Chemistry of Heterocyclic Compounds, Vol. 30, No. 4, 1994

CHEMISTRY OF HETEROANALOGS OF ISOFLAVONES. 16.* BENZTHIAZOLE ANALOGS OF ISOFLAVONES

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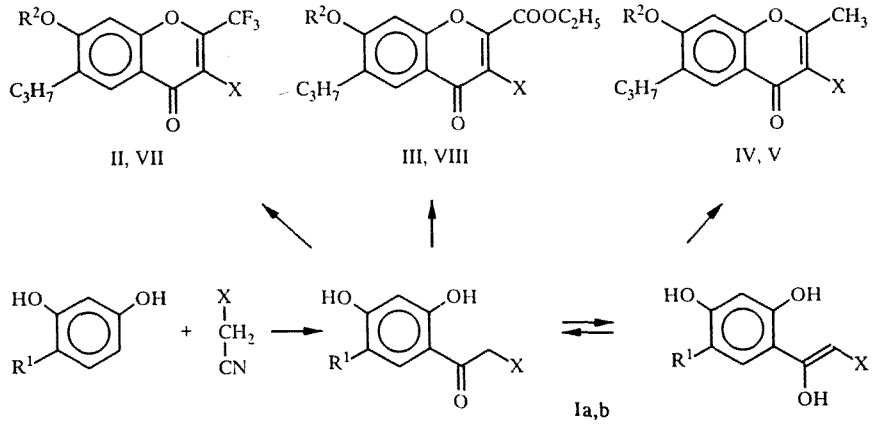
The reaction of α-(2-benzthiazolyl)-2,4-dihydroxy-5-alkylacetophenones with anhydrides and chlorides of carboxylic acids yielded 3-(2-benzthiazolyl)chromones with electron-acceptor and electron-donor substituents, as well as chromones unsubstituted in the 2-position. Their acylation, alkylation, and aminoacylation reactions and their interaction with electrophilic and nucleophilic reagents were studied.

The great attention paid in recent years to heterocyclic analogs of isoflavonoids is explained by the presence of general and specific types of biological activity. In view of the importance and insufficient study of azole analogs of isoflavones as potential physiologically active substances, methods have been developed for the synthesis of imidazole [2], pyrazole [3], and isoxazole [4] analogs of isoflavones. Pharmacological tests have shown that some of these compounds exhibit high hypolipidemic, anti-inflammatory, and sugar-lowering activity.

Continuing investigations in the field of the chemistry and pharmacology of chromones with nitrogen-containing heterocycles, in this work we synthesized and studied certain properties of benzthiazole analogs of isoflavones (see scheme), among which only two representatives have been described [5].

The starting materials for the synthesis of new 3-(2-benzthiazolyl)-chromones were α-(2-benzthiazolyl)-2,4-dihydroxy-6-propylacetophenone (Ia) and α-(2-benzthiazolyl)-2,4-dihydroxy-6-hexylacetophenone (Ib), produced by condensation of 2-benzthiazolylacetonitrile with 4-alkylresorcinols under modified conditions of the Hoesch reaction.



*For communication 15, see [1].

Taras Shevchenko Kiev University, Kiev 252017. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 464-471, April, 1994. Original article submitted March 5, 1994.

