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CHEMISTRY OF HETEROANALOGS OF ISOFLAVONES. 23.* SYNTHESIS OF AMINOACYL DERIVATIVES OF 3-PHENOXYCHROMONE

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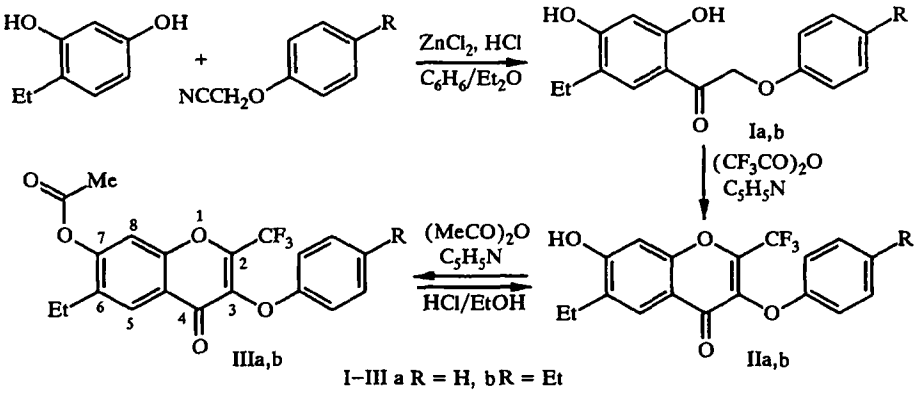
Reaction of Boc-protected amino acids with 3-phenoxy-2-trifluoromethylchromones gave new, previously unknown aminoacyl derivatives.

One of the most important problems of modern organic chemistry is the search for highly effective bioregulators having a broad spectrum of biological action at comparatively low toxicity. Modification of the structure of flavones by obtaining conjugates with amino acids is one of the routes for constructing new classes of biologically active substances, the properties of which are caused by the presence of several pharmacophore centers. As a result of biological screening among known aminoacyl derivatives of isoflavone, preparations have been found with high hypolipidemic and analeptic [3,4], hepatoprotective [5], antioxidant [3], and cholagogic [3] action. 2-Alkyl-3-phenoxychromones have been obtained recently [2]. Aminoacylation of 3-phenoxy-2-trifluoromethylchromones have been investigated in the present study.

The starting materials for the synthesis of 3-aryloxy-2-trifluoromethyl chromones were α-phenoxy-2,4-dihydroxyacetophenones Ia-b, obtained by the condensation of the corresponding aryloxyacetonitriles with 4-ethylresorcinol under the conditions of the Hoesch-Houben reaction in a mixture of ether and benzene in the presence of zinc chloride. Ketones Ia,b were high melting colorless crystalline substances, readily soluble in acetone, chloroform, and alcohols, and gave an intense red-brown coloration with an alcoholic solution of ferric chloride caused by the formation of an intramolecular complex. In the ^{1}H NMR spectra of ketones Ia,b (acetone-d_6) the proton of the hydroxyl group at position 2, participating in the formation of a hydrogen bond with the neighboring carbonyl group, was displayed as a singlet at 12.10, but the 4-OH group proton resonated at 9.51 ppm. Protons 3-H and 6-H of the phenolic fragment resonated at 6.34 and 7.73 ppm respectively, the aromatic protons of



I–III a R = H, b R = Et

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TABLE 1. Parameters of the ^1H NMR Spectra of 7- Hydroxychromones IIa,b and 7-Acetoxychromones IIIa,b

Compound	Chemical shift, δ, ppm						
	Protons of the heterocycle					Protons of the phenoxyl fragment	Solvent
	7-AcO-	7-OH	5-H	6-Et	8-H		
IIa		10.5	7.75	1.17 2.66	6.9	6.98-7.4 (2H. 6-H)	DMSO-d_6
IIb		10.5	7.74	1.17 2.66	6.9	6.98 (3-H. 5-H); 7.42 (2H. 6-H)	DMSO-d_6
IIIa	2.38		8.07	1.24 2.66	6.9	6.9-7.4 (2-H. 6-H)	$CDCl_3$
IIIb	2.38		8.07	1.23 2.64	6.9	6.98 (3-H. 5-H); 7.42 (2H. 6-H)	$CDCl_3$

the phenoxy group 3-H, 5-H, and 2-H and 6-H in compound Ib were displayed as doublets (coupling constant 8 Hz) at 7.08 and 6.84 ppm respectively. The protons of the phenoxyl fragment of compound Ia were displayed as a multiplet with center at 6.95 ppm.

