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THIAZOLE ANALOGS OF CHALCONE AND FLAVONE

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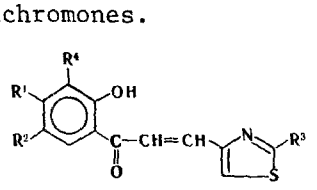
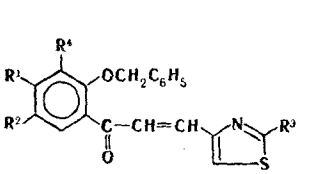
New thiazole analogs of chalcones and their epoxides were obtained. Thiazole analogs of flavone and isoflavone were synthesized for the first time on the basis of these compounds. It is shown that o-hydroxyphenylpyrazole derivatives are formed by the action of hydrazine hydrate on 2-(4-thiazolyl)chromones. The PMR spectra of the new substances are presented and discussed.

Continuing our research [1] on 2-hetarylchromones we have realized the synthesis of chromones that contain a thiazole ring in the 2 position of the pyrone ring. We became interested in these compounds because of the prevalence of the thiazole ring among natural biologically active substances and also because of the fact that some thiazole analogs of isoflavones display considerable hypolipidemic activity [2]. Thiazole analogs of chalcone (Ia-j), which were obtained by condensation of the corresponding o-hydroxyacetophenones with 2-methyl- or 2-phenyl-4-formylthiazole [3] by the method in [4], served as the starting compounds for the synthesis of 2-thiazolylchromones.



Ia-j



IIa-f

o-Benzyloxyacetophenones, which were in turn obtained by alkylation of o-hydroxyacetophenones with benzyl bromide, were used for the synthesis of thiazolylpropenones IIa-f with a protected hydroxy group in a similar condensation.

Thiazole analogs (I and II) of chalcones are primarily high-melting, crystalline, yellow compounds that are quite soluble in organic solvents. To confirm their structure we used NMR spectroscopy. The physical constants and spectral characteristics of the synthesized compounds are presented in Table 1. A narrow singlet of a hydroxy proton is observed in the PMR spectra of thiazolylpropenones Ia-j at weakest field (12.38-13.42 ppm). Its position in the spectrum changes somewhat from compound to compound; however, no correlation between the chemical shift of the signal of the hydroxy proton and the electronegativities or volumes of

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TABLE 1. Thiazole Analogs of Chalcone

Compound	R^1	R^2	R^3	R^4	mp, °C	UV spectrum, λ_{max}, nm (log ε)	PMR spectrum, δ, ppm: protons of the phenol part: 2-OH or 2-OCH_2Ph	3-H	4-R^1	5-R^2	6-H	—C—CH=CH— ‖ O	thiazole protons: 2-CH_3 or 2-Ph	4-H	S found, %	Empirical formula	S calc., %	Yield, %
Ia	H	H	CH_3	H	115	203 (4,24); 324 (4,28)	12,75	6,66—7,57			7,94	7,92; 7,70	2,74	7,36	13,0	$C_{13}H_{11}NO_2S$	13,1	71
Ib	OCH_3	H	CH_3	H	136	203 (4,43); 260 (3,80); 335 (4,32)	13,42	6,49	OCH_3 3,92	H 6,49	7,87	7,84; 7,71	2,84	7,37	12,2; N 5,3	$C_{14}H_{13}NO_3S$	11,6; N 5,1	67
Ic	CH_3	CH_3	CH_3	H	147	202 (4,54); 263 (3,89); 322 (4,33)	12,73	6,81	CH_3 2,26	CH_3 2,26	7,71	7,94; 7,74	2,80	7,41	11,8	$C_{15}H_{15}NO_2S$	11,7	65
Id	CH_3	H	CH_3	H	127	203 (4,35); 268 (3,77); 327 (4,27)	12,87	6,81	CH_3 2,38	H 6,71	7,85	7,92; 7,71	2,78	7,38	12,5	$C_{14}H_{13}NO_2S$	12,4	63
Ie	H	CH_3	CH_3	H	138	203 (4,30); 268 (3,83); 327 (4,25)	12,65	6,89	H 7,30	CH_3 2,35	7,81	7,96; 7,77	2,80	7,40	12,2	$C_{14}H_{13}NO_2S$	12,4	58
If	H	H	CH_3	CH_3	112	202 (4,31); 325 (4,29)	12,98	2,37*	H 7,25	H 6,82	7,70	7,97; 7,67	2,84	7,36	12,5	$C_{14}H_{13}NO_2S$	12,4	50
Ih	H	Cl	CH_3	H	157	203 (4,19); 225 (4,16); 330 (4,13)	12,69	6,93	H 7,39	—	7,91	7,78; 7,78	2,78	7,41	11,5; Cl 12,9	$C_{13}H_{10}ClNO_2S$	11,5; Cl 12,7	75
Ig	H	Br	CH_3	H	172	202 (4,27); 225 (4,18); 330 (4,11)	12,56	6,91	H 7,52	—	8,02	7,77; 7,77	2,87	7,40	9,6; Br 24,5	$C_{13}H_{10}BrNO_2S$	9,9; Br 24,7	73
Ii	H	OCH_3	CH_3	H	119	203 (4,36); 223 (4,21); 258 (3,99); 325 (4,34)	12,38	6,91	H 7,08	OCH_3 3,83	7,38	7,86; 7,71	2,77	7,38	11,6	$C_{14}H_{13}NO_3S$	11,6	64
Ij	CH_3	CH_3	C_6H_5	H	150	203 (4,46); 270 (4,09); 330 (4,23)	12,62	6,87	CH_3 2,41	CH_3 2,41	7,70	8,00; 7,77		7,50	10,0	$C_{20}H_{17}NO_2S$	9,6	85
IIa	H	H	CH_3	H	103	218 (4,36); 313 (4,21)	5,12	6,85—7,73				7,73; 7,51	2,68		9,7	$C_{20}H_{17}NO_2S$	9,6	90
IIb	OCH_3	H	CH_3	H	122	204 (4,61); 322 (4,25)	5,14	6,54	OCH_3 3,81	H 6,54	7,75	7,83; 7,53	2,68	7,26	8,4	$C_{21}H_{19}NO_3S$	8,8	91

