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2-R-6-ETHYL-7-HYDROXY-3-(5-PHENYL-1,3,4-THIADIAZOLYL-2)CHROMONES

T. V. Shokol, V. V. Semenyuchenko, and V. P. Khilya

α-(5-Phenyl-1,3,4-thiadiazolyl-2)-6-ethyl-2,4-dihydroxyacetophenone was synthesized by the condensation of 4-ethylresorcinol with 2-cyanomethyl-5-phenyl-1,3,4-thiadiazole. Interaction of the former with carboxylic acid anhydrides and halides and subsequent hydrolysis gave 2-R-6-ethyl-7-hydroxy-3-(5-phenyl-1,3,4-thiadiazoyl)chromones.

Keywords: 2-R-7-acyloxy-6-ethyl-3-(5-phenyl-1,3,4-thiadiazolyl-2)chromones, 2-R-6-ethyl-7-hydroxy-3-(5-phenyl-1,3,4-thiadiazolyl-2)chromones, α-(5-phenyl-1,3,4-thiadiazolyl-2)-6-ethyl-2,4-dihydroxy-acetophenone.

3-Hetarylchromones, the synthetic analogs of natural isoflavones, possess a wide range of biological effects [1-3]. Derivatives of 3-thiazolylchromones have anticancer activity which is increased by the introduction of a phenyl group into the thiazole ring [4]. It seemed of interest to follow the change in activity on substituting a carbon atom in the thiazole ring by a heteroatom, in particular nitrogen, i.e., to synthesize the thiadiazole analogs of isoflavone with a phenyl radical in the thiadiazole ring and to investigate their properties.

2-Cyanomethyl-5-phenyl-1,3,4-thiadiazole (**1**) was chosen as the starting material for this objective [5]. The 7-dialkylamino-3-(5-phenyl-1,3,4-thiadiazolyl-2)coumarines, isomeric to chromones, were synthesized by condensation of the starting nitrile **1** with 4-dialkylamino-2-hydroxybenzaldehyde and have found use as yellow-green fluorescent materials in textiles and plastics [6]. However 3-(5-phenyl-1,3,4-thiadiazolyl-2)-chromones have not been obtained. An attempt to synthesize 7-hydroxy-3-(-5-phenyl-1,3,4-thiadiazolyl-2)-chromone from the corresponding 2-hydroxyacetophenone using acetoformic anhydride was reported in the literature, but the reaction was only carried out qualitatively and the reaction products were not isolated [7].

With the objective of synthesizing the previously unknown 2-R-6-ethyl-7-hydroxy-3-(5-phenyl-1,3,4-thiadiazolyl-2)chromones nitrile **1** was used in the Hess reaction with 4-ethylresorcinol and boron trifluoride etherate to give, after hydrolysis, the key product – α-(5-phenyl-1,3,4-thiadiazolyl-2)-5-ethyl-2,4-dihydroxy-acetophenone (**2**) in 55% yield. It should be noted that, in contrast to the thiazole analogs [8,9] the reaction was carried out at room temperature because heating the reaction mixture led to a considerable decrease in the yield of the required product (Scheme 1).

Compound **2** can exist in keto and enol forms. The presence in the ^{1}H NMR spectrum, recorded in deuteroacetone (and also $CDCl_3$ and CD_3OD), of a two proton singlet for the methylene group at 5.05 ppm and only two weak field singlets for the hydroxy groups at 12.13 and 9.75 ppm indicates that compound **2** exists exclusively in the keto form in these solvents. Of the two hydroxy groups 2-OH, which can form a hydrogen bond with the oxygen atom of the carbonyl group, absorbs at weaker field, whereas the 4-OH group cannot

