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CHEMISTRY OF MODIFIED FLAVONOIDS. XVIII.* THIAZOLE ANALOGS OF ISOFLAVONES. HOMOLOGOUS AND ISOMERIC SERIES

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Homologous and isomeric series of thiazole derivatives of isoflavones were produced on the basis of α-(4-methyl-2-thiazolyl)-2-hydroxyacetophenones. A study of α-(4-methyl-2-thiazolyl)-2-hydroxyacetophenones by PMR spectroscopy showed that these compounds exist in most nonpolar and low-polarity organic solvents exclusively in the ketone form, but in dimethyl sulfoxide solution both the ketone and enol forms are observed in various ratios. A simple and effective preparative method of synthesis of homologs of 3-(2-diazolyl)-chromones was developed, and their alkylation at the phenolic hydroxyl was studied. Data of biological tests of the compounds synthesized are presented.

Numerous investigations on the chemistry and pharmacology of thiazole analogs of isoflavones have already been conducted. The 3-diazolylchromones, in which the thiazole ring is bonded to the chromone C-4 atom, have been investigated more systematically and fully [2-16]. There is little information on the synthesis and properties of 3-(5-thiazolyl)chromones [17] and 3-(2-thiazolyl)chromones [18]. The high physiological activity of the 3-thiazolylchromone derivatives described earlier [13-16] dictated the goal of the present investigation: to develop convenient preparative methods of synthesis of homologs of thiazole analogs of isoflavones with the general formula 2-H(CF_3)-3-(4-methyl-2-thiazolyl)-6-alkyl-7-hydroxychromones and isomeric 3-(2-thiazolyl)chromones for the further study of their chemical and biological properties and the establishment of the dependence of the influence of the nature of the substituents both in the chromone ring and in the thiazole ring on the physiological activity.

The α-(4,methyl-2-thiazolyl)-2-hydroxyacetophenones (I-IX) necessary for the synthesis of the thiazole analogs of isoflavones were produced by condensation of the cyanomethyl derivative of thiazole with resorcinol, 4-alkylresorcinols, and orcinol in boron trifluoride etharate in a stream of dry hydrogen chloride. In the reaction of 4-methyl-2-thiazolylacetonitrile with resorcinol and alkylresorcinols we might have expected the formation of two isomeric compounds. However, chromatographic analysis showed that in practice one isomer is formed. Its structure was determined on the basis of the PMR spectra measured in DMSO (Table 1). For compounds I-VII there are signals of the OH groups in the region of 12.0 and 10.7-10.8 ppm and singlets of the protons of the phenolic portion in the region of 6.3-6.4 and 7.7-8.0 ppm, which is a confirmation of the structures I-VII. For the isomeric structures Ia-VIIa we should have expected that the signals of the aromatic protons would take the form of the spin system AB, and the signals of the OH groups would merge into one peak. We also found by PMR spectroscopy that compounds I-VII are characterized by keto-enol tautomerism. In most nonpolar and low-polarity organic solvents these substances exist exclusively in the ketone form, but in dimethyl sulfoxide solution they are enolized to various degrees (see Table 1). Such enolization is supported by the doubled number of signals of the protons of the hydroxyl groups, the decrease in the intensity of the peak of the protons of the methylene unit, and the appearance of the signal of the methine proton of the olefinic fragment of the enol form. To refine the assignments of the signals of various forms on the example of

*For communication 17, see [1].