IIc	CH_3	CH_3	CH_3	H	136	207 (4,41); 310 (4,23)	5,15	6,83	CH_3 2,22	CH_3 2,28	7,49	7,81; 7,53	2,70	7,27	8,8	$C_{22}H_{21}NO_2S$	8,8	70
IId	H	Cl	CH_3	H	160		5,12	6,91	7,40—7,13	—	7,53	7,58; 7,58	2,71	7,21	8,7; Cl 9,5	$C_{20}H_{16}ClNO_2S$	8,7; Cl 9,6	85
IIe	CH_3	CH_3	C_6H_5	H	136	205 (4,60); 260 (3,93); 315 (4,21)	5,13	6,82	CH_3 2,23	CH_3 2,29	7,87	6,91—8,05		7,25	7,5	$C_{27}H_{23}NO_2S$	7,5	90
IIf	H	H	C_6H_5	H	113		5,19		6,75—7,8						8,1	$C_{25}H_{19}NO_2S$	8,0	77
IIIa	H	H	CH_3	H	116	212 (4,44); 255 (4,06); 318 (3,64)	5,07; 7,26		6,80—7,46		7,79	4,90; 4,14†	2,62	7,04	8,9	$C_{20}H_{17}NO_3S$	9,1	68
IIIb	OCH_3	H	CH_3	H	121	237 (4,20); 280 (4,03); 318 (3,94)	5,01; 7,24	6,47	OCH_3 3,80	H 6,55	7,87	4,87; 4,08†	2,60	7,01	8,2	$C_{21}H_{19}NO_4S$	8,4	65
IIIc	CH_3	CH_3	CH_3	H	77	208 (4,37); 268 (4,05); 325 (3,65)	4,96; 7,08	6,64	CH_3 2,24	CH_3 2,29	7,40	4,82; 4,08†	2,63	6,84	8,4	$C_{22}H_{21}NO_3S$	8,5	90
IIId	CH_3	CH_3	C_6H_5	H	115	205 (4,56); 270 (4,20)	4,98; 7,08	6,75	CH_3 2,24	CH_3 2,21	7,58	4,91; 4,20†		7,05	7,4	$C_{27}H_{23}NO_3S$	7,3	65
IIIe	H	H	C_6H_5	H	115	203 (4,60); 215 (4,05); 300 (4,13)	4,94; 6,91		6,74—7,66			4,86; 4,18†	6,74—7,66		7,8	$C_{25}H_{19}NO_3S$	7,8	70

*The CH_3 protons.

†The protons of the epoxide fragment.