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Taras Shevchenko Kiev National University, Kiev 01033, Ukraine; e-mail: vikhilya@mail.univ.kiev.ua.
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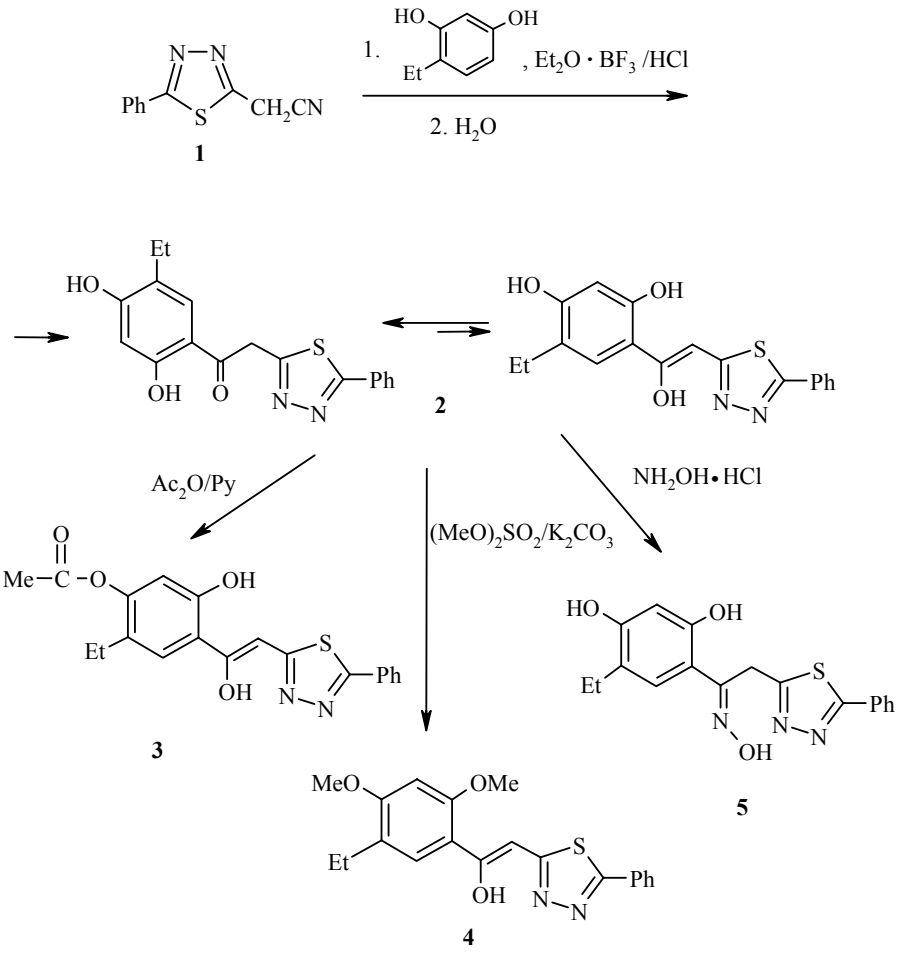
undergo such an interaction but underwent deuterium exchange on the addition of D_2O. The product **2** also exists as the keto form in $CDCl_3$ and CD_3OD. When the ^1H NMR spectrum of **2** was recorded in DMSO-d_6 both tautomers were observed as demonstrated by the appearance of a singlet for the methylene group at 6.60 ppm in addition to the singlet at 4.96 ppm and of a weak field singlet for the enol proton at 13.79 ppm. Doubling of the signals of the hydroxy groups and the aromatic protons were also observed. According to the integrated intensities, the tautomeric equilibrium consists of 85% ketone and 15% enol.

Scheme 1



On acetylation of compound **2** with an equimolar mixture of acetic anhydride and pyridine in the cold the monoacetylated derivative **3** was formed as indicated by the presence in the ^1H NMR spectrum, recorded in DMSO-d_6, along with the signals of the ethyl and aromatic protons, of a three proton singlet of the acetyl group at 2.71 ppm and a signal of only one OH group (10.29 ppm) in position 2. The weak field singlet of the enolic proton at 12.76 ppm and the singlet of the methine proton 6.28 ppm, together with the absence of a signal in the region for methylene protons indicates that the acetoxy derivative **3** in DMSO-d_6 solutions exists only in the enol form in contrast to the starting material **2**.

