CHEMISTRY OF HETEROANALOGS OF ISOFLAVONES

II. *SYNTHESIS AND PROPERTIES OF THIAZOLE ANALOGS OF ISOFLAVONES

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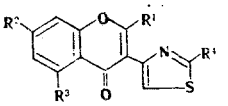
Thiazole analogs of natural isoflavones were synthesized, and their reactions with alkalis, phosphorus pentasulfide, and alkylating and acylating agents were studied. Data on the biological activity of the compounds are presented.

Continuing our studies of thiazole analogs of isoflavones, we have obtained new 3-(4-thiazolyl)chromones with structure A. We used two methods to obtain chromones without substituents in the 2 position from the acetophenones (I-III) that we previously obtained in [1]. In one of these two methods, the indicated acetophenones were treated with excess methyl formate in a condensation of the Claisen type [2] with subsequent cyclization of the α-formylacetophenones to IV-VI.



A

In the second method, which consisted in heating acetophenones I-III with ethyl orthoformate in pyridine in the presence of catalytic amounts of piperidine [3], the chromone system was formed immediately, and chromones IV-VI were isolated directly from the reaction mixture without additional treatment. The two methods give practically identical yields of the chromones.

The thiazole analogs of natural isoflavones can also be synthesized by removal of the 2-ethoxycarbonyl group from the appropriate chromones by heating them with pyridine hydrochloride [2]; this was shown in the case of chromone VII, previously obtained in [1]. This reaction served as an additional proof of the formation of IV from acetophenone I, but this method for the synthesis of 2-unsubstituted chromones is less convenient than direct ring closing of 2,4-dihydroxyacetophenones.

The synthesis of chromones containing a trifluoromethyl group in the 2 position seems of definite interest. This was achieved by reaction of trifluoroacetic anhydride with pyridine solutions of ketones I-III. The same method was used to obtain 2-trifluoromethyl chromones VIII-X and XXVIII-XXX from α-(2-methyl-4-thiazolyl)-2,4,6-trihydroxy-, α-(4-thiazolyl)-2,4-dihyroxy-6-methyl- and α-(4-thiazolyl)-2,6-dihydroxy-4-methylacetophenones [1, 4]. Acetyl (XI-XIII) or methyl (XIV-XVII) derivatives at the 7-hydroxy group were synthesized for IV-VI and IX and X, and the acetyl derivatives can be successfully used for the preparation of α-thiazolyl-2-hydroxy-4-methoxyacetophenones XVIII and XIX, inasmuch as nonsolidifying oils were formed in attempts to directly methylate the 4-hydroxy group of acetophenones I-III with methyl iodide or dimethyl sulfate.

*See [2] for communication I.

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TABLE 1. Characteristics of the 3-Thiazolylchromones (A)*