TABLE 2. 2- and 3-Thiazolylchromones

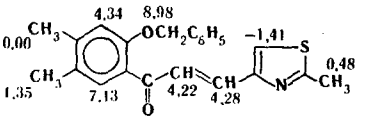
Compound	mp, °C	UV spectrum, λ_{max}, nm (log ε)	PMR spectrum, δ, ppm							S found, %	Empirical formula	S calc., %	Yield, %
			chromone protons					thiazole protons					
			3-H	5-H	6-R	7-R	8-H	2-CH_3	5-H				
IVa	160	210 (4,48); 310 (4,34)	7,77	8,04	H 6,93	OCH_3 3,92	6,83	2,77	6,99	11,6	$C_{14}H_{11}NO_3S$	11,7	40
IVb	182	206 (4,45); 265 (4,13); 308 (4,34)	7,75	7,86	CH_3 2,34	CH_3 2,37	7,21	2,77	7,01	11,7	$C_{15}H_{13}NO_2S$	11,8	25
IVc	167	205 (4,42); 208 (4,05); 223 (4,30); 306 (4,35)	7,79	8,04	H 7,14	CH_3 2,46	7,22	2,76	7,03	12,3	$C_{14}H_{11}NO_2S$	12,5	30
V	201	203 (4,61); 258 (4,54); 300 (4,16);	8,99*	8,47	CH_3 2,36	CH_3 2,36	7,20	—	7,98	9,4	$C_{20}H_{15}NO_2S$	9,6	33

*Chromone 2-H

the substituents in either the benzene or thiazole rings of the investigated chalcone analogs was observed. The signals of the olefinic protons of products Ia-j form an AB system with a small (up to 0.2 ppm) difference between the chemical shifts of the doublets corresponding to each of the protons. The constant of coupling of the olefinic protons (14-15 Hz) indicates the trans structure of all of the products obtained. The signals of the remaining aromatic and aliphatic protons are located in the regions of the spectrum that are characteristic for nuclei situated in the given magnetic environment (see Table 1).

In the case of benzyl derivatives IIa-f the PMR spectra in the aromatic region have a complex form because of the superimposition of the signals of the protons of the chalcone and benzyl fragments of the molecule. To simplify the spectra and assign the signals we used the lanthanide shift reagent (LSR) europium(III) tris(1,1,1,2,2,3,3,-heptafluoro-7,7-dimethyl-octane-4,6-dionate)[Eu(FOD)$_3$]. We found that thiazolylpropenones IIa-f form adducts with Eu(FOD)$_3$, the PMR spectra of which contain significant induced shifts of the signals (see also [5]). Signals of all of the aromatic protons can be observed individually at a certain LSR:substrate ration, and by extrapolation of the induced shifts to zero concentration of the LSR one can precisely determine the positions of the signals in the spectra recorded in the absence of a shift reagent. We used this method to find some of the chemical shifts of IIa-f presented in Table 1.

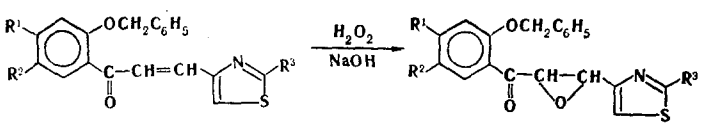
It is interesting to note that in the case of interaction of the benzylated analogs of chalcones with Eu(FOD)$_3$ one observed diamagnetic shifts in addition to paramagnetic shifts. Thus in the case of IIc we obtained the following specific induced shifts (in parts per million):*



The greatest shifts are observed for the signal of the benzyl methylene group, the signals of the olefin protons, and the signals of the protons of the benzene ring of IIc. This indicates coordination of the LSR at the carbonyl group or at the ether oxygen atom. However, attempts to establish the geometrical structure of the LSR–substrate adduct by the method in [6] with the aid of the McConnell–Robertson formula were unsuccessful. It is likely that both of these coordination centers participate in complexing with the LSR. The weak induced shifts of the signals of the protons of the thiazole ring indicate the absence of an appreciable interaction of the shift reagent with the thiazole nitrogen atom.

It is apparent from Table 1 that the chemical shifts of the signals of the olefinic protons of IIa-f are extremely close, and this makes it impossible to make a reliable assignment. The LSR method also proved to be inadequate for this purpose in view of the fact that the induced shifts for the signals of these protons also virtually coincide. In order to make a reliable assignment we synthesized deuterated analogs of the series of IIa-f products. For this, the preparation of thiazolylpropenone was carried out in deuterated methanol in the presence of NaOD. Under these conditions, as a consequence of enolization, the acetyl group of the starting acetophenone is deuterated, while the aldehyde proton of the thiazole component undergoes virtually no exchange by deuterium. As a result of the reaction we obtained a propenone in which a deuterium atom is found in the olefinic fragment adjacent to the carbonyl group. Recording of the PMR spectra of the deuterated products showed that the signal of the olefinic proton closest to the carbonyl group is located at weaker field.

