SYNTHESIS AND BIOLOGICAL ACTIVITY OF THIAZOLE ANALOGS OF ISOFLAVONES

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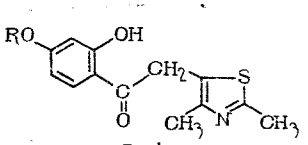
Flavonoids are a vast and unusual group of natural compounds interest in which has constantly attracted the attention of many investigators. Flavonoids display significant physiological activity and are nontoxic; consequently they are used widely for medicinal purposes. Highly effective drugs based on the natural flavonoids caused in their turn the growth of investigations towards the development of methods of obtaining synthetic flavonoids. Recently communications have appeared on the synthesis and properties of furan, thiophen, pyridine, quinoline, pyrrole, benzthiazole, banzimidazole, indole, selenophen, and tetrazole analogs of flavones among which are compounds possessing marked pharmacological activity. In the isoflavone series only natural analogs possessing strong pharmacological action are known [1, 2].

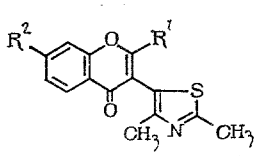
In view of the importance and little study of heterocyclic analogs of isoflavones as potential physiologically active substances we have developed methods of synthesis of furan [3], benzofuran [4-6], pyrazole [7], and thiazole [8] analogs of isoflavones. In the present communication we present the synthesis of thiazole analogs of isoflavones of structure (V). The starting material for the synthesis of these compounds was 2,4-dimethyl-5-thiazolylacetonitrile [1], reaction of which with resorcinol led to the corresponding 2,4-dihydroxyacetophenone (IIa). The specified reaction was carried out in the presence of hydrogen chloride in boron trifluoride etherate, which acts simultaneously both as solvent and as catalyst for the reaction [8].

As a result of condensation of acetonitrile (I) with orcinol a mixture of two isomeric acetophenones of structure (III) and (IV) was isolated. This was resolved into homogeneous compounds by double crystallization from aqueous alcohol since compound (III) is formed in a larger amount than compound (IV). A choice between the isomers was made on the basis of the different chemical environment of the aromatic protons and the protons of the hydroxyl groups in acetophenones (III) and (IV). In the PMR spectrum (in dimethylsulfoxide) of compound (III) the following signals were found, ppm [9]: 9.79 (4-OH), 10.23 (2-OH), 6.21 (3-H), 6.35 (5-H), 4.31 (CH_2), and for compound (IV) 11.95 (2 or 6-OH), 6.45 (3 or 5-OH), and 4.68 (CH_2).



II a,b

a) R=H; b) R=CH_3



V a-e

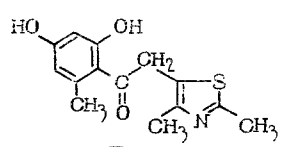
a) $R^1=CH_3$, $R^2=OCOCH_3$

b) $R^1=CH_3$, $R^2=OH$

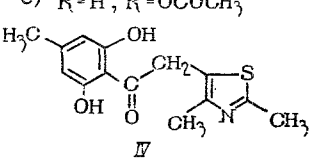
c) $R^1=H$, $R^2=OH$

d) $R^1=H$, $R^2=OCH_3$

e) $R^1=H$, $R^2=OCOCH_3$



III



IV

T. G. Shevchenko Kiev University. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 10, No. 8, pp. 74-78, August, 1976. Original article submitted December 8, 1975.

TABLE 1. α-(2,4-Dimethyl-5-thiazolyl)-2-hydroxyacetophenones

Compound*	Yield, %	Melting point, °C	Found, % S	Empirical formula	Calculated, % S	IR spectrum: λ max, cm^{-1}		
						thiazole ring	$\nu_{C=O}$	ν_{OH}
IIa	58	232	12,46	$C_{13}H_{13}NO_3S$	12,14	1518	1620	3000
IIb	98	121	11,62	$C_{14}H_{15}NO_3S$	11,60	1520	1646	—
III	58	228	11,52	$C_{14}H_{15}NO_3S$	11,60	1512	1688	3330
IV	17	237	11,64	$C_{14}H_{15}NO_3S$	11,60	1520	1640	—

*Here and in Table 2 compounds were needles recrystallized from aqueous alcohol.