The monomethyl derivative was not obtained when compound **2** was alkylated with an equimolar amount of dimethyl sulfate in the presence of potassium carbonate in either acetone or benzene solution. In both cases the reaction went further and the dimethoxy derivative **4** was obtained on the addition of a further mole of dimethyl sulfate. This was confirmed by the appearance in the ^1H NMR spectrum, recorded in deuteroacetone,

of two three proton singlets at 3.87 (CH_3O-4) and 4.00 ppm (CH_3O-2) and just one weak field singlet at 13.90 ppm which we ascribe to the enol proton. Two singlets at 6.69 and 6.40 ppm were observed in the 6 ppm region, one of which belongs the methyne proton of the enol and the other to proton H-3. On addition of D_2O to the sample, the signals of the enol and methyne protons are extinguished as a result of deuterium exchange, while the singlet of the H-3 proton is unaffected (6.42 ppm). Thus, in contrast to the ketone starting material **2**, the dimethoxy derivative **4** exists as the enol form in deuteroacetone.

The oxime **5** was obtained by reaction of the ketone **2** with hydroxylamine hydrochloride in pyridine. The ^{1}H NMR spectrum of **5** has three monoprotonic weak field singlets at 11.67 (N-OH), 10.92 (2-OH), and 9.45 ppm (4-OH) and a two proton singlet for the methylene group at 4.63 ppm.

Compounds **2**, **3**, and **5** form chelate complexes with iron(III) chloride with green, blue, and violet colors respectively.

Reaction of ketone **2** with an excess of trifluoroacetic anhydride or ethyl oxalyl chloride in pyridine did not stop at the stage of the diacyl derivative but was accompanied by cyclodehydration to give condensation products. After treatment of the reaction mixture with water 2-trifluoromethyl- or 2-ethoxycarbonyl-6-ethyl-7-hydroxy-3-(5-phenyl-1,3,4-thiadiazolyl-2)chromones (**6a,b**) respectively were isolated.

TABLE 1. Characteristics of Compounds **2-7**

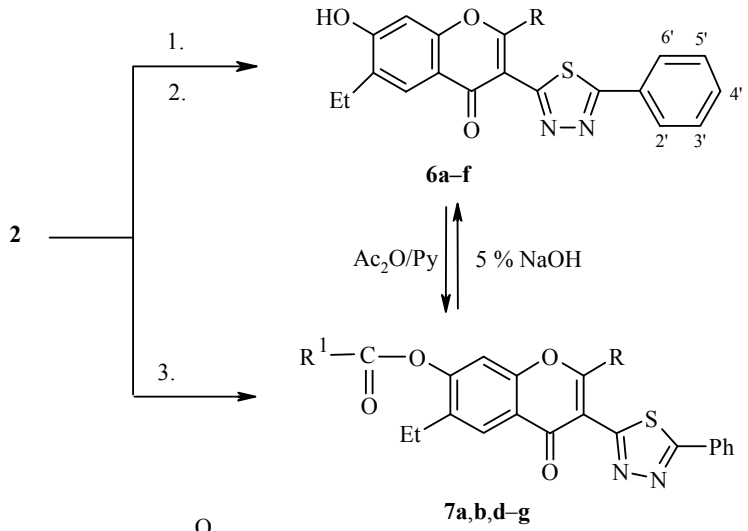
Compound	Empirical formula	Found, % / Calculated, %		mp, °C	Recrystallization solvent	Yield, %
		N	S			
2	$C_{18}H_{16}N_2O_3S$	8.50 / 8.23	9.64 / 9.42	239	Ethanol	50
3	$C_{20}H_{18}N_2O_4S$	7.58 / 7.33	8.60 / 8.38	333	Ethanol	85
4	$C_{20}H_{20}N_2O_3S$	7.57 / 7.62	8.63 / 8.73	185	Ethyl acetate	63
5	$C_{18}H_{15}N_3O_3S$	8.12 / 7.93	9.19 / 9.07	222	Ethyl acetate	58
6a	$C_{20}H_{13}F_3N_2O_3S$	6.53 / 6.70	7.87 / 7.66	256	Dioxane	86
6b	$C_{22}H_{18}N_2O_3S$	6.79 / 6.63	7.89 / 7.59	261	Dioxane	82
6c	$C_{22}H_{18}N_2O_5S$	6.85 / 6.63	7.83 / 7.59	282	Ethanol	72
6d	$C_{20}H_{16}N_2O_3S$	7.85 / 7.69	8.90 / 8.80	317	DMF	95
6e	$C_{21}H_{18}N_2O_3S$	7.66 / 7.40	8.75 / 8.47	272	DMF	84
6f	$C_{19}H_{14}N_2O_3S$	8.07 / 8.00	9.30 / 9.15	316	DMF	—*
7a	$C_{22}H_{15}F_3N_2O_4S$	6.22 / 6.09	7.26 / 6.93	155	Ethyl acetate	75
7b	$C_{24}H_{20}N_2O_6S$	6.11 / 6.03	7.19 / 6.90	199	Ethyl acetate	89
7d	$C_{22}H_{18}N_2O_4S$	7.09 / 6.89	8.06 / 7.89	188	Ethyl acetate	86
7e	$C_{24}H_{22}N_2O_4S$	6.53 / 6.45	7.52 / 7.38	167	Ethyl acetate	89
7f	$C_{21}H_{16}N_2O_4S$	7.33 / 7.14	8.32 / 8.17	197	Ethyl acetate	81
7g	$C_{22}H_{16}Cl_2N_2O_4S$	6.12 / 5.89	6.97 / 6.75	193	Acetonitrile	89