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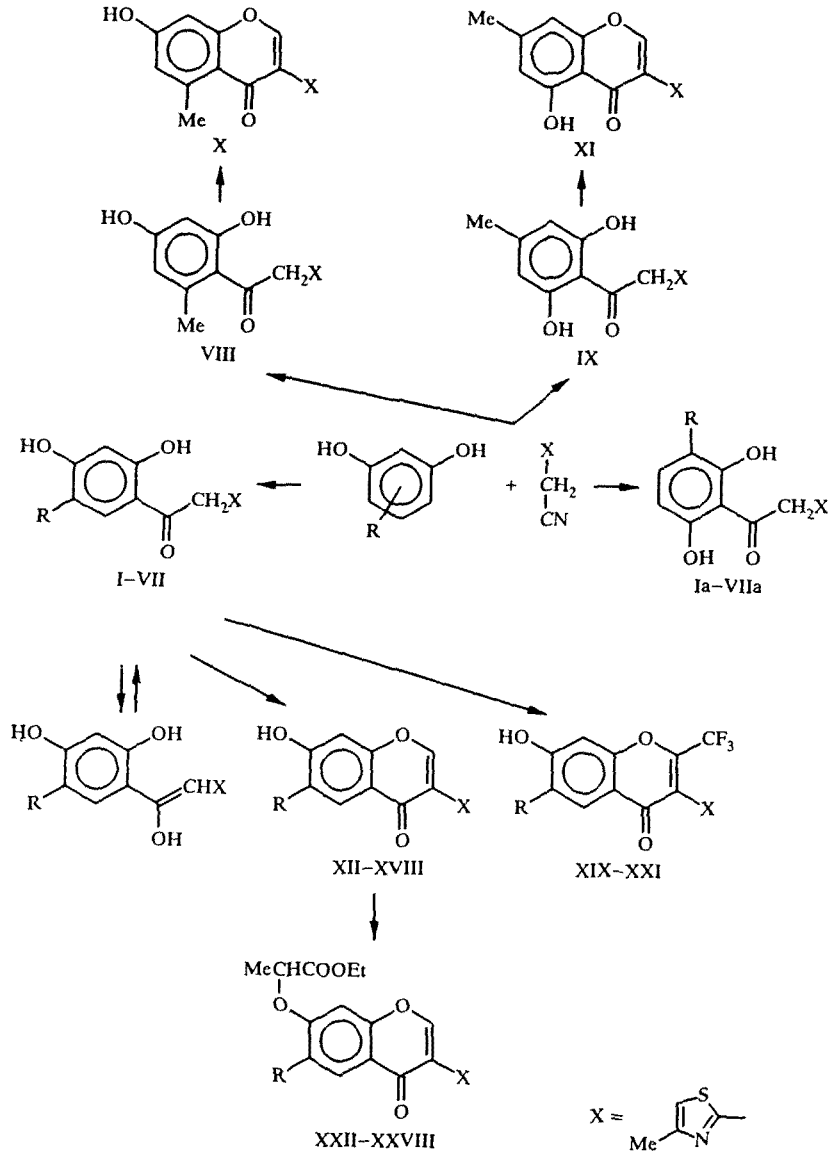
compound I we conducted experiments on the homonuclear Overhauser effect (see Fig. 1). It can be seen that a significant increase in the intensity of the signal of the H-6 proton is observed in the enol form of the compound after irradiation at the frequency of the methylene protons (as well as the reverse effect). This is associated with the rigid fixation of the benzene ring of acetophenone by a hydrogen bond between the 2-OH hydroxyl and the ketone carboxyl and, consequently, the closeness in space of these protons. An analogous nuclear Overhauser effect is observed between the olefinic proton and the 6-H proton of the enol form.



I, XII, XIX, XXII R = H; II, XIII, XXIII R = Me; III, XIV, XXIV R = Et; IV, XV, XX, XXV R = Ph; V, XVI, XXVI R = Bu; VI, XVII, XXI, XXVII R = Am; VII, XVIII, XXVIII R = Hex

We also found that the amount of the enol form of compound I depends greatly on the temperature. Although at room temperature the enol content exceeds the content of the ketone form, at 400 K the proportion of the enol form in the mixture of tautomers drops to 20%. Figure 2 shows the temperature dependence of the composition of the tautomeric mixture for compound I. The rate of interconversion of the tautomers proves to be rather high, and their equilibrium ratio is established virtually instantaneously.