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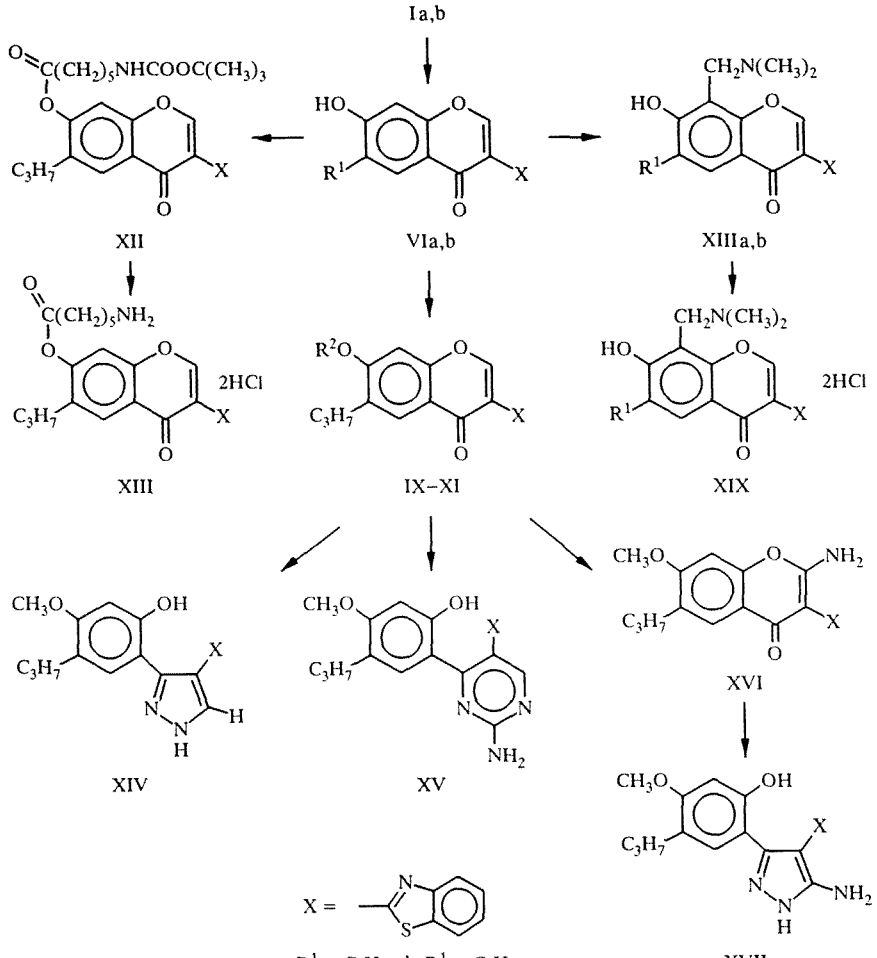
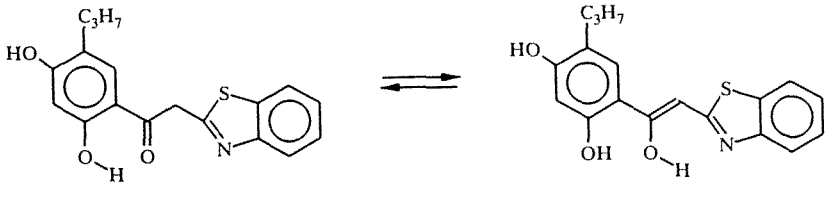


The ketones Ia,b are high-boiling yellowish crystalline substances, which give a colored chelate complex with an alcohol solution of ferric chloride. The dark-green color of this complex suggested the presence of tautomeric equilibrium between the ketone and enol forms for compounds Ia,b in solution. In an analysis of the PMR spectra of compound Ia in various deuterosolvents, we found that in nonpolar solvents, such as chloroform and benzene, it exists exclusively in the ketone form, whereas in the more polar acetone a certain amount of the enol form is observed. In dimethyl sulfoxide, the ketone Ia is 80% enolized, as indicated by the doubled number of signals of the protons of the hydroxyl groups and a consideration of the integral intensity of nonexchangeable aromatic protons of the phenolic portion, as well as a decrease in the intensity of the peak of the protons of the methylene unit, the appearance and increase in the intensity of the signal of the methine proton of the olefinic fragment of the molecule (see Fig. 1). The ketone Ib is 85% enolized in dimethyl sulfoxide. The greater content of the enol form may be associated with its stabilization by the intermolecular hydrogen bond that arises between the enol hydroxyl and dimethyl sulfoxide.



As a result of the reaction of the ketone Ia with trifluoroacetic anhydride or ethoxalyl chloride in pyridine in the cold, the chromones II and III, containing trifluoromethyl and ethoxycarbonyl groups in the 2-position, respectively, were obtained. The reaction of acetic anhydride with the same ketone proceeds in pyridine medium at room temperature with the formation