Epoxides IIIa-e are formed in the reaction of thiazole analogs IIa-c,e,f with hydrogen peroxide in an alkaline medium, in agreement with the data in [4]. The PMR spectra of the



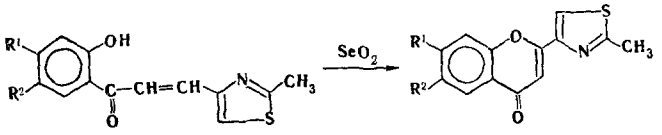
IIa-c, e, f IIIa-e

epoxides obtained in this way differ from the spectra of the starting compounds in that two doublets with coupling constant 2.5-3 Hz that correspond to the signals of the protons of

*The shift of a signal to weak field is regarded as positive.

the epoxide ring appear in place of the AB system of olefinic protons. One of the signals is located at 4.08-4.20 ppm, while the other is located at 4.8-4.9 ppm (Table 1). For the positive assignment of the signals we obtained epoxides from deuterated thiazolylpropenones. A singlet at around 4.1 ppm is observed in the PMR spectra of these products. Thus the weak-field signal of epoxides IIIa-e corresponds to the proton located near the carbonyl group.

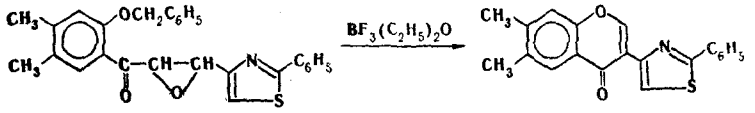
Thiazolylpropenones Ib-d were converted to thiazole analogs IVa-c of flavone by oxidative cyclization with selenium dioxide in amyl alcohol [7].



Ib,d IVa-c

Ib, IVa $R^1=OCH_3$, $R^2=H$; Ic, IVb $R^1=R^2=CH_3$; Id, IVc $R^1=CH_3$, $R^2=H$

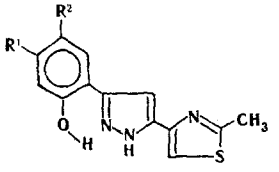
In order to obtain thiazole analogs of isoflavone we made an attempt to carry out the rearrangement of epoxide IIIb under the influence of boron trifluoride etherate by the method in [8]; however, this attempt was unsuccessful for epoxides IIIa-c. 3-(2-Phenyl-4-thiazolyl)-6,7-dimethylchromone (V) was obtained in low yield (33%) when this reaction was carried out with IIId, which contains a phenyl group in the 2 position of the thiazole ring:



IIId V

Compounds IV and V are colorless crystalline substances with high melting points that are soluble in organic solvents. Their physical constants and spectral parameters are presented in Table 2. The structure of chromones IV and V is confirmed by their PMR and UV spectra. Thus the PMR spectrum of V contains a singlet at 8.99 ppm, which is characteristic for the signal of a proton in the 2 position of the chromone system, while the spectra of IVa-c contain a singlet at 7.75-7.80 ppm, which corresponds to the signal of the proton in the 3 position. In addition, the signal of the 5-H proton of the chromone ring is located at weaker field (by 0.3-0.4 ppm) than the signal of the corresponding proton in the starting epoxide.

It is known [9, 10] that chromones do not give the normal carbonyl reaction with hydrazine hydrate but rather undergo recyclization to o-hydroxyphenylpyrazole derivatives. Reaction products VIa,b were obtained by the action of hydrazine hydrate on alcohol solutions of 3-(4-thiazolyl)chromones IVa,b. They readily dissolve in a 2 N solution of sodium hydroxide and give a blue-green coloration with an alcohol solution of ferric chloride; this constitutes evidence for the development of a phenolic hydroxy group in their molecules. However, the rate of formation of pyrazoles (1 h for VIa and 3 h for VIb) proved to be considerably slower than for the analogous derivatives of 3-hetarylchromones, which undergo instantaneous recyclization [11].



VIa $R^1=OCH_3$, $R^2=H$; b $R^1=R^2=CH_3$

The structure of the resulting pyrazoles is confirmed unambiguously by their PMR spectra: A broad signal of a phenolic hydroxy group is observed at 12.9-13.2 ppm, a narrower NH signal is observed at 10.3-10.5 ppm, and a signal at 7.47-7.50 ppm, which corresponds to the 6-H proton of the phenolic part of the pyrazole molecule, is observed in the spectrum instead of the signal of the 5-H proton of the chromone ring at 7.86-8.04 ppm. The shift of the signal to strong field may be associated with the noncoplanarity of the pyrazole molecule and, consequently, with the weaker effect of the unshared electron pair of the pyrazole nitrogen atom on the shift of the signal of the 6-H proton as compared with the signal of the 5-H proton of the starting chromone.