TABLE 1. Characteristics of α-(4-Methyl-2-thiazolyl)-2-hydroxyacetophenones I-IX

Compound	Empirical formula	mp, °C	PMR spectrum, δ, ppm										Yield, %
			protons of phenolic portion					$-CH_2-$, $-C=CH$, OH	protons of thiazole		NMR solvent	tautomeric composition	
			2-OH	3-H	4-OH, 4-Me	5-R	6-H, 6-Me		$4-CH_3$	5-H			
1	2	3	4	5	6	7	8	9	10	11	12	13	14
I	$C_{12}H_{11}NO_3S$	171...172	12,22	6,40	9,75	6,50	7,92	4,72	2,37	7,07	Acetone		63
			12,11	6,35	10,72	6,40	7,87	4,72	2,34	7,19	DMSO	Ketone 50	
			12,35	6,20	9,84	6,23	7,43	14,66, 6,43	2,19	6,40		Enol 50	
II	$C_{13}H_{13}NO_3S$	209...210	11,99	6,35	9,76	2,07	7,75	4,70	2,31	7,14	DMSO	Ketone 50	55
				6,20	9,76	2,07	7,28	14,37, 6,46	2,20	6,38		Enol 50	
III	$C_{14}H_{15}NO_3S$	170...171	12,29	6,39	9,70	1,19, 2,60	7,87	4,70	2,36	7,07	Acetone		68
			12,00	6,14	9,25	1,17, 2,53	7,32	4,53	2,50	6,93	Chloroform		
			12,65	6,23	8,78	1,23, 2,60	7,15	3,99	2,12	6,16	Benzene		
				6,28		1,81, 2,56	7,67	4,65	2,40	7,06	Methanol		
			12,84	6,80		1,31, 2,73	7,97	4,92	2,35	7,01	Pyridine		
			12,01	6,34	10,73	1,13, 2,51	7,75	4,73	2,33	7,17	DMSO	Ketone 65	
			12,27	6,21	9,81	1,13, 2,51	7,28	14,41, 6,50	2,20	6,42		Enol 35	
IV	$C_{15}H_{17}NO_3S$	168...169	12,27	6,38	9,65	0,93, 1,63, 2,56	7,86	4,69	2,36	7,07	Acetone		69
			11,99	6,33	10,66	0,89, 1,54, 2,48	7,72	4,70	2,33	7,18	DMSO	Ketone 65	
			12,25	6,20	9,75	0,89, 1,54, 2,48	7,26	14,37, 6,48	2,19	6,40		Enol 35	

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10	11	12	13	14
V	$C_{16}H_{19}NO_3S$	175...176	12,27	6,38	9,65	0,93, 1,48, 2,59	7,86	4,69	2,36	7,07	Acetone		53
			11,99	6,33	10,76	0,90, 1,40, 2,39	7,73	4,71	2,33	7,17	DMSO	Ketone 65	
			12,20	6,20	9,77	0,90, 1,40, 2,39	7,26	14,39, 6,48	2,20	6,40		Enol 35	
VI	$C_{17}H_{21}NO_3S$	156...157	12,27	6,38		0,90, 1,38, 1,63, 2,59	7,87	4,69	2,37	7,07	Acetone		62
			12,00	6,33	10,71	0,87, 1,36, 2,46	7,73	4,71	2,33	7,18	DMSO	Ketone 60	
			12,25	6,19	9,77	0,87, 1,36, 2,46	7,25	14,37, 6,48	2,20	6,41		Enol 40	
VII	$C_{18}H_{23}NO_3S$	126...127	12,27	6,38	9,70	0,90, 1,34, 1,59, 2,59	7,86	4,69	2,36	7,07	Acetone		75
			12,00	6,33	10,71	0,86, 1,28, 2,40	7,73	4,70	2,33	7,18	DMSO	Ketone 65	
			12,25	6,19	9,76	0,86, 1,28, 2,40	7,25	14,39, 6,48	2,20	6,42		Enol 35	
VIII	$C_{13}H_{13}NO_3S$	190...191	9,73	6,00	10,21	6,20	2,06	4,49	2,29	7,10	DMSO	Ketone 65	56
			12,38	6,00	9,47	6,20	2,06	13,53, 6,05	2,29	6,18		Enol 35	
IX	$C_{13}H_{13}NO_3S$	231...232	12,49	6,09	2,12	6,09	12,49	4,75	2,32	7,27	DMSO	Ketone 35	11
			12,71	6,09	2,12	6,09	12,71	6,44	2,12	7,15		Enol 65	

