,64	12,89	8,45	6,39	6,66	4,26	7,11	6,90	7,02
VIc	4,65	12,90	8,43	6,41	6,55	4,27	7,11	6,92	7,02
VId	4,65	12,90	8,43	6,42	6,56	4,27	7,11	6,92	7,02
VIe	4,65	12,90	8,44	6,41	6,57	4,27	7,11	6,91	7,04
VIf	4,69	12,89	8,45	6,42	6,56	4,27	7,10	6,94	7,06
VIg	4,97	12,88	8,43	6,40	6,60	4,26	7,10	6,90	7,05
VIh	4,95	12,86	8,41	6,38	6,59	4,25	7,09	6,89	7,05
VIIa	4,68	12,89	8,44	6,47	6,67	4,27	7,10	6,89	7,05
VIIb	4,62	9,35	8,43	6,38	6,54	4,26	7,10	6,90	7,05
VIIc	4,63	12,84	8,42	6,36	6,58	4,26	7,10	6,89	7,00
VIId	4,64	12,90	8,43	6,41	6,57	4,27	7,11	6,91	7,06
VIIe	4,63	12,90	8,43	6,41	6,57	4,26	7,11	6,90	7,07
VIIf	4,65	12,89	8,40	6,42	6,59	4,25	7,08	6,92	7,06
VIIg	4,99	12,91	8,45	6,45	6,65	4,31	7,14	6,93	7,11

Compound	Protons of the amino acid residue (A)*		Chemical shifts, ppm, SSCC (J), Hz	OCH_3
	NH, d, 1H	N—CH, m, 1H		
II	—	—	—	3,73
III	—	—	—	—
IV	—	—	1,21; 1,68 (2 br. s, CH_2—CH_2)	—
VIa	8,61	4,35	1,33 (3H, d, CH_3)	3,64
VIb	8,55	4,55	3,04 (2H, m, CH_2); 7,21 (5H, s, C_6H_5)	3,63
VIc	8,46	4,45	2,90 (2H, d, CH_2); 6,62 (2H, d, J = 8Hz, H_{arom}); 6,98 (2H, d, J = 8Hz, H_{arom}); 9.20 (1H, br. s, OH)	3,62
VId	8,46	4,62	3,23 (2H, d, CH_2); 7,55 (1H, d. d, H_{arom}); 7,33 (1H, d. d, H_{arom})†	3,63
VIe	8,57	4,62	3,23 (2H, d, CH_2); 7,54 (1H, d. d, H_{arom}); 7,34 (1H, d. d, H_{arom})†	3,61
VIf	8,74	4,59	3,12 (2H, d, CH_2); 7,95 (1H, s, H_{arom}); 8,45 (1H, s, H_{arom})	3,65
VIg	—	—	1,93 (4H, m, $2CH_2$); 3,56 (2H, m, CH_2); 3,75 (1H, m, CH)	3,61
VIh	—	—	1,93 (4H, m, $2CH_2$); 3,56 (2H, m, CH_2); 3,75 (1H, d, CH)	3,61
VIIa	8,47	4,35	1,34 (3H, d, CH_3)	—
VIIb	8,14	4,43	3,06 (2H, m, CH_2); 7,17 (5H, s, C_6H_5)	—
VIIc	8,39	4,41	2,95 (2H, d, CH_2); 6,60 (2H, d, J = 8Hz, H_{arom}); 6,97 (2H, d, J = 8 Hz., H_{arom});	—
VIId	8,30	4,62	3,24 (2H, d, CH_2); 7,57 (1H, d. d, H_{arom}); 7,34 (1H, d. d, H_{arom})†	—
VIIe	8,29	4,60	3,24 (2H, d, CH_2O); 7,56 (1H, d. d, H_{arom}); 7,34 (1H, d. d, H_{arom})†	—
VIIf	8,52	4,50	3,02 (2H, d, CH_2); 7,95 (1H, s, H_{arom}); 8,40 (1H, s, H_{arom})	—
VIIg	—	—	2,00 (4H, m, $2CH_2$); 3,65 (2H, m, CH_2); 4,65 (1H, d, CH)	—

*In the case of compound (IV), protons of the succinimide residue.