TABLE 2. Thiazole Analogs of Isoflavones (Va-e)

Compound	Yield, %	Melting point, °C	Found, % S	Empirical formula	Calculated, % S	UV spectrum: λ max, nm (log ε)	
						in ethanol–dioxan (40:1)	in ethanol
Va	80	231	10,12	$C_{17}H_{15}NO_4S$	9,74	300 (4,02)	—
Vb	84	230	10,93	$C_{15}H_{13}NO_3R$	11,16	—	298 (4,35)
Vc	82	>310	11,70	$C_{14}H_{11}NO_3S$	11,72	305 (4,20)	—
Vd	81	171	11,20	$C_{15}H_{13}NO_3S$	11,16	—	—
Ve	90	169	10,31	$C_{16}H_{13}NO_4S$	10,16	300 (4,03)	300 (4,15)

The acetophenone (IIa) was converted into chromone (Vb) by heating with acetic anhydride in the presence of triethylamine and subsequent deacylation of compound (Va) with 5% alkali solution by our modified method.

With the aim of obtaining the thiazole analog (Vc) of natural isoflavones, which as a rule do not contain substituents in the 2 position of the chromone system, compound (IIa) was heated in pyridine with ethyl orthoformate in the presence of catalytic amounts of piperidine. Characteristic absorption bands were detected in the IR spectrum of chromone (Vc) corresponding to the stretching vibrations of a chromone C=O (1630 cm^{-1}), chromone C=C (1585 cm^{-1}), and hydroxyl (3080 cm^{-1}), as well as an absorption band at 1520 cm^{-1} due to the asymmetric vibration of the thiazole ring.

3-Thiazolylchromone (Vb) may partake in alkylation and acylation reactions at the phenolic hydroxyl. Thus on interacting compound (Vc) with methyl iodide in acetone solution in the presence of potassium carbonate the 7-methoxychromone (Vd) formed, and treatment of a pyridine solution of (Vc) with acetic anhydride led to 7-acetoxychromone (Ve). On heating compound (Vd) with a fourfold excess of 5% sodium hydroxide solution in aqueous alcohol fission of the pyrone ring occurred with the subsequent formation of 2-hydroxy-4-methoxyacetophenone (IIb).

3-(5-Thiazolyl)chromones and their derivatives were colorless high-melting-point crystalline substances readily soluble in the usual organic solvents. The structure of new substances was confirmed by analytical data and UV and IR spectra (Tables 1 and 2). The main UV absorption maximum of alcoholic solutions of compounds (Va-e) was found at 300 nm, i.e., in the region where isoflavones usually absorb.

On investigating the pharmacological activity of the 3-(4-thiazolyl)chromones synthesized by us previously it was discovered in experiments *in vitro* that some of them possessed significant antitumor activity, and others were regulators of cardiac muscle activity. It turned out that 7-acetoxychromone (Ve) also showed high antiblastic activity. From the data of Table 3 the conclusion may be drawn that the biological activity of the investigated compounds was determined by their structure. The strong influence that the nature of the substituent found in the 2 position of the chromone ring or the thiazole nucleus exerts on the physiological activity of 3-thiazolylchromones is unusual. 2-Methyl-3-(2-phenyl-4-thiazolyl)-7-hydroxychromone which is characterized by appreciable antiblastic activity may be cited as an example. Substitution of the phenyl on the thiazole nucleus by methyl or hydrogen atom