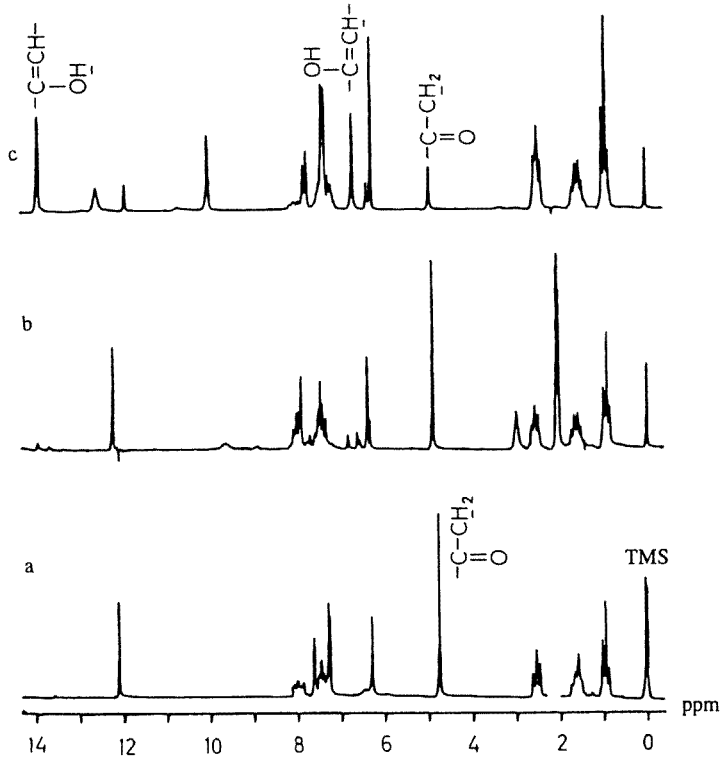


Fig. 1. PMR spectrum of α-(2-benzthiazolyl)-2,4-dihydroxy-5-propylacetophenone: a) in deuterochloroform; b) in deuteroacetone; c) in deuteromethyl sulfoxide.

of 2-methyl-7-acetoxychromone IV, hydrolysis of the latter in alkaline medium leads to 2-methyl-7-hydroxychromone V. The occurrence of cyclization under mild conditions is evidence of increased activity of the α-methylene unit of the ketone Ia, due to the electron acceptor properties of the benzthiazole ring.

To obtain 3-(2-benzthiazolyl)chromones VIa,b, containing no substituent in position 2 of the chromone system, it was possible to use the Venkataraman method, as shown earlier [5] on the example of the benzthiazole analog of isoflavone. However, taking into account the results of [6-8] and the nature of the ketones Ia,b, we decided to study the conditions of their cyclization to the chromones VIa,b under the action of acetic-formic anhydride. The use of this convenient and effective reagent has been found to permit quantitative cyclization even in the absence of a base and to yield a high-quality end product, requiring no further purification.

The PMR spectra of the chromones II-VI, in contrast to the original ketones Ia,b, do not contain signals of the methylene unit and the 2-OH group. Moreover, the presence of signals of the protons of the 2-H methyl and ethoxyl groups in the PMR spectra of the compounds, as well as the negative reaction with an alcohol solution of ferric chloride, are evidence of completeness of the conversion of the ketones Ia,b to the corresponding chromones (see Table 1).

The benzthiazole analogs of isoflavones II, III, V, and VI that we synthesized are readily acylated at the phenolic hydroxyl. The action of acetic anhydride on pyridine solutions of these compounds at room temperature leads to the formation of the corresponding 7-acetoxy derivatives IV, VII-IX, which are quantitatively converted to the corresponding 7-hydroxychromones II, III, V, and VI under the influence of a 5% NaOH solution. Methylation at the 7-OH group of the chromone ring proceeds smoothly when the chromone VIa is treated with dimethyl sulfate in acetone solution in the presence of potash, which leads to the chromone X. Alkylation by the methyl ester of monobromoacetic acid in dioxane solution in the presence of potash proceeds just as readily, with the formation of 7-O-methoxycarbonylmethoxychromone XI. Alkylation of the chromone VIa at the nitrogen of the benzthiazole ring in a boiling dioxane solution, however, could not be accomplished with the same reagent but without potash.