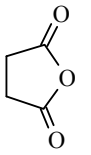
* Yield 46 (A) and 71% (B).

For the reaction of compound **2** with succinic anhydride to form 2-(β-carboxyethyl)-6-ethyl-7-hydroxy-3-(5-phenyl-1,3,4-thiadiazolyl-2)chromone (**6c**) only a brief heating until the reagents had dissolved was necessary. For the condensation of compound **2** with acetic and propionic anhydrides in triethylamine only heating for solution of **2** is necessary, further heating (in contrast to the thiazole analogs) leads only to blackening of the product and a decrease in yield. In these cases, in contrast to products **6a-c**, treatment of the reaction mixture with water did not lead to removal of the acyl group at position 7; instead 2-methyl- or 2-ethyl-substituted 7-acyloxy-6-ethyl-3-(5-phenyl-1,3,4-thiadiazolyl-2)chromones (**7d,e**) were formed. The required 7-hydroxy derivatives **6d,e** were obtained refluxing the 7-acyloxy derivatives **7d,e** for a short time with dilute sodium hydroxide.

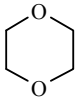
The interaction of ketone **2** with chloracetyl chloride in pyridine occurred extremely vigorously even in the cold to give a tarry product. Chromatographically pure 7-chloracetoxy-2-chloromethyl-6-ethyl-3-(5-phenyl-1,3,4-thiadiazolyl-2)chromone (**7g**) was formed in high yield by refluxing compound **2** with a two fold excess of chloroacetyl chloride and pyridine in dioxane.

6-Ethyl-7-hydroxy-3-(5-phenyl-1,3,4-thiadiazolyl-2)chromone (**6f**) was synthesized by two methods: by heating the initial ketone with ethyl orthoformate and pyridine in the presence of a catalytic amount of piperidine and by Wilsmeier formylation in the presence of boron trifluoride etherate. In the latter case the reaction goes practically at room temperature and the product obtained is purer and in much higher yield.



1. $(CF_3CO)_2O$;  ; $ClCCO_2Et$; $CH(OEt)_3$ / Py or DMF, PCl_5, $BF_3 \cdot Et_2O$;

2. H_2O;

3. Ac_2O, $(EtCO)_2O/Et_3N$ or $ClCH_2COCl$, Py / 

6 a R = CF_3, **b** R = CO_2Et, **c** R = CH_2CH_2COOH, **d** R = Me, **e** R = Et, **f** R = H; **7a** R = CF_3, R^1 = Me; **b** R = CO_2Et, R^1 = Me; **d** R = R^1 = Me; **e** R = R^1 = Et; **f** R = H, R^1 = Me; **g** R = R^1 = CH_2Cl

The 7-hydroxychromones **6a,b,f** are easily acylated with acetic anhydride in pyridine in the cold to give the 7-acetoxy derivatives **7a, b, f** in high yield. However acylation of product **6c** under the same conditions was unsuccessful.