EXPERIMENTAL

The homogeneousness of the compounds synthesized was monitored using TLC on plates of Silufol UV-254. Eluents were the 9:1 mixture of chloroform – methanol and the 4:1:1 mixture of n-butanol – acetic acid – water. The PMR spectra were recorded on the Bruker WP-100 SY instrument in DMSO-D_6. The characteristics of the compounds (II)-(VII) are presented in Table 1, and the PMR spectral data are presented in Table 2.

Methyl (5-Hydroxy-3′,4′-ethylenedioxyisoflavonyl-7)oxyacetate (II). To the solution of 30.4 g (0.097 mole) of the chromone in 100 ml of DMF are added 27.6 g (0.2 mole) of ground, freshly calcined, potassium carbonate prior to the addition, dropwise with stirring and heating (50-60°C), of 9.5 ml (0.1 mole) of methyl bromoacetate. After 30 min, the reaction mixture is cooled and poured into 1 liter of water. The residue of the product (II) is filtered off and recrystallized from DMF.

5-Hydroxy-3′,4′-ethylenedioxyisoflavonyl-7-oxyacetic Acid (III). The solution of 11.52 g (0.03 mole) of the ester (II) in the mixture of 50 ml of acetic acid and 15 ml of sulfuric acid is boiled until the disappearance of the initial compound is effected according to TLC. The reaction mixture is cooled, and the product (III) which separated out is filtered off and washed with water. The mother liquor is diluted with water, and the product (III) is filtered off; it is combined with the portion washed with water, prior to recrystallization from DMF.

Succinimide Ester of (5-Hydroxy-3′,4′-ethylenedioxyisoflavonyl-7)oxyacetic Acid (IV). To the solution, cooled to 0°C, of 9.25 g (0.025 mole) of the acid (III) in 160 ml of DMF are added 3.12 g (0.027 mole) of hydroxysuccinimide, and the resulting mixture is maintained for 1 h at −10°C prior to the addition of 5.56 g (0.027 mole) of dicyclohexylcarbodiimide; the mixture is stirred for 24 h at room temperature. The dicyclohexylurea is filtered off, and the solvent is evaporated *in vacuo* while heating the mixture to not higher than 40°C. The residue is brought to boiling in 100 ml of 2-propanol, and the mixture is cooled prior to filtering off the product (IV).

Methyl Esters of N-(5-Hydroxy-3′,4′-ethylenedioxyisoflavonyl-7-oxyacetyl)amino Acids (VIa-h). To the solution of 5 mmole of the hydrochloride of the methyl ester of the amino acid (Va-h) is added, with cooling and stirring, 0.7 ml (6 mmole) of N-methylmorpholine. After 20 min, 1.87 g (4 mmole) of the succinimide ester (IV) are added, and the reaction mass is stirred at room temperature for 5 h and is further held at the same temperature for ~16 h. The mixture is poured into the mixture of 50 ml of 1 N H_2SO_4 and 50 ml of water. The residue is filtered off and dissolved in 50 ml of ethyl acetate or dichloromethane. The solution is washed with 2 × 50 ml of 1 N H_2SO_4, 5% Na_2CO_3, and water, and dried with Na_2SO_4. Further, the solvent is evaporated *in vacuo*, and the residue is brought to boiling in 2-propanol and cooled prior to filtering off the product (VI).

N-(5-Hydroxy-3′,4′-ethylenedioxyisoflavonyl-7-oxyacetyl)amino Acids (VIIa-h). The methyl ester (VI) (2 mmole) is boiled in the mixture of 30 ml of acetone and 20 ml of 5% Na_2CO_3 until the disappearance of the initial compound is effected according to TLC (1-6 h). The acetone is evaporated *in vacuo*, and the residue is diluted with water and acidified with 1 N H_2SO_4 prior to the filtration of the product (VII).

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