TABLE 1. Characteristics of 3-(2-Benzthiazolyl)chromones III-XIII, XVI, XVIII

Compound	Gross formula	mp, °C	PMR spectrum, δ, ppm*					Yield, %
			protons of chromone ring				protons of benzthiazole	
			2-R	5-H	6-Alk	7-R	8-R	
III	$C_{22}H_{19}NO_5S$	245...247	4,47 1,24	7,92	0,93; 1,64; 2,65	11,31	7,02	8,20 (4-H); 7,52 (5-, 6-H); 8,00 (7-H)	75
IV	$C_{22}H_{19}NO_4S$	167...168	3,04	8,19	0,97; 1,68; 2,64	2,39	7,29	8,02 (4-, 7-H); 7,44 (5-, 6-H)	87
V	$C_{20}H_{17}NO_3S$	278...279	2,97	7,82	0,91; 1,59; 2,61	10,95	6,91	8,07 (4-, 7-H); 7,47 (5-, 6-H)	70
VIa	$C_{19}H_{15}NO_3S$	280...282	9,33	7,90	0,94; 1,63; 2,64	11,11	6,99	8,18 (4-H); 7,42 (5-H); 7,62 (6-H); 8,03 (7-H)	98
VI b	$C_{22}H_{21}NO_3S$	267...268	9,33	7,90	0,94; 1,65; 2,65	11,05	7,00	8,15 (4-H); 7,48 (5-, 6-H); 8,03 (7-H)	97
VII	$C_{22}H_{16}F_3NO_4S$	108...110	—	8,13	0,97; 1,68; 2,66	2,40	7,45	8,05 (4-, 7-H); 7,50 (5-, 6-H)	85
VIII	$C_{24}H_{21}NO_6S$	165...168	4,51 1,34	8,20	0,97; 1,70; 2,65	2,39	7,39	7,98 (4-, 7-H); 7,44 (5-, 6-H)	80
IX	$C_{21}H_{17}NO_4S$	220...222	9,25	8,25	0,98; 1,69; 2,65	2,39	7,37	8,01 (4-, 7-H); 7,45 (5-, 6-H)	72
X	$C_{20}H_{17}NO_3S$	202...204	9,19	8,08	0,97; 1,67; 2,63	3,94	6,89	7,97 (4-, 7-H); 7,45 (5-, 6-H)	80
XI	$C_{22}H_{19}NO_4S$	225...226	9,20	8,14	0,99; 1,68; 2,77	3,84 4,77	6,78	8,02 (4-, 7-H); 7,44 (5-, 6-H)	78
XII	$C_{30}H_{34}N_2O_6S$	165	9,20	8,25	0,98; 1,60; 2,70	*2	7,38	8,01 (4-H); 7,46 (5-, 6-H); 8,01 (7-H)	56
XIII	$C_{25}H_{28}Cl_2N_2O_4S$	286	9,47	8,14	0,92; 1,61; 2,71	*3	7,60	8,14 (4-, 7-H); 7,50 (5-, 6-H)	95
XVI	$C_{20}H_{18}N_2O_3S$	308...310	9,46 10,87	7,83	0,93; 1,61; 2,65	3,95	6,96	8,01 (4-, 7-H); 7,42 (5-, 6-H)	90
XVIIIa	$C_{22}H_{22}N_2O_3S$	125...126	9,21	7,80	0,92; 1,60; 2,57	8,77	4,08 2,46	8,05 (4-, 7-H); 7,47 (5-, 6-H)	77
XVIII b	$C_{25}H_{28}N_2O_3S$	137...138	9,16	7,75	0,83; 1,26; 1,49; 2,41	10,48	4,04 2,41	8,13 (4-H); 7,43 (5-, 6-H); 7,98 (7-H)	70

*PMR spectra of compounds III, V, VIa,b, XII, XIII, and XVI were measured in DMSO-D_6, and those of compounds IV, VII–XI in $CDCl_3$.

*2$(CH_3)_3$ C–O–CO–NH–$(CH_2)_5$COO– 1.46, 4.52, 2.65, 1.70, 3.17.

*2H_3N^+–$(CH_2)_5$COO– 8.00, 2.71, 1.61, 2.71.

As a result of condensation of the chromone VIa with N-tert-butyloxycarbonyl-6-aminocaproic acid in tetrahydrofuran medium in the presence of dicyclohexylcarbodiimide, an aminoacyl derivative XII was obtained; subsequent acetolysis of it leads to the hydrochloride of 3-(2-benzthiazolyl)-7-(6-aminocaproyl)hydroxychromone XIII.

The structure and individuality of the newly synthesized 7-substituted chromones IV, VII-XII were confirmed by the data of elementary analysis, thin-layer chromatography, and PMR spectroscopy (see Table 1).