Compound	R^1	R^2	R^3	R^4	mp, °C	Empirical formula	S, % found	S, % calc.	λ_{max}, nm (lg ε) in ethanol–dioxane (40:1)	λ_{max}, nm (lg ε) in ethanol	ν_{as} of the thiazole ring, cm^{-1}	$\nu C=O$ of the chromone, cm^{-1}	$\nu C=C$ of the chromone, cm^{-1}	ν_{OH}, cm^{-1}	Yield, %, by methods: a	b	other
IV	H	OH	H	H	252	$C_{12}H_7NO_3S$	13,2	13,1	307 (3,94)	305 (4,00)	1515	1629	1585	3280	89	92	83
V	H	OH	H	CH_3	284	$C_{13}H_9NO_3S$	12,3	12,4	308 (4,08)	305 (3,85)	1505	1630	1590	3100	93	91	
VI	H	OH	H	C_6H_5	299	$C_{18}H_{11}NO_3S$	10,0	10,0	303 (4,27)		1515	1625	1583	3235		92	
VIII	CF_3	OH	H	H	189	$C_{13}H_6F_3NO_3S$	10,3	10,2	310 (3,70)		1520	1650	1605	3280			63
IX	CF_3	OH	H	CH_3	157	$C_{14}H_8F_3NO_3S$	9,9	9,8	310 (3,81)		1525	1660	1615	3500			82
X	CF_3	OH	H	C_6H_5	248	$C_{19}H_{10}F_3NO_3S$	8,4	8,2	297 (3,97)		1516	1650	1602	3230			68
XI	H	$OCOCH_3$	H	H	179	$C_{14}H_9NO_4S$	11,2	11,5	310 (3,96)	305 (3,96)							85
XII	H	$OCOCH_3$	H	CH_3	186	$C_{15}H_{11}NO_4S$	10,7	10,6	310 (3,86)	305 (3,99)	1519	1644	1620				82
XIII	H	$OCOCH_3$	H	C_6H_5	185	$C_{20}H_{13}NO_4S$	8,9	8,8	303 (4,28)	300 (4,38)							88
XIV	H	OCH_3	H	H	171	$C_{13}H_9NO_3S$	12,2	12,4								80	64
XV	H	OCH_3	H	C_6H_5	186	$C_{19}H_{13}NO_3S$	9,4	9,6							70	71	84
XVI	CF_3	OCH_3	H	CH_3	169	$C_{15}H_{10}F_3NO_3S$	9,5	9,4			1510	1662	1619				74
XVII	CF_3	OCH_3	H	C_6H_5	162	$C_{20}H_{12}F_3NO_3S$	7,9	8,0									80
XXV†	CH_3	OCH_3	H	H	167	$C_{14}H_{11}NO_2S_2$	22,1	22,2		375 (4,45) 315 (4,24)	1496	1620	1603				64
XXVI†	CH_3	OCH_3	H	CH_3	178	$C_{15}H_{13}NO_2S_2$	20,8	21,1		375 (4,41) 317 (4,17)	1507	1622					75
XXVII†	CH_3	OCH_3	H	C_6H_5	182	$C_{20}H_{15}NO_2S_2$	17,8	17,5		375 (4,13) 310 (4,12)	1500	1622	1610				69
XXVIII	CF_3	OH	OH	CH_3	210	$C_{14}H_8F_3NO_4S$	9,1	9,3	310 (3,72) 330 (3,66)		1525	1670	1595	3540			44
XXIX	CF_3	OH	CH_3	H	274	$C_{14}H_8F_3NO_3S$	10,1	9,8	308 (3,94)		1483	1660	1605	3255			58
XXX	CF_3	CH_3	OH	H	125	$C_{14}H_8F_3NO_3S$	9,8	9,8	330 (3,42)		1515	1660	1607				80
XXXIII	CH_3	$OCH_2COOC_2H_5$	H	H	106,5	$C_{17}H_{15}NO_5S$	9,3	9,4									71
XXXIV	CH_3	OCH_2COOH	H	H	209	$C_{15}H_{11}NO_5S$	10,2	10,1									95
XXXV	CH_3	OCH_2CONH $HOCH_2CH_2$	H	H	190,5	$C_{17}H_{16}N_2O_5S$	8,9	8,9									86