EXPERIMENTAL

The purity of the compounds obtained was monitored by thin-layer chromatography (TLC) on Silufol UV-254 plates in benzene–ethanol systems (90:10 or 95:5). The UV spectra of $0.3 \cdot 10^{-4}$ mole solutions of the compounds in alcohol were recorded with a Specord UV-vis spectrophotometer. The PMR spectra of solutions in $CDCl_3$ were measured with a ZKR-60 spectrometer relative to tetramethylsilane as the internal standard.

1-(2-Hydroxyphenyl)-3-(4-thiazolyl)propenones (Ia-j) and 1-(2-Benzyloxyphenyl)-3-(4-thiazolyl)propenones (IIa-f). A 6-ml sample of 50% sodium hydroxide solution was added with stirring to a heated (to 80-90°C) alcohol solution of 20 mmole of 4-formylthiazole and 20 mmole of the corresponding acetophenone, after which the mixture was allowed to stand at room temperature for 24-48 h. The resulting precipitate was suspended in water, and the suspension was neutralized with dilute acetic acid. The solid material was removed by filtration and recrystallized from alcohol or aqueous alcohol.

1-(2-Benzyloxyphenyl)-3-(4-thiazolyl)-2,3-epoxy-1-propenones (IIIa-e). A 3-ml sample of 30% hydrogen peroxide and 4.7 ml of 2 N sodium hydroxide solution were added at 20°C to a solution of 4.7 mmole of IIa-c,e,f in the minimum amount of a mixture (5:1) of acetone and methanol, and the mixture was allowed to stand at 20°C until the solution became colorless. The solution was then diluted with water, and the resulting precipitate was removed by filtration and recrystallized from a mixture of benzene and petroleum ether.

2-(4-Thiazolyl)chromones (IVa-c). A 48-mmole sample of finely ground selenium dioxide was added to a solution of 16 mmole of the 1-(2-hydroxyphenyl)-3-(4-thiazolyl)propenone (Ib-d) in the minimum amount of freshly distilled amyl alcohol, and the mixture was refluxed for 30-50 h with monitoring of the course of the reaction by means of TLC. The selenium metal was removed by filtration, and the amyl alcohol was evaporated *in vacuo* (with a water aspirator). The residue was recrystallized successively from aqueous alcohol and heptane.

3-(2-Phenyl-4-thiazolyl)-6,7-dimethylchromone (V). This compound was obtained by the method in [8].

3-(2-Hydroxy-4,5-dimethylphenyl)-5-(2-methyl-4-thiazolyl)pyrazoles (VIa,b). A 12-mmole sample of hydrazine hydrate was added to a solution of 1 mmole of IVa,b in the minimum amount of alcohol, and the mixture was refluxed for 1-3 h with monitoring of the course of the reaction by means of TLC. The reaction mixture was then added to 50-60 ml of water, and the precipiate was removed by filtration to give colorless needles of VIa (90%) with mp 176°C (from aqueous alcohol). UV spectrum in alcohol, λ_{max} (log ε): 214 (4.57), 257 (4.47), and 300 nm (4.03). PMR spectrum (in DMSO): protons of the phenolic part: 12.94 (2-OH), 6.45 (3-H), 3.76 (4-OCH_3), 6.43 (5-H), and 7.50 (6-H); pyrazole protons: 10.57 (N–H) and 7.64 (4-H); thiazole protons: 2.78 (2-CH_3) and 6.97 ppm (5-H). Found: S 11.4%. $C_{14}H_{13}N_3O_2S$. Calculated: S 11.2%. Compound VIb was obtained in 85% yield as colorless needles with mp t 192°C (from alcohol). UV spectrum in alcohol, λ_{max} (log ε): 215 (4.59), 258 (4.42), and 305 nm (3.97). PMR spectrum (in DMSO): protons of the phenolic part: 13.19 (2-OH), 6.72 (3-H), 2.18 (4-CH_3 and 5-CH_3), and 7.47 (6-H); thiazole protons: 2.72 (2-CH_3) and 7.12 (5-H); pyrazole protons: 10.33 (N–H) and 7.79 ppm (4-H). Found: N 14.6; S 11.3%. $C_{15}H_{15}N_3OS$. Calculated: N 14.7; S 11.2%.

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