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AMINO ACID DERIVATIVES OF 2-R-7-HYDROXY-3′,4′-ETHYLENEDIOXYISOFLAVONES

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A number of 7-O-aminoacyl derivatives of isoflavones have been obtained by the interaction of 2-R-7-hydroxy-3′,4′-ethylenedioxyisoflavones with the symmetrical anhydrides of N-protected amino acids.

It appeared of interest to unite within a single molecule two bioactive classes of natural compounds, such as amino acids and flavanoids. To fulfill this task we have used readily available amino acids and the 7-hydroxyisoflavones (**1**—**3**) with established biological activity [1—3].

To obtain amino acid derivatives of isoflavones we used a known approach consisting in the formation of an ester bond between an amino acid and a phenolic compound [4]. The most convenient method of aminoacylating 7-hydroxyisoflavones is their interaction with symmetrical amino acid anhydrides [5].

Symmetrical anhydrides of N-protected amino acids were obtained by condensing dicyclohexylcarbodiimide (DCC) with a double amount of the appropriate N-protected amino acids in absolute tetrahydrofuran (THF) at 0°C. The amine functions of the amino acids were blocked with tert-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz), and *p*-toluenesulfonyl (Tos) groupings. The acylation of the 7-hydroxychromones (**1**—**3**) was performed with the amino acid anhydrides so obtained at 0°C in absolute THF in the presence of catalytic amounts of 4-dimethylaminopyridine (DMAP). The result of this reaction was the formation of a number of 7-aminoacyl derivatives of isoflavones (**4**—**27**) containing residues of glycine (compounds **9** and **16**), alanine (**4**, **7**, **11** and **17**), β-alanine (**18** and **25**), γ-aminobutyric acid (**22** and **26**), ε-aminocaproic acid (**27**), valine (**5**, **10**, **12**, and **19**), leucine (**13** and **20**), isoleucine (**21**), methionine (**6**, **8**, **14**, and **23**), and phenylalanine (**15** and **24**). The physicochemical properties of compounds (**4**—**27**) are given in Table 1 and Table 2.

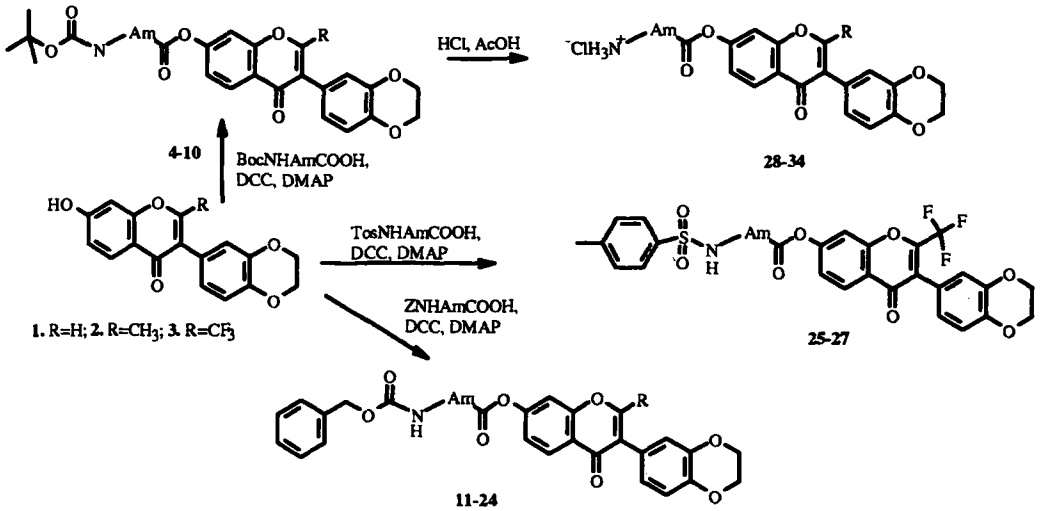

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TABLE 1. Detales of PMR Spectra of Compounds (4—34) (δ, ppm)