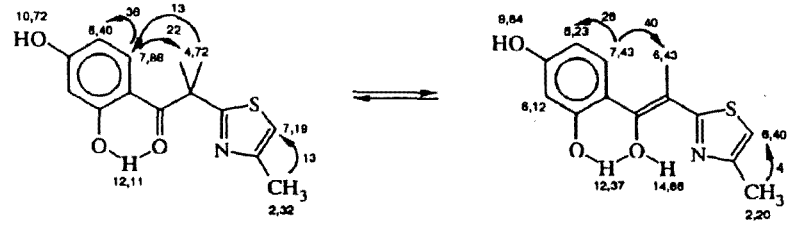


Fig. 1. Values of the NOE between protons of compound I. The chemical shifts of the signals (ppm) and increase in signal intensity (%) are indicated.

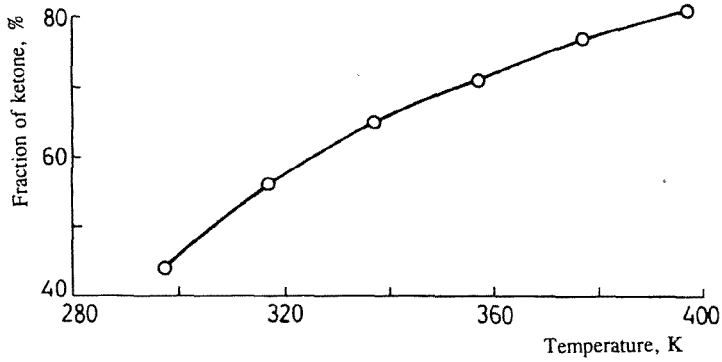


Fig. 2. Temperature dependence of the content of the ketone and enol forms in compound I.

In the condensation of 2-cyanomethyl-4-methylthiazole with orcinol, two isomeric ketones VIII and IX are formed; the yield of the isomer VIII is greater than that of the isomer IX. These compounds are also characterized by keto-enol tautomerism. The content of the enol form in the ketone IX reaches 65%, which is probably due to supplementary stabilization of the enol on account of the phenolic hydroxyl 6-OH. In the isomeric ketone VIII there is no such supplementary stabilization, as a result of which the enol content is reduced to 35%.

To obtain homologous and isomeric series of thiazole analogs of natural isoflavones, containing no substituent in the $C_{(2)}$ position of the chromone system, one can use the method of Venkataraman, consisting of heating of the ketones with ethyl orthoformate in absolute pyridine in the presence of catalytic amounts of piperidine at 120-130°C (method A). Compounds X-XII were produced in precisely this way [18]. However, cyclization to chromones under the influence of acetic-formic anhydride (method B) is more convenient preparatively [19]. The use of this convenient and effective reagent made it possible to conduct the cyclization under mild conditions in the absence of the base in a short time, often almost quantitatively. The method is preparatively convenient, since it is simple to perform, makes it possible to eliminate various side processes, and gives the target compounds in chromatographically pure form. The chromones XII-XVIII were produced according to method B.

Interaction of the ketones I, IV, and VI with trifluoroacetic anhydride in pyridine under mild conditions leads to the formation of thiazole analogs of the natural isoflavones XIX-XXI, containing a trifluoromethyl group in the 2-position of the chromone system.

Homologs of the 3-(4-methyl-3-thiazolyl)-6-alkyl-7-hydroxychromone series XII-XVIII are readily alkylated at the phenolic fragment by the ethyl ester of α-bromopropionic acid in absolute acetone or dioxane in the presence of potash, resulting in the formation of alkoxy derivatives of the chromones XXII-XXVIII.