TABLE 2. ^{1}H NMR Spectra of Compounds **2-7**

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)*
2	1.25 (3H, t, *J* = 7, CH_3); 2.65 (2H, q, *J* = 7, $C\underline{H}_2CH_3$); 5.06 (2H, s, $CH_2C(O)$); 6.43 (1H, s, H-3); 7.57 (3H, m, H_{Ph}-3',4',5'); 7.93 (1H, s, 6-H); 8.04 (2H, m, H_{Ph}-2',6'); 9.75 (1H, s, OH-4); 12.13 (1H, s, OH-2)
3	1.18 (3H, t, *J* = 7, $C\underline{H}_3CH_2$); 2.53 (2H, q, *J* = 7, $C\underline{H}_2CH_3$); 2.71 (3H, s, $CH_3C(O)O$); 6.28 (1H, s, =CH); 7.39 (1H, s, H-3); 7.57 (3H, m, H_{Ph}-3',4',5'); 7.89 (2H, d, *J* = 7, H_{Ph}-2',6'); 8.31 (1H, s, H-6); 10.29 (1H, s, OH-2); 12.76 (1H, s, HO–C=)
4	1.16 (3H, t, *J* = 7, $C\underline{H}_3CH_2$); 2.54 (2H, q, *J* = 7, $C\underline{H}_2CH_3$); 3.87 (3H, s, CH_3O-4); 4.00 (3H, s, CH_3O-2); 6.40 (1H, s, H-3); 6.69 (1H, s, =CH); 7.56 (3H, m, H_{Ph}-3',4',5'); 7.73 (1H, s, H-6); 7.89 (2H, m, H_{Ph}-2',6'); 13.90 (1H, s, HO–C=)
5	1.14 (3H, t, *J* = 7, CH_3); 2.54 (2H, q, *J* = 7, $C\underline{H}_2CH_3$); 4.63 (2H, s, $C\underline{H}_2$–C=NOH); 6.28 (1H, s, H-3); 7.29 (1H, s, H-6); 7.49 (3H, m, H_{Ph}-3',4',5'); 7.89 (2H, m, H_{Ph}-2',6'); 9.45 (1H, s, OH-4); 10.92 (1H, s, OH-2); 11.67 (1H, s, N–OH)
6a	1.24 (3H, t, *J* = 7, CH_3); 2.69 (2H, q, *J* = 7, CH_2); 6.99 (1H, s, H-8); 7.57 (3H, m, H_{Ph}-3',4',5'); 7.84 (1H, s, H-5); 8.06 (2H, m, H_{Ph}-2',6'); 11.25 (1H, s, OH)
6b	1.26 (3H, t, *J* = 7, $CH_2C\underline{H}_3$-6); 1.32 (3H, t, *J* = 7, $CO_2CH_2C\underline{H}_3$-2); 2.71 (2H, q, *J* = 7, $C\underline{H}_2CH_3$-6); 4.24 (2H, q, *J* = 7, $CO_2C\underline{H}_2CH_3$-2); 6.99 (1H, s, H-8); 7.56 (3H, m, H_{Ph}-3',4',5'); 7.89 (1H, s, H-5); 8.04 (2H, m, H_{Ph}-2',6'); 11.12 (1H, s, OH)
6c	1.25 (3H, t, *J* = 7, $CH_2C\underline{H}_3$-6); 2.70 (2H, q, *J* = 7, $C\underline{H}_2CH_3$-6); 2.83 (2H, t, *J* = 7, $C\underline{H}_2CH_2$–COOH-2); 3.66 (2H, t, *J* = 7, $CH_2C\underline{H}_2$COOH-2); 6.90 (1H, s, H-8); 7.53 (3H, m, H_{Ph}-3',4',5'); 7.84 (1H, s, H-5); 8.03 (2H, m, H_{Ph}-2',6'); 10.88 (1H, s, OH); 12.27 (1H, br. s, COOH)
6d	1.26 (3H, t, *J* = 7, $CH_2C\underline{H}_3$-6); 2.67 (2H, q, *J* = 7, $C\underline{H}_2CH_3$-6); 3.04 (3H, s, CH_3-2); 6.92 (1H, s, H-8); 7.52 (3H, m, H_{Ph}-3',4',5'); 7.84 (1H, s, H-5); 8.02 (2H, m, H_{Ph}-2',6'); 10.82 (1H, s, OH)