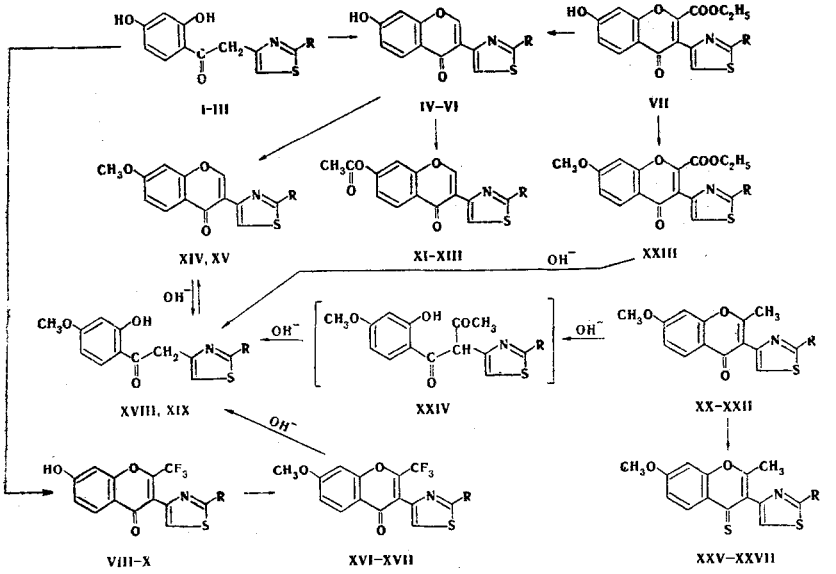
*All of the compounds were obtained as needles that crystallized from aqueous alcohol.

†Data for the thiones are presented.

TABLE 2. Results of Tests for the Antiblastic Activity of Thiazole Analogs of Isoflavones (A)

R^1	R^2	R^3	R^4	Zone diameter, mm, for the following concentrations, μg/ml		
				10	20	30
CH_3	OH	H	H	15	20	
CH_3	OH	H	CH_3	20	20	25
CH_3	OH	H	C_6H_5	50	55	65
CH_3	OCH_3	H	C_6H_5	30	40	
H	$OCOCH_3$	H	C_6H_5	30	40	
H	OH	H	H	15	20	
H	OH	H	CH_3	40	40	50
$COOC_2H_5$	OH	H	H	0	10	
$COOC_2H_5$	OH	H	CH_3	0	10	
$COOC_2H_5$	OH	H	C_6H_5	40	45	50
$COOC_2H_5$	OCH_3	H	C_6H_5	0	10	
CF_3	OH	H	H	0	10	
CF_3	OH	H	CH_3	0	10	
CF_3	OH	H	C_6H_5	0	10	
CF_3	OCH_3	H	C_6H_5	0	10	
CH_3	OH	CH_3	H	0	10	
CH_3	OH	CH_3	CH_3	20	30	30
CH_3	OH	CH_3	C_6H_5	15	20	
CH_3	CH_3	OH	H	0	10	
CH_3	CH_3	OH	CH_3	0	10	
CH_3	OH	OH	CH_3	35	45	
$COOC_2H_5$	OH	OH	CH_3	15	20	
CF_3	OH	OH	CH_3	0	10	
CH_3	OCH_2COOH	H	H	15	20	
CH_3	$OCH_2CONHCH_2CH_2OH$	H	H	15		

We studied the action of alkalis on 3-thiazolylchromones with structures XIV and XVII and on the previously prepared [1] XX, XXII, and XXIII.



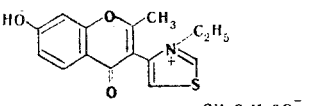
I, IV, VII, VIII, XI, XIV, XVIII, XX, XXIII, XXV R = H; II, V, IX, XII, XVI, XXI, XXVI R = CH_3; III VI, X, XIII, XV, XVII, XIX, XXII, XXVII R = C_6H_5

When the indicated chromones were heated with a fourfold excess of 5% aqueous sodium hydroxide solution, the pyrone ring opened to give ketones XVIII and XIX, probably through a step involving the formation of α-acylacetophenones of the XXIV type. It should be noted that the rate of alkaline cleavage depends on the nature of the substituents in the 2 position of the chromone. 3-Thiazolychromones with electron-acceptor substituents and 2-unsubstituted chromones undergo more rapid ring opening than the corresponding 2-methylchromones. The presence of a free 7-hydroxy group markedly stabilizes the chromones with respect to the action of alkalis. Ring opening of these compounds under similar conditions proceeds very slowly, and the products are obtained in low yields and are difficult to purify. The 4-methoxyacetophenones (XVIII and XIX) obtained by opening of 7-methoxychromones XIV, XXII, and XVII were recyclized to

XIV and XV by reaction with methyl formate or ethyl orthoformate, and this was an additional confirmation of the structure of the chromones mentioned above.