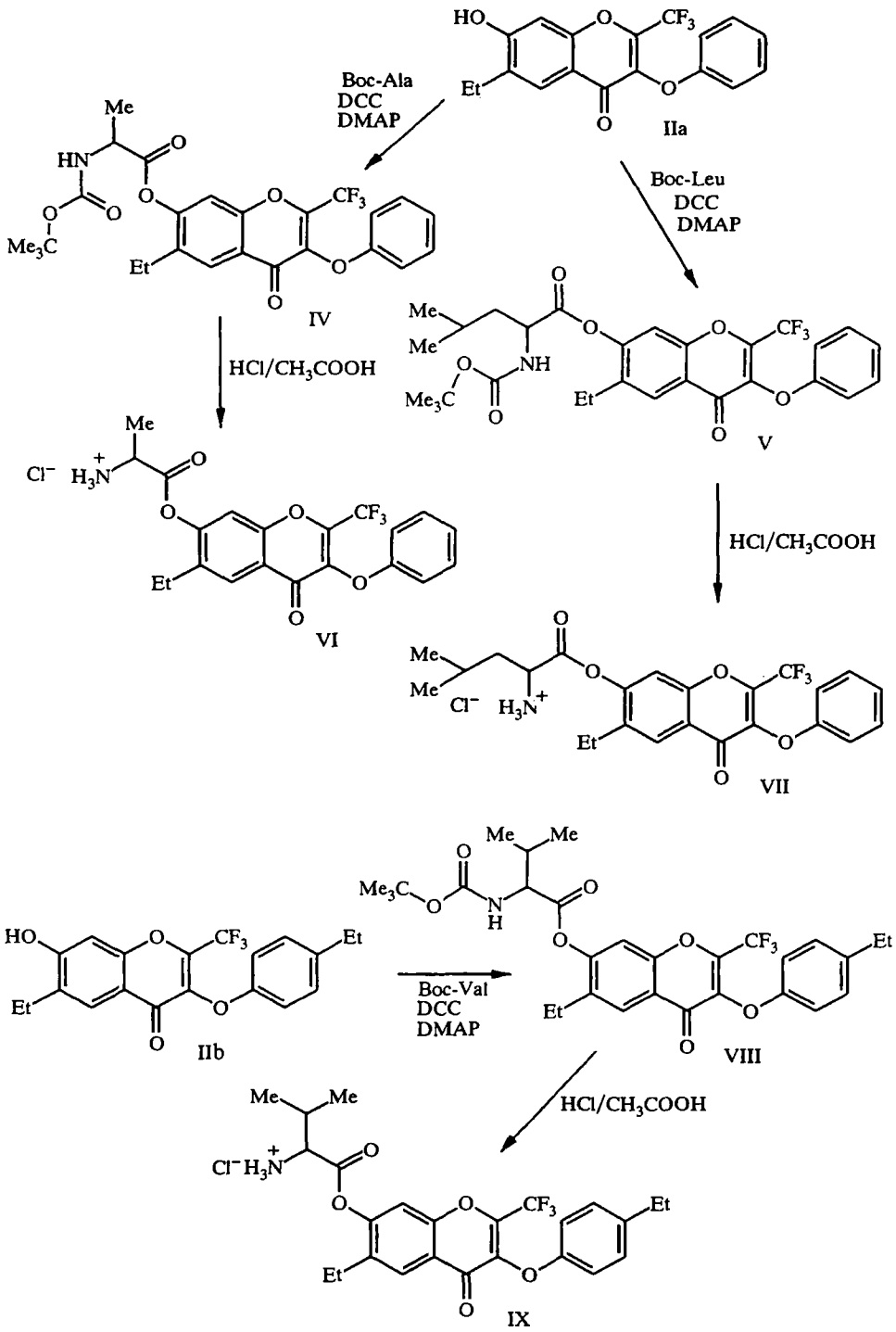
Reaction of ketones Ia,b with trifluoroacetic anhydride in pyridine leads to the formation of 7-hydroxy-3-phenoxy-2-trifluoromethylchromones IIa,b (the corresponding 7-trifluoroacetyl derivatives were unstable). Purification of the compounds was carried out through the 7-acetoxy derivatives IIIa,b with subsequent deacetylation with an ethanolic solution of hydrochloric acid on heating. The singlet for the 2-OH hydroxyl group proton of the ketone and the two-proton singlet for the α-methylene group of the initial ketone had disappeared from the proton spectra of compounds IIa,b, and there was a singlet signal for the 5-H aromatic proton at 7.74 ppm. A low field shift of the 8-H proton signal (7.0 ppm) was caused by the redistribution of electron density between the oxygen atoms after closing the ring (Table 1).