It was of interest to produce peptide derivatives at the 2-carboxyl group of the chromones; therefore, we attempted to saponify the ester group of the chromone III. However, when the chromone III was boiled in aqueous alcohol medium with an equivalent amount of 5% NaOH, no saponification occurred, whereas in the case of boiling with a large amount of alkali, the chromone III was opened to the ketone Ia, as evidenced by the appearance of a positive reaction with an alcohol solution of ferric chloride. The chromone III also behaves analogously in an aqueous alcohol solution of soda. There is also no saponification of the ester group when the chromone III is boiled in an aqueous alcohol solution with a double amount of hydrochloric acid for 6 h. Considering the results of [9], we heated the chromone IV in concentrated hydrochloric acid. After crystallization from ethyl acetate and dimethylformamide, the product that precipitated from the reaction medium was identified as the chromone VI, unsubstituted at the 2-position, i.e., not saponification of the ester group but complete decarboxylation occurred. The structure of the compound obtained is confirmed by the identity of its IR and PMR spectra with the spectra of the basic chromone VI, their identical R_f values on thin-layer chromatographic plates, and the absence of depression in the measurement of the mixed melting point.

We also investigated the reaction of 7-methoxychromone X with bifunctional nucleophilic reagents. Under the influence of hydrazine hydrate and aminoguanidine, 7-methoxychromone X recyclizes to the pyrazole derivative XIV and pyrimidine XV. The structure of these products was confirmed by chemical reactions and by spectral data. The pyrazole XIV and pyrimidine XV dissolve in aqueous solutions of alkalies and give a positive reaction with ferric chloride, which indicates the presence of a free hydroxyl group in their molecule, situated close to the nitrogen atom of the pyrazole or pyrimidine ring. The fact that the reaction proceeds with opening of the pyrone ring is supported by the diamagnetic shifts around 1 ppm of the 6-H proton of the phenolic fragment of the pyrazole and pyrimidine in comparison with the corresponding signal in the original compound X. In the PMR spectrum of the pyrazole XIV the protons of the OH and NH groups are detected in the form of a broadened singlet at 9.7 and 13.2, respectively, while in the PMR spectrum of the pyrimidine XV the 2-OH group is observed in the form of a singlet at 10.2, and the amino group int he form of a two-proton broadened singlet at 7.3 ppm.

In the reaction with hydroxylamine the chromone X undergoes two recyclizations, ending in the formation of the 2-aminochromone XVI. The structure of the latter agrees with the data of PMR spectroscopy. The amino group is detected by two signals at 9.5 and 10.9 ppm, which is an indication of its participation in the formation of an intramolecular hydrogen bond with the nitrogen atom of the benzthiazole ring. The chemical shift of the 5-H proton of the chromone ring is observed in the same region as in the original compound and is evidence of preservation of the pyrone structure in compound XVI. An aminochromone structure is also supported by the data of IR spectroscopy ($\nu_{C=O}$ 1645, ν_{NH2} 3235, 3065 cm^{-1}). The nitrogen atom of the amino group in the ^{15}N NMR spectrum (in nitromethane) appears in the form of a triplet at 95.04 ppm with $J_{N,H}$ 90.33 Hz.

Under the action of hydrazine hydrate, the 2-aminochromone XVI recyclizes to the 5-aminopyrazole XVII, which forms a blue-green complex with an alcohol solution of ferric chloride. Signals belonging to the protons of the hydroxyl and amino groups and the 1-H proton of the pyrazole ring are detected in the PMR spectrum of this compound, confirming the pyrazole structure of the recyclization product. In the ^{15}N NMR spectrum of compound XVII the nitrogen atom of the amino group is detected at 50.8 ppm in the form of a triplet with $J_{N,H}$ 82.4 Hz.

Electrophilic substitution in the series of benzthiazole analogs of isoflavones was studied on the example of the aminomethylation reaction. The reaction of the chromones VIa,b with bis-dimethylaminomethane in dioxane medium with heating leads to the formation of the Mannich bases XVIIIa,b. The dimethylaminomethyl group is incorporated into the 8-position of the chromone ring, as evidenced by the disappearance of the signal of the 8-H proton of the chromone ring in the PMR spectrum and the appearance of signals corresponding to the methylene protons and the protons of the dimethylamino group. When dry hydrogen chloride is passed into a solution of the chromone XVIIIa in dry chloroform, a precipitate of the corresponding hydrochloride XIX is formed; its composition was confirmed by the data of elementary analysis.