Compound No.	Chromone protons				Hetaryl protons				Protons of the amino acid residue	Solvent
	R2-2 s	H-5 d	H-6 d	H-8 dd	H-5 d	H-7 dd	H-8 d	$O(CH_2)_2O$		
4	8.49 (H)	8.18	7.25	7.47	7.06	6.93	7.14	4.27	Boc NH CH (CH_3); 1.42; 7.59; 4.29; 1.45	DMSO-d_6
5	8.50 (H)	8.22	7.25	7.46	7.07	6.91	7.15	4.27	Boc NH CH CH (CH_3)$_2$ 1.43; 7.53; 4.11; 2.21; 1.02	DMSO-d_6
6	8.50 (H)	8.19	7.27	7.51	7.06	6.92	7.15	4.27	Boc NH CH CH_2 CH_2 S CH_3 1.42; 7.62; 4.39; 2.61; 2.12; 2.09	DMSO-d_6
7	2.31 (Me)	8.25	7.12	7.28	6.77	6.74	6.92	4.28	Boc NH CH (CH_3); 1.48; 5.10; 4.54; 1.58	$CDCl_3$
8	2.33 (Me)	8.25	7.13	7.29	6.79	6.74	6.93	4.29	Boc NH CH CH_2 CH_2 S CH_3 1.49; 5.23; 4.67; 2.69; 2.22; 2.16	$CDCl_3$
9	-(CF_3)	8.26	7.26	7.45	6.92	6.83	6.79	4.29	Boc NH CH_2; 1.49; 5.17; 4.20	$CDCl_3$
10	-(CF_3)	8.25	7.23	7.41	6.93	6.77	6.71	4.30	Boc NH CH CH (CH_3)$_2$ 1.9; 5.07; 4.44; 2.36; 1.09	$CDCl_3$
11	2.32 (Me)	8.22	7.12	7.25	6.79	6.72	6.92	4.29	Ph CH_2OCONH CH (CH_3) 7.36; 5.16; 5.34; 4.64; 1.62	$CDCl_3$
12	2.32 (Me)	8.23	7.12	7.28	6.77	6.74	6.92	4.29	Ph CH_2 OCONH CH CH (CH_3)$_2$ 7.37; 5.16; 5.35; 4.57; 2.29; 1.08	$CDCl_3$
13	2.32 (Me)	8.22	7.12	7.25	6.79	6.72	6.92	4.28	Ph CH_2OCONH CH CH_2CH (CH_3)$_2$ 7.36; 5.16; 5.27; 4.63; 1.80; 1.02	$CDCl_3$
14	2.32 (Me)	8.23	7.13	7.26	6.78	6.74	6.92	4.28	Ph CH_2OCONH CH CH_2 CH_2 S CH_3 7.36; 5.16; 5.53; 4.76; 2.67; 2.21; 2.14	$CDCl_3$
15	2.31 (Me)	8.25	7.12	7.25	6.79	6.72	6.92	4.27	Ph CH_2 OCONH CH CH_2 Ph 7.34; 5.14; 5.30; 4.89; 3.26; 7.34	$CDCl_3$
16	-(CF_3)	8.20	7.34	7.57	6.92	6.83	6.79	4.32	Ph CH_2OCONH CH_2; 7.38; 5.15; 6.99; 4.28	$(CD_3)_2CO$
17	-(CF_3)	8.23	7.23	7.41	6.93	6.74	6.79	4.29	Ph CH_2OCONH CH (CH_3) 7.36; 5.15; 5.37; 4.64; 1.61	$CDCl_3$
18	-(CF_3)	8.18	7.33	7.58	6.92	6.83	6.79	4.32	Ph CH_2OCONH CH_2 CH_2 7.37; 5.10; 6.69; 3.62; 2.92	$(CD_3)_2CO$
19	-(CF_3)	8.23	7.19	7.26	6.95	6.77	6.71	4.29	Ph CH_2OCONH CH CH (CH_3)$_2$ 7.38; 5.15; 5.37; 4.55; 2.37; 1.09	$CDCl_3$
20	-(CF_3)	8.23	7.19	7.26	6.95	6.77	6.71	4.29	Ph CH_2OCONH CH CH_2 CH (CH_3)$_2$ 7.38; 5.15; 5.37; 4.61; 1.79; 1.09	$CDCl_3$
21	-(CF_3)	8.23	7.19	7.26	6.95	6.77	6.71	4.30	Ph CH_2OCONH CH CH (CH_2CH_3)CH_3 7.38; 5.16; 5.33; 4.57; 2.07; 1.06; 1.21	$CDCl_3$
22	-(CF_3)	8.15	7.32	7.56	6.91	6.83	6.78	4.32	Ph CH_2OCONH CH_2 CH_2 CH_2 7.34; 5.08; 6.50; 3.33; 1.97; 2.75	$(CD_3)_2CO$
23	-(CF_3)	8.23	7.19	7.26	6.95	6.77	6.71	4.30	Ph CH_2 OCONH CH CH_2 CH_2 S CH_3 7.37; 5.16; 5.51; 4.77; 2.68; 2.30; 2.14	$CDCl_3$
24	-(CF_3)	8.23	7.19	7.26	6.95	6.77	6.71	4.29	Ph CH_2 OCONH CH CH_2 Ph 7.36; 5.15; 5.29; 4.88; 3.26; 7.36	$CDCl_3$
25	-(CF_3)	8.18	7.33	7.58	6.92	6.83	6.79	4.32	4-CH_3 $C_6H_4SO_2$ NH CH_2 CH_2 2.42; 7.43; 7.82; 6.82; 3.33; 2.89	$(CD_3)_2CO$
26	-(CF_3)	8.15	7.32	7.56	6.91	6.83	6.78	4.32	4-CH_3 $C_6H_4SO_2$ NH CH_2 CH_2 CH_2 2.43; 7.43; 7.82; 6.55; 3.92; 1.98; 2.91	$(CD_3)_2CO$
27	-(CF_3)	8.15	7.32	7.56	6.91	6.83	6.78	4.32	4-$CH_3C_6H_4SO_2$ NH CH_2 CH_2 CH_2 CH_2 CH_2 2.45; 7.44; 7.85; 6.82; 4.05; 1.92; 0.90; 1.43; 2.95	$(CD_3)_2CO$
28	8.49 (H)	8.22	7.25	7.46	7.07	6.91	7.15	4.28	ClH_3N CH (CH_3) 8.95; 4.45; 1.61	DMSO-d_6
29	8.49 (H)	8.19	7.27	7.51	7.06	6.92	7.16	4.29	ClH_3N CH CH (CH_3)$_2$ 9.05; 4.48; 2.32; 1.12	DMSO-d_6
30	8.50 (H)	8.19	7.27	7.46	7.06	6.92	7.15	4.27	ClH_3N CH CH_2 CH_2 S CH_3 9.04; 4.43; 2.76; 2.33; 2.10	DMSO-d_6
31	2.31 (Me)	8.12	7.23	7.61	6.91	6.75	6.82	4.26	ClH_3N CH (CH_3); 8.90; 4.45; 1.61	DMSO-d_6
32	2.33 (Me)	8.13	7.25	7.63	6.95	6.76	6.81	4.26	ClH3N CH CH_2 CH_2 S CH_3 9.00; 4.43; 2.76; 2.33; 2.10	DMSO-d_6
33	-(CF_3)	8.19	7.51	7.86	6.95	6.78	6.82	4.28	ClH_3N CH_2; 9.00; 4.68	DMSO-d_6
34	-(CF_3)	8.21	7.55	7.81	6.98	6.76	6.84	4.29	ClH3N CH CH (CH_3)2;9.00; 4.45; 2.31; 1.12	DMSO-d_6