The isomeric 3-(4-methyl-2-thiazolyl)chromones X and XI obtained and representatives of the homologous series of 3-(4-methyl-2-thiazolyl)-6-alkyl-7-hydroxychromones XII-XVIII, trifluoromethyl-3-(4-methyl-2-thiazolyl)-6-alkyl-7-hydroxychromones XIX-XXI, and alkoxy derivatives of 3-(4-methyl-2-thiazolyl)-6-alkylchromones XXII-XXVIII are colorless

TABLE 2. Characteristics of 3-(4-Methyl-2-thiazolyl)chromones X-XXVIII

Compound	Empirical formula	mp, °C	PMR spectrum, δ, ppm							Yield, %
			protons of chromone ring					protons of thiazole		
			2-H	5-H, 5-CH_3	6-R	7-R	8-H	4-CH_3	5-H	
X	$C_{14}H_{11}NO_3S$	265...266	8,86	2,81	6,68	10,64	6,88	2,47	7,19	92
XI	$C_{14}H_{11}NO_3S$	198...199	8,90	12,08	6,63	2,41	6,72	2,50	6,95	71
XII	$C_{13}H_9NO_3S$	260...261*	9,05	7,99	6,97	10,81	6,91	2,44	7,26	97
XIII	$C_{14}H_{11}NO_3S$	287...289*[2]	9,04	7,89	2,22	10,93	6,93	2,40	7,28	95
XIV	$C_{15}H_{13}NO_3S$	273...275*[2]	9,04	7,86	1,18, 2,63	10,94	6,94	2,40	7,29	98
XV	$C_{16}H_{15}NO_3S$	266...267	9,05	7,87	0,97, 1,60, 2,68	11,05	6,98	2,47	7,32	98
XVI	$C_{17}H_{17}NO_3S$	245...247	9,04	7,84	0,89, 1,47, 2,63	10,89	6,94	2,41	7,28	94
XVII	$C_{18}H_{19}NO_3S$	237...238	9,04	7,84	0,86, 1,30, 1,57, 2,62	10,88	6,94	2,40	7,28	96
XVIII	$C_{19}H_{21}NO_3S$	224...225	9,06	7,85	0,83, 1,29, 1,55, 2,63	10,92	6,95	2,41	7,29	94
XIX	$C_{14}H_8F_3NO_3S$	169...170	—	7,93	7,02	11,22	6,94	2,44	7,52	94
XX	$C_{17}H_{14}F_3NO_3S$	208...210	—	7,81	0,92, 1,60, 2,64	11,28	6,98	2,42	7,56	90
XXI	$C_{19}H_{18}F_3NO_3S$	178...180	—	7,78	0,85, 1,29, 1,56, 2,62	11,22	6,95	2,41	7,54	88
XXII	$C_{18}H_{17}NO_5S$	167,5	9,01	8,26	7,05	1,69, 4,27, 1,27, 4,80	6,90	2,50	7,00	52
XXIII	$C_{19}H_{19}NO_5S$	147...148	8,99	8,09	2,37	1,71, 4,26, 1,27, 4,84	6,71	2,50	6,99	65
XXIV	$C_{20}H_{21}NO_5S$	127	8,99	8,11	1,29, 2,78	1,71, 4,26, 1,26, 4,87	6,72	2,50	7,00	87
XXV	$C_{21}H_{23}NO_5S$	103...104	8,99	8,09	0,98, 1,71, 2,75	1,71, 4,23, 1,26, 4,84	6,72	2,49	6,99	64
XXVI	$C_{22}H_{25}NO_5S$	168	8,99	8,09	0,96, 1,42, 2,76	1,70, 4,26, 1,26, 4,89	6,72	2,49	7,00	76
XXVII	$C_{23}H_{27}NO_5S$	107...108	8,99	8,09	0,91, 1,33, 2,75	1,70, 4,23, 1,26, 4,84	6,72	2,49	6,99	51
XXVIII	$C_{24}H_{29}NO_5S$	78...79	8,99	8,09	0,89, 1,33, 2,75	1,71, 4,24, 1,26, 4,85	6,72	2,49	6,99	53

*With decomposition.

*[2]With sublimation. The spectra of compounds X-XXII were measured in DMSO-D_6, the rest in deuterochloroform.

crystalline compounds, readily soluble in polar organic solvents. Their structure was confirmed by the data of elementary analysis and PMR spectroscopy (see Table 2).