EXPERIMENTAL

The course of the reactions and the purity of the compounds obtained were monitored by TLC on Silufol UV-254 plates, with mixtures of chloroform–methanol, benzene–ethanol (9:1) as eluents, while ethyl acetate was used as the eluent for Mannich bases. The ^1H NMR spectra were recorded on Bruker WP-100SY and Bruker CXP-200 instruments relative to TMS (internal standard), and the ^{15}N NMR spectra were recorded on a Bruker CXP-200 instrument relative to nitromethane (an external standard). The IR spectra were determined in potassium bromide tablets on the Pye Unicam SP-3-300 instrument.

The data of elementary analysis of the new compounds for S, N, and Cl correspond to the calculated values.

α-(2-Benzthiazolyl)-2,4-dihydroxy-5-propylacetophenone (Ia, $C_{18}H_{17}NO_3S$). Dry hydrogen chloride was passed through a mixture of 8.7 g (50 mmoles) 2-benzthiazolylacetonitrile and 8.8 g (51 mmoles) 4-propylresorcinol in 80 ml of boron trifluoride etherate with mixing and heating to 60°C for 10-12 h. Then the reaction mixture was introduced into 500 ml of hot water, boiled for 1.5 h, and neutralized to pH 7 with a solution of alkali. After cooling, the precipitate was filtered and washed well with water. Yield of the crude was 17 g. Purification was performed by reprecipitation from alkaline solution and crystallization from alcohol. Yield 12 g (73%). Yellowish crystals with mp 175°C. PMR spectrum ($CDCl_3$): protons of the phenolic portion: 12.08 (2-OH); 6.28 (3-H); 8.5 (4-OH); 0.95; 1.58; 2.53 (5-C_3H_7); 7.60 (6-H); 4.73 (−CH_2−); protons of benzthiazole: 8.01 (4-H); 7.44 (5-, 6-H); 7.89 ppm (7-H). PMR spectrum (DMSO-d_6): protons of the phenolic portion for the ketone form: 11.92 (2-OH); 6.37 (3-H); 10.69 (4-OH); 0.92; 1.55; 2.47 (5-C_3H_7); 7.82 (6-H); 4.94 (−CH_2−); protons of the phenolic portion for the enol form: 12.57 (2-OH); 6.27 (3-H); 10.00 (4-OH); 7.34 (6-H); 13.91; 6.71 (−C(OH)=CH−); protons of benzthiazole: 7, 9 (4-, 7-H); 7.35 ppm (5-, 6-H). IR spectrum, $\nu_{C=O}$ 1643, ν_{OH} 3060, 3400 cm^{-1}.

α-(2-Benzthiazolyl)-2,4-dihydroxy-5-hexylacetophenone (Ib, $C_{21}H_{23}NO_3S$). The compound Ia was produced analogously from 8.7 g (50 mmoles) 2-benzthiazolylacetophenone and 10.1 g (51 mmoles) 4-hexylresorcinol. Yellowish crystals with mp 154-156°C. Yield 5.5 g (30%). PMR spectrum (DMSO-d_6): protons of the phenolic portion for the ketone form: 11.90 (2-OH); 6.36 (3-H); 10.68 (4-OH); 0.92; 1.34; 2.50 (5-C_6H_{13}); 7.80 (6-H); 4.92 (−CH_2); protons of the phenolic portion for the enol form: 12.57 (2-OH); 6.25 (3-H); 9.99 (4-OH); 0.90; 1.34; 1.52; 2.59 (5-C_6H_{13}); 7.30 (6-H); 13.87; 6.68 (−C(OH)=CH−); protons of benzthiazole: 7.9 (4-, 7-H); ppm (5-, 6-H).

2-Trifluoromethyl-3-(2-benzthiazolyl)-6-propyl-7-hydroxychromone (II). To a solution of 3.27 g (10 mmoles) of the ketone Ia in a minimal volume of pyridine, 2.8 ml (20 mmoles) of trifluoroacetic anhydride was added dropwise with cooling. After standing for 48 h at room temperature, the reaction mixture was poured out into 100 ml of water, and the precipitate formed was filtered off. The compound was identified in the form of the acetyl derivative VII.