6e	1.25 (3H, t, *J* = 7, $CH_2C\underline{H}_3$-6); 1.46 (3H, t, *J* = 7, $CH_2C\underline{H}_3$-2); 2.67 (2H, q, *J* = 7, $C\underline{H}_2CH_3$-6); 3.44 (2H, q, *J* = 7, $C\underline{H}_2CH_3$-2); 6.92 (1H, s, H-8); 7.52 (3H, m, H_{Ph}-3',4',5'); 7.83 (1H, s, H-5); 8.03 (2H, m, H_{Ph}-2',6'); 10.85 (1H, s, OH)
6f	1.25 (3H, t, *J* = 7, CH_3); 2.67 (2H, q, *J* = 7, CH_2); 6.98 (1H, s, H-8); 7.53 (3H, m, H_{Ph}-3',4',5'); 7.89 (1H, s, H-5); 8.02 (2H, m, H_{Ph}-2',6'); 9.29 (1H, s, H-2); 10.94 (1H, s, OH)
7a	1.25 (3H, t, *J* = 7, $CH_2C\underline{H}_3$-6); 2.39 (3H, s, $CH_3C(O)O$-7); 2.69 (2H, q, *J* = 7, $C\underline{H}_2CH_3$-6); 7.58 (3H, m, H_{Ph}-3',4',5'); 7.68 (1H, s, H-8); 8.07 (3H, m, H-5 and H_{Ph}-2',6')
7b	1.26 (3H, t, *J* = 7, $CH_2C\underline{H}_3$-6); 1.32 (3H, t, *J* = 7, $CO_2CH_2C\underline{H}_3$-2); 2.39 (3H, s, $CH_3C(O)O$-7); 2.69 (2H, q, *J* = 7, $C\underline{H}_2CH_3$-6); 4.45 (2H, q, *J* = 7, $CO_2C\underline{H}_2CH_3$-2); 7.56 (3H, m, H_{Ph}-3',4',5'); 7.63 (1H, s, H-8); 8.06 (2H, m, H_{Ph}-2',6'); 8.12 (1H, s, H-5)
7d	1.26 (3H, t, *J* = 7, $CH_2C\underline{H}_3$-6); 2.38 (3H, s, $CH_3C(O)O$-7); 2.69 (2H, q, *J* = 7, $C\underline{H}_2CH_3$-6); 3.06 (3H, s, CH_3-2); 7.51 (1H, s, H-8); 7.55 (3H, m, H_{Ph}-3',4',5'); 8.04 (2H, m, H_{Ph}-2',6'); 8.08 (1H, s, H-5)
7e	1.25 (6H, t, *J* = 7, $CH_2C\underline{H}_3$-6 and $C\underline{H}_3CH_2C(O)O$-7); 1.46 (3H, t, *J* = 7, $CH_2C\underline{H}_3$-2); 2.70 (4H, m, $C\underline{H}_2CH_3$-6 and $CH_3C\underline{H}_2C(O)O$-7); 3.46 (2H, q, *J* = 7, $C\underline{H}_2CH_3$-2); 7.51 (1H, s, H-8); 7.55 (3H, m, H_{Ph}-3',4',5'); 8.02 (2H, m, H_{Ph}-2',6'); 8.07 (1H, s, H-5)
7f	1.27 (3H, t, *J* = 7, $CH_2C\underline{H}_3$-6); 2.38 (3H, s, $CH_3C(O)O$-7); 2.68 (2H, q, *J* = 7, $C\underline{H}_2CH_3$-6); 7.53 (3H, m, H_{Ph}-3',4',5'); 7.59 (1H, s, H-8); 8.03 (2H, m, H_{Ph}-2',6'); 8.13 (1H, s, H-5); 9.44 (1H, s, H-2)
7g	1.28 (3H, t, *J* = 7, $CH_2C\underline{H}_3$-6); 2.73 (2H, q, *J* = 7, $C\underline{H}_2CH_3$-6); 4.70 (2H, s, $ClCH_2C(O)O$-7); 5.51 (2H, s, CH_2Cl-2); 7.56 (3H, m, H_{Ph}-3',4',5'); 7.72 (1H, s, H-8); 8.07 (2H, m, H_{Ph}-2',6'); 8.14 (1H, s, H-5)