We replaced the carbonyl oxygen atom of the chromones by a sulfur atom by heating XX-XXII in pyridine with phosphorus pentasulfide. The formation of thiones shows up distinctly in the UV spectra with respect to the shift in the absorption maximum to the long-wave region by 80 nm as compared with the starting compounds [1]. In contrast to the starting colorless chromones, the thiones obtained are red-orange crystalline substances.

In the alkylation of 7-hydroxychromones the formation of derivatives involving the nitrogen atom of the thiazole ring, in addition to derivatives involving the phenolic hydroxyl group, is possible. Thus in the reaction of 2-methyl-3-(4-thiazolyl)-7-hydroxychromone [1] with ethyl bromoacetate in acetone solution in the presence of potassium carbonate, alkylation takes place at the 7-hydroxy group, whereas when it is heated with ethyl p-toluenesulfonate the nitrogen atom of the thiazole ring undergoes reaction to give quaternary salt XXXI.



XXXI

For convenience in pharmacological tests of the compounds obtained from 2-methyl-3-(4-thiazolyl)-7-ethoxycarbonylmethoxychromone (XXXIII), water-soluble compounds – acid XXXIV and amide XXXV – were prepared.

The 3-thiazolylchromones and their derivatives are colorless crystalline substances with rather high melting points and are quite soluble in ordinary organic solvents. The structure of the new substances is confirmed by the results of elementary analysis, UV and IR spectra (Table 1), and, in a number of cases, by alternative syntheses.

Tests of the antiblastic activity of the synthesized thiazole analogs of isoflavones were made in vitro experiments by the method of series cultures and diffusion in agar-agar [5, 6] at concentrations from 10 to 30 μg of the substance per milliliter of solvent. Staphylococcus aureus UF_3 was used as the starting test culture. The activity of the tested compound was evaluated from the diameter of the zone in which the growth of the Staphylococcus aureus UF_3 was absent. A 10 μg per milliliter sample of the individual substance was taken for the quantitative evaluation of the activity per unit effect. The data presented in Table 2 constitute evidence for a relationship between the biological activity of the 3-thiazolylchromones and their structure. The nature of substituent R^1 and R^4 has a particularly pronounced effect on the physiological activity of the investigated chromones. Thus, for example, 2-methyl-3-(2-phenyl-4-thiazolyl)-7-hydroxychromone displays considerable antiblastic activity. Replacement of the phenyl group in the thiazole ring of this chromone by a methyl group or a hydrogen atom and increasing the electronegativity of substituent R^1 are accompanied by a sharp drop in the biological activity.

EXPERIMENTAL METHOD

The UV spectra of ethanol solutions of the compounds ($2 \cdot 10^{-5}$ and $5 \cdot 10^{-5}$ mole) and of ethanol solutions of the compounds containing dioxane ($2 \cdot 10^{-5}$ mole) were recorded with SF-4A and Unicam SP-800 spectrophotometers, respectively. The IR spectra of KBr pellets of the compounds were recorded with a UR-10 spectrometer. The purity of the chromones was monitored by thin-layer chromatography (TLC) on Merck G silica gel. A mixture of chloroform and methanol (9 : 1) and, in some cases, a mixture of benzene and ethanol (95 : 5) were used as the eluents.