2-Ethoxycarbonyl-3-(2-benzthiazolyl)-6-propyl-7-hydroxychromone (III). It was produced analogously to compound II from 10 mmoles of the ketone Ia and 20 mmoles of ethoxalyl chloride and purified by crystallization from alcohol.

2-Methyl-3-(2-benzthiazolyl)-6-propyl-7-acetoxychromone (IV). To a solution of 6.54 g (20 mmoles) of the ketone Ia in a minimum amount of absolute pyridine we added 10.2 g (100 mmoles) of acetic anhydride and left the reaction mixture overnight at room temperature; then the precipitate was filtered off, washed with cold water, and crystallized from hexane.

2-Methyl-3-(2-benzthiazolyl)-6-propyl-7-hydroxychromone (V). To a solution of 1.9 g (4.8 mmoles) of compound IV in 50 ml of alcohol we added 4 ml of a 5% solution of sodium hydroxide. After several minutes the boiling solution was diluted with water, boiled for 5 min, and neutralized with dilute hydrochloric acid to pH 7; the precipitate formed was filtered off and crystallized from alcohol.

3-(2-Benzthiazolyl)-6-alkyl-7-hydroxychromones (VIa,b). A mixture of 10 mmoles of the ketone Ia or Ib and 10 ml of acetic-formic anhydride was mixed for a brief time and then heated at 80-100°C for 1-1.5 h; after cooling of the reaction mixture, the precipitate was filtered and washed with cold alcohol. Compound VIa was crystallized from propyl alcohol and VIb from alcohol.

3-(2-Benzthiazolyl)-6-propyl-7-acetoxychromones (VII, VIII, IV, IX). To a solution of 1 mmole of the corresponding 7-hydroxychromone in a minimum amount of pyridine we added 5 ml of acetic acid and left the reaction mixture for 24 h at room temperature. The precipitate formed was filtered off, washed with cold alcohol, and crystallized from hexane (VII) or from acetic anhydride (VIII, IX).

3-(2-Benzthiazolyl)-6-propyl-7-alkoxychromones (X, XI). To a boiling mixture of 3.37 g (10 mmoles) of the 7-hydroxychromone VIa and 4.1 g (30 mmoles) of potash in absolute dioxane, 1.14 ml (12 mmoles) of dimethyl sulfate or 1.33 ml (12 mmoles) of the methyl ester of monobromoacetic acid was added dropwise and boiled for 4-10 h; the hot solution was

filtered off from the inorganic precipitate, the solvent was distilled off, and compound X was crystallized from ethyl acetate, and XI from DMF.

3-(2-Benzthiazolyl)-6-propyl-7-O-(N-tert-butyloxycarbonyl-6-aminocaproyl)chromone (XII). To a solution of 2.3 g (10 mmoles) of N-tert-butyloxycarbonyl-6-aminocaproic acid in 20 ml of tetrahydrofuran, cooled to 0°C, we added 1 g (0.5 mmole) of dicyclohexylcarbodiimide. The reaction mixture was mixed for 1 h at 0°C. The dicyclohexylurea that precipitated was filtered off, and 1.3 g (4 mmoles) of the chromone VI and 12 mg (0.01 mmole) of N,N-dimethylaminopyridine were added to the filtrate. The solution obtained was mixed at room temperature for 2 h, the solvent was distilled off under vacuum, and the residue was dissolved in 300 ml of ethyl acetate and washed successively with 50 ml of water, with a saturated solution of sodium bicarbonate (2 × 50 ml), with 50 ml of water, and with a saturated solution of sodium chloride (2 × 50 ml). The organic phase was dried with anhydrous magnesium sulfate; the solvent was distilled off under vacuum, and the residue was recrystallized from methanol.

3-(2-Benzthiazolyl)-6-propyl-7-O-(6-aminocaproyl)hydroxychromone Hydrochloride (XIII). A suspension of 1 g of compound XII in 50 ml of ether, saturated with hydrogen chloride, was mixed for 1 h, and the precipitate was filtered off. It was purified by reprecipitation with ether from methanol solution.