TABLE 3. Antiblastic Activity of Thiazole Analogs of Isoflavones

Compound	Diameter of zone with absence of growth, mm		
	compound concentration		
	10 μg/ml	20 μg/ml	30 μg/ml
2-Methyl-3-(4-thiazolyl)-7-hydroxychromone	15	20	30
2-Methyl-3-(2-methyl-4-thiazolyl)-7-hydroxychromone	20	20	25
2-Methyl-3-(2-phenyl-4-thiazolyl)-7-hydroxychromone	50	55	25
2-Methyl-3-(2-phenyl-4-thiazolyl)-7-methoxychromone	30	40	—
3-(2-Phenyl-4-thiazolyl)-7-acetoxychromone	30	40	—
3-(4-Thiazolyl)-7-hydroxychromone	15	20	—
3-(2-Methyl-4-thiazolyl)-7-hydroxychromone	40	45	50
2-Ethoxycarbonyl-3-(4-thiazolyl)-7-hydroxychromone	0	10	—
2-Ethoxycarbonyl-3-(2-methyl-4-thiazolyl)-7-hydroxychromone	0	10	—
2-Ethoxycarbonyl-3-(2-phenyl-4-thiazolyl)-7-hydroxychromone	40	45	50
2-Trifluoromethyl-3-(4-thiazolyl)-7-hydroxychromone	0	10	—
2-Trifluoromethyl-3-(2-methyl-4-thiazolyl)-7-hydroxychromone	0	10	—
2-Trifluoromethyl-3-(2-phenyl-4-thiazolyl)-7-hydroxychromone	0	10	—
2-Methyl-3-(4-thiazolyl)-5-methyl-7-hydroxychromone	0	10	—
2-Methyl-3-(2-methyl-4-thiazolyl)-5-methyl-7-hydroxychromone	20	30	30
2-Methyl-3-(2-phenyl-4-thiazolyl)-5-methyl-7-hydroxychromone	15	20	—
2-Methyl-3-(4-thiazolyl)-5-hydroxy-7-methylchromone	0	10	—
2-Methyl-3-(2-methyl-4-thiazolyl)-5-hydroxy-7-methylchromone	0	10	—
2-Methyl-3-(2-methyl-4-thiazolyl-5,7-dihydroxychromone	35	45	—
3-(2,4-Dimethyl-5-thiazolyl)-7-acetoxychromone	50	—	—

and also an increase in the electronegativity of the substituent in position 2 of the chromone ring were accompanied by a sharp fall in biological activity.

EXPERIMENTAL

PMR spectra were taken on a ZKR-60 spectrometer for 0.25 M solutions in dimethylsulfoxide at 25° with tetramethylsilane (internal standard). UV spectra were taken on an SF-4A spectrometer for $2 \cdot 10^{-5}$ M solutions in ethanol and in ethanol with added dioxan. IR spectra were taken on a UR-10 spectrometer in potassium bromide disks. The purity of the obtained compounds was checked by thin layer chromatography on silica gel G (Merck). A mixture of chloroform and methanol (9:1) was used as eluant.

Testing the antiblastic activity of the synthesized thiazole analogs of isoflavones was carried out in *in vitro* experiments by serial dilution and diffusion in agar [10, 11] over the concentration range 10 to 30 μg/ml solvent. Activity of the test compound was calculated from the diameter of the zone of absence of growth of *Staph. aureus* UF_3.

2,4-Dimethyl-5-thiazolylacetonitrile (I). 2,4-Dimethyl-5-thiazolylacetamide [12] and phosphorus pentoxide in the ratio 1:1.5 were heated with simultaneous distillation of the resulting nitrile in vacuum [13]. Yield was 62%, bp 102-103° (0.4 mm), mp 87-88° (from alcohol). By a more laborious procedure [14] the nitrile mentioned was obtained by dehydration of the corresponding amide with phosphorus oxychloride and had bp 123° (2.5 mm), mp 87-88° (from alcohol). Yield was 64%.

α-(2,4-Dimethyl-5-thiazolyl)-2,4-dihydroxyacetophenone (IIa). A stream of dry hydrogen hydrochloride was passed for 2 h at room temperature into a stirred solution of compound (I) (6.07 g: 40 mmole) and resorcinol (5.28 g: 48 mmole) in boron trifluoride etherate (35 ml) cooled to 2-3°, and then for a further 4 h at 40-50°. The mixture was left overnight at room temperature, water (150 ml) was added, the solution was boiled for 2 h, and made alkaline with ammonia to pH 3.0-4.0. The precipitate which separated was filtered off from the cold solution. Yield was 6.15 g.

α-(2,4-Dimethyl-5-thiazolyl)-2-hydroxy-4-methoxyacetophenone (IIb). A solution of (Vd) (0.29 g: 1 mmole) in alcohol (15 ml) and water (10 ml) was boiled for 30 min with 5% sodium hydroxide solution (3.2 ml: 4 mmole), after which the solution was diluted twofold with

water, and neutralized with dilute hydrochloric acid to pH 6.0. The precipitate which separated was filtered off. Yield was 0.27 g.