3-Thiazolyl-7-hydroxychromones (IV-VI). A) A 10-mmole sample of sodium tert-butoxide was added with stirring in an atmosphere of an inert gas to a cooled (to 0-3°) solution of 1 mmole of acetophenone (I-III) in 4 ml of dry methyl formate. After 10-15 min, the mixture was heated to 22° and stirring was continued for 3 h, after wich the solvent was evaporated, and the dry residue was treated with 45 ml of 1% hydrochloric acid solution to pH 1, and the resulting precipitate was removed by filtration. An alcohol solution of the precipitate was refluxed with hydrochloric acid (0.5 ml of concentrated HCl per gram of the compound) for 10 min. The mixture was cooled, and the solid was removed by filtration and washed with water to remove the acid.

B) A mixture of 1 mmole of acetophenone (I-III) and 6 mmole of ethyl orthoformate in 1 ml of pyridine was heated in the presence of one to two drops of piperidine at 120-130° for 3-5 h (the end of the reaction was determined from a negative test with an alcohol solution of ferric chloride or by chromatography). The mixture was then poured into 25 ml of water, and the solid product was removed by filtration.

3-(4-Thiazolyl)-7-hydroxychromone (IV). A mixture of 0.63 g (2 mmole) of VII and 2.1 g (18 mmole) of pyridine hydrochloride was heated gradually with raising of the temperature from 160-170° to 210-220° in 1 h (the end of the reaction was determined from cessation of the evolution of bubbles of carbon dioxide), after which it was diluted with 6 ml of water, and the resulting precipitate was removed by filtration and washed on the filter with sodium bicarbonate solution and water to give 0.4 g of product.

2-Trifluoromethyl-3-thiazolylchromones (VIII-X, XXVIII-XXX). A 2-mmole sample of trifluoroacetic anhydride was added dropwise to a cooled (to 0°) solution of 1 mmole of acetophenone in the minimum volume of absolute pyridine, after which the mixture was cooled with shaking for 5-10 min and allowed to stand at room temperature for 24 h. It was then added to 70-90 ml of water, and the solid precipitate was removed by filtration.

3-Thiazolyl-7-acetoxy-chromones (XI-XIII). A 5-mmole sample of acetic anhydride was added to a warm solution of 1 mmole of IV-VI in pyridine, and the mixture was allowed to stand at room temperature for 24 h. The product was then removed by filtration and washed on the filter with ether.

3-Thiazolyl-7-methoxychromones (XIV-XVII). An acetone solution of 1 mmole of chromone (IV-VI, IX, and X) and 4 mmole of methyl iodide was stirred at 40-50° for 3-5 h with 3 mmole of freshly calcined potassium carbonate, after which the hot solution was filtered. The solid remaining after removal of the solvent by distillation was washed with a small amount of alcohol.

3-(2-Phenyl-4-thiazolyl)-7-methoxychromone (XV). A) A 0.48-g (5 mmole) sample of sodium tert-butoxide was added with stirring in an inert gas atmosphere to a cooled (to 0-3°) solution of 0.16 g (0.5 mmole) of XIX in absolute methyl formate, after which stirring was continued at 15-20° for 4 h. The solvent was then evaporated, and the dry residue was treated with 0.5 ml of concentrated hydrochloric acid, 0.5 ml of glacial acetic acid, and 1-2 ml of water. The resulting solid was refluxed for 30 min with 0.2 ml of concentrated HCl in 15 ml of methanol, after which the cold solution was diluted with 5 ml of water, and the resulting crystals were removed by filtration to give 0.12 g of product.

B) The method used to obtain IV was used to prepare chromone XV from 0.32 g (1 mmole) of XIX and 1 ml of ethyl orthoformate in 1 ml of pyridine in the presence of two drops of piperidine. The reaction time was 30 min, and the yield was 0.24 g (71%).

3-(4-Thiazolyl)-7-methoxychromone (XIV). Method B for the preparation of XV was used to obtain this compound from XVIII.