3-(2-Hydroxy-4-methoxy-5-propylphenyl)-4-(2-benzthiazolyl)pyrazole (XIV, $C_{20}H_{19}N_3O_2S$). To a solution of 0.7 g (2 mmoles) of the chromone X in 25 ml of alcohol we added 12 ml of a 2 N alcohol solution of hydrazine hydrate and boiled the reaction mixture for 5-10 min. A yellow color appeared, disappearing at the end of the reaction. After dilution of the solution with water, the precipitate was filtered off and crystallized from alcohol. Yield 0.5 g (90%). Colorless crystals with mp 247°C. PMR spectrum (DMSO-d_6): protons of the phenolic portion: 9.72 (2-OH) 6.59 (3-H); 3.81 (4-OCH_3); 0.87; 1.52; 2.45 (5-C_3H_7); 7.06 (6-H); protons of pyrazole: 13.2 (N−H); 8.13 (5-H); protons of benzthiazole: 7.92 (4-, 7-H); 7.29 (5-H); 7.44 ppm (6-H).

2-Amino-4-(2-hydroxy-4-methoxy-5-propylphenyl)-5-(2-benzthiazolyl)pyrimidine (XV, $C_{21}H_{20}N_4O_2S$). To a solution of 0.92 g (0.04 mole) sodium in 50 ml of absolute alcohol we added 1.91 g (0.02 mole) of guanidine hydrochloride, and after 5 min, filtered off the sodium chloride precipitate. To the filtrate obtained we added 3.5 g (0.01 mole) of the chromone X and boiled the reaction mixture for 20 h. The dry residue after evaporation of the alcohol under vacuum was dissolved in 100 ml of cold water and acidified with dilute hydrochloric acid to pH 6. The product formed was filtered and crystallized from alcohol. Yield 2.9 g (75%). Yellowish crystals with mp 236-238°C. PMR spectrum (DMSO-d_6): protons of the phenolic portion 10.17 (2-OH); 6.42 (3-H); 3.77 (4-OCH_3); 0.87; 1.53; 2.45 (5-C_3H_7); 6.95 (6-H); 7.30 (2-NH_2); 8.85 (6-H); Protons of the pyrimidine ring: Protons of benzthiazole: 7.95 (4-, 7-H); 7.39 ppm (5-, 6-H).

2-Amino-3-(2-benzthiazolyl)-6-propyl-7-methoxychromone (XVI). A mixture of 0.35 g (1 mmole) of the chromone X, 0.2 g (3 mmoles) of hydroxylamine hydrochloride, and 2 ml of absolute pyridine was heated at 100-120°C for 3 h. The precipitate was filtered off and crystallized from dimethylformamide.

3-(2-Hydroxy-4-methoxy-5-propylphenyl)-4-(2-benzthiazolyl)-5-aminopyrazole (XVII, $C_{20}H_{20}N_4O_2S$), was produced analogously to compound XIV from 0.73 g (2 mmoles) of the chromone XVI in alcohol and 12 ml of a 2 N alcohol solution of hydrazine hydrate by boiling for 5-10 min and purified by crystallization from alcohol. Yield 0.58 g (78%). Colorless crystals with mp 236-238°C. PMR spectrum (DMSO-d_6): protons of the phenolic portion: 9.46 (2-OH); 6.58 (3-H); 3.81 (4-OCH_3); 0.88; 1.53; 2.46 (5-C_3H_7) 6.94 (6-H); protons of pyrazole: 12.03 (N−H); 5.7 (5-NH_2); protons of benzthiazole: 7.85 (4-H); 7.32 (5-, 6-H); 7.85 ppm (7-H).

3-(2-Benzthiazolyl)-6-alkyl-7-hydroxy-8-dimethylaminomethylchromones (XVIIIa,b). A mixture of 5 mmoles of the corresponding chromone VIa or VIb and 2.5 ml of bis-dimethylaminomethane in 25 ml of absolute dioxane was boiled for 1.5-2 h. Dioxane and excess amine were distilled off at reduced pressure, and XVIIIa was recrystallized from hexane and XVIIIb from alcohol.

3-(2-Benzthiazolyl)-6-propyl-7-hydroxy-8-dimethlaminomethylchromone Hydrochloride (XIX). The Mannich base XVIIIa was dissolved in dry chloroform, and dry HCl was passed through until formation of a precipitate ceased. The precipitate was filtered off and dried. Yield quantitative.

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