* Spectra were recorded in deuteroacetone (compounds **2** and **4**) and DMSO-d_6 (the rest).

The chromones **6** are colorless high melting compounds. In their ^{1}H NMR spectra there are signals of the ethyl group protons at position 6, signals of the aromatic protons of the phenyl groups, singlets of the aromatic protons of chromone H-8 (6.90-6.99 ppm and H-5 (7.83-7.89 ppm), a weak field singlet of the 7-OH group in the 10.82-11.25 ppm range, and also for the corresponding substituents at position 2 (Table 2).

The stretching vibrations of the C=O groups of the chromone ring were observed in the range 1635-1610 cm^{-1} in their IR spectra.

In the ^1H NMR spectra of the 7-acetoxy derivatives **7a,b,d,f** the weak field singlet s missing and a three proton singlet of the acetoxy groups appears in the 2.38-2.39 ppm range. In the spectrum of the 7-propionyl derivative **7e** the signals of this group and of the ethyl group in position 6 overlap, but the signals of the 2-CH_2CH_3 group appear at weaker field. The ^1H NMR spectrum of compound **7g** is characterised by two singlets for the methylene groups of the 7-chloracetoxy group at 4.70 ppm and of the 2-CH_2Cl group at 5.51 ppm. In the IR spectra of the 7-acyloxy compounds **7** the C=O stretch of the chromone ring occurs at 1640-1650 cm^{-1} and that for the acyl groups in the 1750-1770 cm^{-1} region.

Thus starting from α-(5-phenyl-1,3,4-thiadiazolyl-2)-2,4-dihydroxy-5-acetophenone a series of 7-hydroxy-3-(5-phenyl-1,3,4-thiadiazolyl-2)-6-ethylchromones with different positions at position 2 and their 7-acyloxy derivatives have been synthesized.

EXPERIMENTAL

The purity of the compounds synthesized was monitored by TLC on Silufol UV-254 strips with 9:1 chloroform as eluant. ^1H NMR spectra were recorded on a Mercury 400 (Varian) (400 MHz) machine and IR spectra of KBr discs on a Pye-Unicam SP 3-300 spectrophotometer.

The characteristics of compounds are given in Table 1 and their ^1H NMR spectra in Table 2.

α-(5-Phenyl-1,3,4-thiadiazolyl-2)-5-ethyl-2,4-dihydroxyacetophenone (2). A stream of dry hydrogen chloride was passed through a stirred suspension of 2-cyanomethyl-5-phenyl-1,3,4-thiadiazole (**1**) (20.1 g, 100 mmol) in borontrifluoride etherate (100 ml) for 6 h at room temperature. After 1 day the reaction mixture was added in portions to hot water (700 ml) and was refluxed for 3 h with 1 ml of sulphuric acid.. The precipitate which formed was filtered hot. The crude product was reprecipitated from 5% sodium hydroxide solution with 20% acetic acid and was then refluxed in ethanol.

α-(5-Phenyl-1,3,4-thiadiazolyl-2)-4-acetoxy-5-ethyl-2-hydroxyacetophenone (3). Acetic anhydride (0.2 g, 2 mmol) was added to a solution of ketone **2** (0.68 g, 2 mmol) in pyridine (4 ml). The mixture was kept in a refrigerator for 48 h and the precipitate which formed was filtered off.

α-(5-Phenyl-1,3,4-thiadiazolyl-2)-5-ethyl-2,4-dimethoxyacetophenone (4). A mixture of ketone **2** (0.34 g, 1 mmol), freshly dried potassium carbonate (0.7 g, 4.5 mmol), and dimethyl sulfate (0.14 g, 1.1 mmol) was refluxed for 6 h in benzene or acetone. More dimethyl sulfate (0.14 g, 1.1 mol) was then added and the mixture was refluxed for further hour. The course of the reaction was monitored by TLC. The potassium carbonate was filtered off and the mother liquor evaporated.

α-(5-Phenyl-1,3,4-thiadiazolyl-2)-5-ethyl-2,4-dihydroxyacetophenone oxime (5). A solution of ketone **2** (1.02 g, 3 mmol) and hydroxylamine hydrochloride (0.63 g, 9 mmol)in absolute pyridine was refluxed for 1 h and was then kept at room temperature for 12 h. Th reaction mixture was poured into water (100 ml) and the water was changed until the oil formed did not crystallize and the residue was then filtered.