α-(2,4-Dimethyl-5-thiazolyl)-2,4-dihydroxy-6-methylacetophenone (III) and α-(2,4-Dimethyl-5-thiazolyl)-2,6-dihydroxy-4-methoxyacetophenone (IV). Compound (I) (1.52 g: 10 mmole) and orcinol (1.45 g: 12 mmole) in boron trifluoride etherate (10 ml) were stirred at 60° in a stream of dry hydrogen chloride for 6 h and the reaction mixture was then left overnight at room temperature. Further treatment was the same as in the preparation of (IIa). The yield of the mixture of isomers was 2.55 g (92%). After recrystallization from 50% alcohol, (IV) (0.48 g) was obtained and on dilution of the filtrate twice with water compound (III) (1.62 g) was precipitated.

2-Methyl-3-(2,4-dimethyl-5-thiazolyl)-7-acetoxychromone (Va). A mixture of (IIa) (0.53 g: 2 mmole), acetic anhydride (1.02 g: 10 mmole), and triethylamine (1.01 g: 10 mmole) was heated for 4-5 h at 110-115° and then poured into cold water (300 ml). The solid obtained was washed many times with water. Yield was 0.52 g.

2-Methyl-3-(2,4-dimethyl-5-thiazolyl)-7-hydroxychromone (Vb). To a hot solution of (Va) (0.16 g: 0.5 mmole) in alcohol (20 ml) was added 5% sodium hydroxide solution (0.4 ml: 0.5 mmole). The solution was boiled for several seconds and boiled for a further 30 min while adding water (30 ml). The solution was neutralized with dilute hydrochloric acid to pH 5.0-6.0 and the solid was filtered off. Yield was 0.12 g.

3-(2,4-Dimethyl-5-thiazolyl)-7-hydroxychromone (Vc). Acetophenone (IIa) (1 mmole) and ethyl orthoformate (6 mmole) in pyridine (1 ml) were heated in the presence of piperidine (1-2 drops) for 3 h at 120-130°. The reaction mixture was poured into water (25 ml) and the solid product was filtered off.

3-(2,4-Dimethyl-5-thiazolyl)-7-methoxychromone (Vd). An acetone solution of chromone (Vc) (1 mmole) and methyl iodide (4 mmole) was stirred for 3-5 h at 40-45° with freshly calcined potassium carbonate after which the hot solution was filtered. The residue after distilling off the solvent was washed with a small quantity of alcohol.

3-(2,4-Dimethyl-5-thiazolyl)-7-acetoxychromone (Ve). To a warm solution of (Vc) (1 mmole) in pyridine was added acetic anhydride (5 mmole), the reaction mixture was left for a day at room temperature, then the product was filtered off, and washed on the filter with ether.

LITERATURE CITED

1. S. Gronovitz and R. Ekman, Ark. Kemi, 17, No. 9, 93-99 (1960); Chem. Abs., 55, 27294 (1966).
2. Belgian Patent No. 633436; Chem. Abs., 61, 1840 (1964).
3. V. P. Khilya, L. G. Grishko, and V. Sabo, Khim. Geterosikl. Soedin., No. 10, 1317-1320 (1972).
4. V. P. Khilya, L. G. Grishko, N. V. Sukharenko, et al., Zh. Org. Khim., 8, 1085-1090 (1972).
5. V. P. Khilya, L. S. Grishko, L. L. Gontar', et al., Khim. Geterosikl. Soedin., No. 10, 1324-1328 (1972).
6. V. P. Khilya, L. G. Grishko, L. I. Shevchenko, et al., Khim. Geterosikl. Soedin., No. 9, 1202-1208 (1973).
7. V. P. Khilya, L. G. Grishko, T. I. Sokolova, et al., Zh. Org. Khim., 9, 2572-2577 (1973).
8. V. P. Khilya, V. Sabo, L. G. Grishko, et al., Zh. Org. Khim., 9, 2561-2567 (1973).
9. M. Yu. Kornilov, V. P. Khilya, and L. G. Grishko, Zh. Org. Khim., 9, 2568-2572 (1973).
10. V. S. Dmitrieva and S. M. Semenov, The Microbiological Checking of the Activity of Antibiotic Preparations [in Russian], Moscow (1965).
11. N. S. Egorov, Basic Instruction on Antibiotics. Higher School [in Russian], Moscow (1969).
12. A. Burger and G. E. Ullyott, J. Org. Chem., 12, 342-355 (1947).
13. E. Kraft and B. Stauffer, Chem. Ber., 15, 1729-1731 (1882).