TABLE 2. Physicochemical Properties of Compounds (4—34)

Compound No.	Empirical formula	Yield, %	mp, °C	Compound No.	Empirical formula	Yield, %	mp, °C
4	$C_{25}H_{25}NO_8$	81	131	20	$C_{32}H_{28}NO_8$	72	108
5	$C_{27}H_{29}NO_8$	75	118	21	$C_{32}H_{28}NO_8$	79	103
6	$C_{27}H_{29}NO_8S$	71	102	22	$C_{30}H_{24}F_3NO_8$	85	125
7	$C_{26}H_{27}NO_8$	78	127	23	$C_{31}H_{26}NO_8S$	81	112
8	$C_{28}H_{30}NO_8S$	69	93	24	$C_{35}H_{26}F_3NO_8$	87	156
9	$C_{25}H_{22}F_3NO_8$	88	154	25	$C_{28}H_{22}F_3NO_8S$	91	262
10	$C_{28}H_{28}NO_8$	81	126	26	$C_{29}H_{24}F_3NO_8S$	86	135
11	$C_{29}H_{25}NO_8$	79	132	27	$C_{31}H_{28}F_3NO_8S$	69	117
12	$C_{31}H_{29}NO_8$	76	116	28	$C_{20}H_{18}ClNO_6$	92	245
13	$C_{32}H_{31}NO_8$	71	99	29	$C_{22}H_{22}ClNO_6$	89	232
14	$C_{31}H_{29}NO_8S$	85	106	30	$C_{22}H_{22}ClNO_6S$	94	234
15	$C_{35}H_{29}NO_8$	89	152	31	$C_{21}H_{20}ClNO_6$	91	251
16	$C_{28}H_{20}F_3NO_8$	82	158	32	$C_{23}H_{24}ClNO_6S$	84	229
17	$C_{29}H_{22}F_3NO_8$	81	139	33	$C_{20}H_{15}F_3ClNO_6$	95	265
18	$C_{29}H_{22}F_3NO_8$	86	148	34	$C_{22}H_{19}F_3ClNO_6$	88	241
19	$C_{31}H_{26}NO_8$	76	121				