6-Ethyl-7-hydroxy-3-(5-phenyl-1,3,4-thiadiazolyl-2)-2-trifluoromethylchromone (6a). Trifluoro-acetic anhydride (4.2 g, 20 mmol) was added dropwise to a solution of ketone **(2)** (1.7 g, 5 mmol) in pyridine (10 ml) cooled to 0°C. The mixture was kept at room temperature for 48 h, poured into ice water (100 ml), and the precipitate was filtered off.

2-Ethoxy-6-ethyl-7-hydroxy-3-(5-phenyl-1,3,4-thiadiazolyl-2)chromone (6b) was synthesized analogously from ketone **2** (1.7 g, 5 mmol) and ethyl oxalyl chloride (1.56 g, 11.4 mmol).

2-(β-Carboxyethyl)-6-ethyl-7-hydroxy-3-(5-phenyl-1,3,4-thiadiazolyl-2)chromone (6c). A mixture of ketone **2** (1.7 g, 5 mmol) and succinic anhydride (3.5 g, 30 mmol) in pyridine (5 ml, 60 mmol) was heated rapidly until all had dissolved and was then kept at room temperature. After 12 h the precipitate was filtered off, washed with methanol, transferred into water (50 ml), filtered, and washed with water and methanol.

2-Alkyl-7-alkoxy-6-ethyl-3-(5-phenyl-1,3,4-thiadiazolyl-2)chromones (7d,e). A mixture of ketone **2** (1.7 g, 5 mmol), triethylamine (2.52 g, 25 mmol), and acetic or propionic anhydride (25 mmol) was rapidly heated until all had dissolved and was then kept at room temperature for 12 h. The product was isolated as for **6c**.

2-Alkyl-6-ethyl-7-hydroxy-3-(5-phenyl-1,3,4-thiadiazolyl-2)chromones (6d,e). A 5% solution of sodium hydroxide (1 ml) and water (25 ml) were added to a solution of the corresponding 7-alkoxy derivative **7d,e** (1 mmol) in ethanol (50 ml). The mixture was refluxed for 5 min, more water (25 ml) was added, the mixture was cooled, neutralized to pH 7 with hydrochloric acid, and the precipitate was filtered off.

6-Ethyl-7-hydroxy-3-(5-phenyl-1,3,4-thiadiazolyl-2)chromone (6f). A. Piperidine (3 drops) was added to a solution ketone **2** (0.68 g, 2 mmol) and ethyl orthoformate (2.1g, 12 mmol) in pyridine (4 ml) and the mixture was heated at 100°C for 45 min. . The mixture was cooled , the precipitate was filtered off an washed with water. Yield 0.32 g (46%).

B. Boron trifluoride etherate (4.23 g, 30 mmol) was added dropwise to a stirred suspension of ketone **2** (1.7 g, 5 mmol) in DMF (7.3 g, 0.1 mmol), then phosphorus pentachloride (1.25 g, 6 mmol) was added in portions, and the mixture was kept at 50°C for 15 min.. The mixture was poured into water (10 ml), refluxed for 15 min, cooled and the precipitate was filtered off. Yield 1.24 g (71%).

2-R-7-Acetoxy-6-ethyl-3-(5-phenyl-1,2,4-thiadiazolyl-2)chromones (7a,b,f). The corresponding 7-hydroxyproduct **6a,b,f** (2 mmol) was dissolved in a mixture of pyridine (2 ml) and acetic anhydride (0.82 g, 8 mmol) and kept at room temperature for 24 h. The precipitate was filtered off and washed with methanol and water.

7-Chloracetoxy-2-chloromethyl-6-ethyl-3-(5-phenyl-1,3,4-thiadiazolyl-2)chromone (7g). Pyridine (0.34 g ,4.4 mmol) and chloroacetyl chloride (0.5 g, 4.4 mmol) were added to a solution of ketone **2** (0.68 g, 2 mmol) in absolute dioxane (15 ml) and the mixture was refluxed for 6 h. The mixture was cooled, the precipitate was filtered off, the mother liquor was evaporated, treated with water and an additional amount of product was filtered off.

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