The signals for the 7-acetoxy group protons were observed at 2.38 ppm in compounds IIIa,b. The chemical shifts of the phenoxyl protons of compounds IIa,b and IIIa,b were analogous to those in the spectra of the corresponding ketones Ia,b (see Table 1).

TABLE 2. Parameters of the ^1H NMR Spectra of 7-Aminoacyloxy-chromones IV-IX

Compound	Chemical shift, δ, ppm											
	Protons of the heterocycle										Phenoxyl protons	Solvent
	5-H	6-Et	8-H	Boc-	-NH-	$-NH_2$ ·HCl	CH_3-	-CH-	$(CH_3)_2CH$-	$-CH_2$-		
IV	8.07	1.24; 2.66	6.9	1.48	5.05	—	1.61	4.69	—	—	6.9-7.4 (2-H. 6-H)	$CDCl_3$
V	8.07	1.24; 2.66	6.9	1.48	5.05	—	—	4.59	1.05; 2.50	1.90	6.9-7.4 (2-H. 6-H)	$CDCl_3$
VI	8.07	1.24; 2.66	6.9	—	—	9.08	1.69	4.51	—	—	6.9-7.4 (2-H. 6-H)	DMSO-d_6
VII	8.07	1.24; 2.66	6.9	—	—	8.91		4.35	1.0; 2.50	1.9	6.9-7.4 (2-H. 6-H)	DMSO-d_6
VIII	8.07	1.24; 2.66	6.9	1.48	5.02	—		4.50	1.10; 2.48	—	6.98 (3-H. 5-H) 7.42 (2-H. 6-H)	DMSO-d_6
IX	8.07	1.24; 2.66	6.9	—	—	8.98	—	4.29	1.19; 2.50	—	6.98 (3-H. 5-H) 7.42 (2-H. 6-H)	DMSO-d_6

The N-protected aminoacyl derivatives IV, V, and VII were obtained in good yield by the condensation of chromones IIa,b and the symmetrical anhydrides of N-*tert*-butyloxycarbonylamino acids in the presence of dimethylaminopyridine in absolute THF solution with cooling.



Deblocking the amino group with 3M HCl in glacial acetic acid solution at 0°C leads to the hydrochloride of the corresponding aminoacyl chromone VI, VII, and IX. The chemical shifts of the protons in the ^{1}H NMR spectra of aminoacyl derivatives IV-IX are given in Table 2.

TABLE 3. Physicochemical Properties of Compounds I-IX

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	N	Cl		
Ia	$C_{16}H_{16}O_4$	70.46 / 70.58	5.86 / 5.92			145.5	85
Ib	$C_{18}H_{20}O_4$	71.88 / 71.98	6.65 / 6.71			137	87
IIa	$C_{18}H_{13}F_3O_4$	61.67 / 61.72	3.69 / 3.74			106	91
IIb	$C_{20}H_{17}F_3O_4$	63.43 / 63.49	4.48 / 4.53			75	95
IIIa	$C_{20}H_{15}F_3O_5$	61.18 / 61.23	3.82 / 3.85			262	93
IIIb	$C_{22}H_{19}F_3O_5$	62.81 / 62.86	4.52 / 4.56			265	92
IV	$C_{26}H_{26}F_3NO_7$	59.81 / 59.88	5.04 / 5.09	2.63 / 2.69		165	91
V	$C_{29}H_{32}F_3NO_7$	61.78 / 61.81	5.67 / 5.72	2.40 / 2.49		147	92
VI	$C_{21}H_{19}F_3ClNO_5$	54.09 / 55.09	4.10 / 4.18	2.98 / 3.06	7.80 / 7.74	210	87
VII	$C_{24}H_{25}F_3ClNO_5$	56.95 / 57.66	4.94 / 5.09	2.75 / 2.80	7.12 / 7.09	224	86
VIII	$C_{30}H_{34}F_3NO_7$	62.31 / 62.38	5.86 / 5.93	2.37 / 2.42		142	90
IX	$C_{23}H_{27}F_3ClNO_5$	56.30 / 56.39	5.49 / 5.55	2.80 / 2.86	7.27 / 7.24	205	88