α-(4-Thiazolyl)-2-hydroxy-4-methoxyacetophenone (XVIII). A solution of 0.4 g (1.54 mmole) of XVII in 20 ml of alcohol and 15 ml of water was refluxed for 10 min with 5.1 ml (6.4 mmole) of 5% sodium hydroxide solution, after which the solution was diluted to twice its original volume with water and neutralized to pH 6 with dilute hydrochloric acid. The resulting precipitate was removed by filtration to give 0.35 g (92%) of product. Compound XVIII was similarly obtained in 52% yield from chromone XX (reaction time 50 min) and from chromone XXIII in 92% yield (reaction time 35 min); mp 82° (from aqueous alcohol). IR spectrum: 1630 (C = O) and 1520 cm^{-1}. Found: N 5.7; S 12.2%. $C_{12}H_{11}NO_3S$. Calculated: N 5.6; S 12.4%.

α-(2-Phenyl-4-thiazolyl)-2-hydroxy-4-methoxyacetophenone (XIX). As in the preparation of XVIII, this compound was obtained from chromone XVII in 64% yield (reaction time 20 min) and from chromone XXII in 61% yield (reaction time 50 min); mp 75° (from aqueous alcohol). IR spectrum: 1645 (C = O) and 1522 cm^{-1}. Found: N 4.2; S 9.9%. $C_{18}H_{15}NO_3S$. Calculated: N 4.3; S 9.9%.

2-Methyl-3-thiazolyl-4-thioxo-7-methoxychromones (XXV-XXVII). A finely ground mixture of 1 mmole of chromone (XX-XXII) and 0.6 mmole of phosphorus pentasulfide in 5-6 ml of absolute pyridine was heated at 100° for 1.5 h, after which it was added to 50 ml of water, and the resulting precipitate was removed by filtration, washed thorougly on the filter with water, and recrystallized from alcohol.

4-(2-Methyl-7-hydroxy-3-chromonyl)-3-ethylthiazolium Tosylate (XXXI). A mixture of 0.52 g (2 mmole) of 2-methyl-3-(4-thiazolyl)-7-hydroxychromone [1] and 0.8 g (4 mmole) of ethyl p-toluenesulfonate was heated at 130-140° for 3.5 h, after which it was cooled, and the red-brown melt was triturated with

benzene. The mixture was filtered, and the solid was washed on the filter with ether to give 0.65 g (70%) of colorless needles with mp 122-123° (from water). Found: S 14.2%. $C_{22}H_{21}NO_6S_2$. Calculated: S 14.0%. Perchlorate XXXII, with mp 189°, was formed by the action of sodium perchlorate on an aqueous solution of the tosylate. Found: Cl 8.4; S 7.7%. $C_{15}H_{14}ClNO_7S$. Calculated: Cl 8.8; S 8.0%.

2-Methyl-3-(4-thiazolyl)-7-ethoxycarbonylmethoxychromone (XXXIII). This compound was obtained from 2.08 g (8 mmole) of 2-methyl-3-(4-thiazolyl)-7-hydroxychromone [1] and 4.44 g (32 mmole) of ethyl bromoacetate in the presence of 3.36 g (24 mmole) of freshly calcined potassium carbonate. The reaction time was 2 h, and the yield was 1.97 g.

2-Methyl-3-(4-thiazolyl)-7-carbomethoxychromone (XXXIV). A solution of 0.35 g (1 mmole) of XXXIII in 5 ml of alcohol was refluxed for a few seconds with 0.8 ml (1 mmole) of 5% sodium hydroxide solution, after which the solution was diluted with 3.5 ml of hot water, and the resulting mixture was refluxed for another minute and neutralized to pH 6 with dilute hydrochloric acid. The yield was 0.3 g.

2-Methyl-3-(4-thiazolyl)-7-N-ethylolcarbamoylmethoxychromone (XXXV). A solution of 0.35 g (1 mmole) of XXXIII in 5 ml of absolute alcohol was refluxed with 3 ml of an 1 N solution of monoethanolamine in alcohol for 3 h, after which the mixture was cooled, and the resulting solid was removed by filtration and washed with alcohol. The yield was 0.38 g.

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