The structures of the compounds obtained (4—27) were confirmed by the results of quantitative elementary analysis and PMR spectroscopy. The PMR spectra of each of these compounds showed characteristic signals of an isoflavone, an amino acid residue, and a protective grouping. In the 1.4—1.5 ppm region there was a strong nine-proton signal of a Boc group; a two proton singlet in the 5.0—5.2 ppm region and a five-proton multiplet in the 7.3—7.4 ppm region belonged to the signals of the Cbz group; and characteristic for the Tos grouping were a three-proton singlet of a methyl group at 2.4 ppm and two doublets at 7.8 and 7.4 ppm.

The protective grouping was eliminated from the 7-O-Boc-aminoacylisoflavone derivatives (4—10) by acidolysis under the action of a 3 M solution of dry hydrogen chloride in glacial acetic acid at 0°C. The 7-O-aminoacylchromone hydrochlorides (28—34) so obtained were crystalline substances readily soluble in water and other polar solvents. The structures of these salts (28—34) were shown by quantitative elementary analysis and PMR spectroscopy. The PMR spectra of these substances measured in DMSO-d_6 lacked signals of the protective group, while signals of the hydrochloride of the amino group were present in the 8.9—9.1 ppm region.

EXPERIMENTAL

The course of the reactions was followed and the purity of the substances was checked by TLC on Silufol UV-254 plates in the chloroform—methanol (9:1) and (95:5) systems. PMR spectra were measured on Bruker WP 100SY and Varian VXR-300 instruments in DMSO-d_6, $CDCl_3$, and deuteroacetone relative to TMS (internal standard).

The elementary analyses for N and Cl corresponded to the calculated figures.

The initial isoflavones (1—3) were obtained as in [1—3].

General Procedure for Synthesizing the N-Protected 7-Aminoacyloxyisoflavones (4—27). A cooled (0°C) solution of 5 mmole of the appropriate N-protected amino acid in 10 ml of absolute THF was treated with 0.5 g (2.5 mmole) of DCC. The reaction mixture was stirred vigorously at 0°C for 20—20 min. The dicyclohexylurea that had precipitated was filtered off, and a solution of 2 mmole 7-hydroxychromone (1—3) in the minimum amount of absolute THF (10—20 ml) and 10 mg of DMAP were added to the mother solution. The reaction mixture was kept at 0°C with vigorous stirring for 20—30 min, the end of the reaction being determined by TLC. The solvent was evaporated off in vacuum, the residue was dissolved in 50 ml of ethyl acetate, and this solution was washed successively with 5% $NaHCO_3$ solution (2 ×25 ml), water (25 ml), and

saturated NaCl solution (25 ml). The organic phase was dried with anhydrous $MgSO_4$, the solvent was distilled off in vacuum, and the residue was crystallized from propan-2-ol. The yields and physicochemical constants of compounds (**4—27**) are given in Table 1.

General procedure for the Synthesis of the 7-Aminoacyloxyisoflavones (28—34). A solution of 2 mmole of a 7-tert-butoxycarbonylaminoacyloxy-3-hetarylchromone (**4—10**) in 5 ml of absolute THF was treated with 10 ml of a 3 M solution of hydrogen chloride in glacial acetic acid, and the mixture was kept at 0°C for 30 min. The end of the reaction was monitored by TLC. The reaction mixture was diluted with 100 ml of absolute ether, and the mixture was kept at 0°C for 30 min after which the precipitate was filtered off an dried. The yields and physicochemical constants of compounds (**28—34**) are given in Table 1.

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