EXPERIMENTAL

The purity of compounds obtained and the progress of reactions were checked by TLC on Silufol UV 254 plates in the system chloroform–methanol, 9:1. The ^1H NMR spectra were recorded on a Bruker WP100 SY spectrometer, internal standard was TMS. The physicochemical constants and yields of compounds obtained are given in Table 3.

2,4-Dihydroxy-α-phenoxyacetophenones (Ia,b). Dry hydrogen chloride was passed for 1 h into a solution of the appropriate phenoxyacetonitrile (0.1 mol) in absolute benzene (75 ml) at 0°C. A solution of 4-ethylresorcinol (16.56 g, 0.12 mol) and freshly calcined zinc chloride (6.8 g, 0.05 mol) in dry ether (50 ml) was then added. Hydrogen chloride was passed for a further 2 h and the reaction mixture then left overnight. The liquid was decanted from the solid, hot water (400 ml) added to the residue, and the mixture boiled for 1 h. After cooling, the solid was filtered off, washed with water to pH 7, and recrystallized from 2-propanol. Yields and characteristics of the compounds obtained are given in Table 3.

7-Hydroxy-3-phenoxy-2-trifluoromethylchromones (IIa,b). A solution of ketone Ia,b (10 mmol) in pyridine (10 ml) was cooled to 0°C, and trifluoroacetic anhydride (5 ml) added slowly with stirring. The reaction mixture was left overnight at room temperature, then boiled for 2 h. After cooling, the mixture was poured into cold water (100 ml) acidified with conc. HCl (15-20 ml), and the precipitated oil triturated. The solid obtained was filtered off, thoroughly washed on the filter with water, and dried in the air. The solid was crystallized from ethyl alcohol. Characteristics and yields of the compounds obtained are given in Table 3.

7-Acetoxy-3-phenoxy-2-trifluoromethylchromones (IIIa,b). A mixture of 7-hydroxychromone IIa,b (10 mmol), acetic anhydride (2.55 g, 25 mmol), and dry pyridine (0.3 ml) was boiled for 3-4 min, and cooled to 0°C. A solid was precipitated, which was filtered off, and washed on the filter with 2-propanol. The solid was crystallized from 2-propanol. The yields and characteristics of compounds IIIa,b are given in Table 3.

7-Boc-aminoacyloxy-3-phenoxy-2-trifluoromethylchromones IV, V, and VIII. A mixture of the initial chromone IIa,b (2 mmol) and Boc-protected amino acid (5 mmol) was dissolved in absolute THF (20 ml) and cooled to 0°C. Dicyclohexylcarbodiimide (0.52 g, 2.5 mmol) and a catalytic amount of 4-dimethylaminopyridine were added to the solution. The mixture was kept for 1 h at room temperature. The end of the reaction was determined

with the aid of TLC. The THF was evaporated in vacuum and the residue dissolved in ethyl acetate (50 ml). The solution was washed twice with 5% sodium bicarbonate solution, with water, and with sodium chloride solution, then dried over sodium sulfate, and the ethyl acetate evaporated in vacuum. The residue was crystallized from isopropyl alcohol. Yields and characteristics of compounds IV, V, and VIII are given in Table 3.

7-Aminoacyloxy-3-phenoxy-2-trifluoromethylchromone Hydrochlorides VI, VII, and IX. A solution of chromone Boc-aminoacyl derivative IV, V, and VIII (2 mmol) in THF (5 ml) was cooled to 0°C, and to it was added a 3M solution (10 ml) of hydrogen chloride in glacial acetic acid. The mixture was left for 1 h at room temperature. The end of the reaction was determined from TLC data, after which the reaction mixture was diluted with dry ether (50 ml), and left in the refrigerator for several hours. The precipitated solid was filtered off and washed with ether. Yields and characteristics of compounds VI, VII, and IX are given in Table 3.

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