Pharmacological investigations of the homologs of the series of 3-(4-methyl-2-thiazolyl)-6-alkyl-7-hydroxychromones obtained and their alkoxy derivatives made it possible to determine the relationship of their biological action to the structure of the molecules. Thus, with increasing length of the hydrocarbon chain in position 6 among homologs of 3-(4-methyl-2-thiazolyl)-6-alkyl-7-hydroxychromones, an appreciable increase in the hypolipidemic activity is observed. Introduction of an alkyl fragment at the phenolic hydroxyl expands the range of biological action of homologs of 3-(4-methyl-2-thiazolyl)-6-alkylchromones. The most interesting compound in the series of 7-alkoxyhomologs proved to be 3-(4-methyl-2-thiazolyl)-6-propyl-7-(1-methyl-1-ethoxycarbonyl)-methoxychromone XXV, which exhibits hypolipidemic, hypoglycemic, and analeptic effects. The indicated properties permit this substance to be considered promising for the creation of a drug with complex action.

EXPERIMENTAL

The purity of the compounds obtained and the course of the reactions were monitored by thin-layer chromatography on Silufol UV-254 plates. Mixtures of benzene and ethanol, chloroform and methanol (9:1) were used as the eluent. The PMR spectra were measured on WP-100 SY and CXP-200 instruments (Bruker) relative to TMS (internal standard).

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

General Method for Producing α-(4-Methyl-2-thiazolyl)-2,4-dihydroxy-5H(alkyl)acetophenones (I-VII). A stream of dry hydrogen chloride was passed for 8 h into a mixture of 21.9 g (0.1 mole) 4-methyl-2-cyanomethylthiazole hydrobromide and 0.11 mole of resorcinol or the corresponding 4-alkylresorcinol in 80-90 ml of boron trifluoride etherate. Then the reaction mixture was introduced into 500 ml of hot water, and hydrolysis was conducted for 1 h. After this the solution was alkalinized to pH 5-6. The precipitate formed was purified by crystallization from methanol for compound I and by reprecipitation from alkaline solution (8% NaOH) with a 10% solution of acetic acid for compounds II-VII, followed by crystallization of compounds II-IV and VII from alcohol and V and VI from benzene.

α-(4-Methyl-2-thiazolyl)-2,4-dihydroxy-6-methylacetophenone (VIII) and α-(4-Methyl-2-thiazolyl)-4-methyl-2,6-dihydroxyacetophenone (IX) were produced analogously to compounds I-VII from 11.04 g (0.08 mole) 4-methyl-2-cyanomethylthiazole and 12 g (0.09 mole) orcinol in 80 ml of boron trifluoride etherate. Yield of the mixture of isomer 16.14 g (77%). The mixture of isomeric ketones was separated into individual compounds by fractional crystallization from aqueous alcohol and benzene.

General Method for Producing 3-(4-Methyl-2-thiazolyl)-5-methyl-7-hydroxychromone (X), 3-(4-Methyl-2-thiazolyl)-5-hydroxy-7-methylchromone (XI), and 3-(4-Methyl-2-thiazolyl)-7-hydroxychromone (XII). A mixture of 0.075 mole of the ketone VIII, IX, or I in 50 ml of ethyl orthoformate, 5 ml of pyridine, and 2 ml of piperidine was heated at 120-130°C for 4 h. The crystals that precipitated upon cooling were filtered off, washed with cold water, and crystallized from alcohol.

General Procedure for Producing 3-(4-Methyl-2-thiazolyl)-6-alkyl-7-hydroxychromones (XII-XVIII). A mixture of 10 mmoles of the corresponding α-(4-methyl-2-thiazolyl)-2,4-dihydroxy-5-alkylacetophenone II-VII in 10 ml of acetic-formic anhydride was heated at 80-100°C for 1-1.5 h. After cooling of the reaction mixture, the precipitate that formed was filtered off and washed with cold alcohol. The course of the reaction was monitored by thin-layer chromatography. Here the fact that the initial ketones give a reaction with an alcohol solution of ferric chloride, whereas the intermediate products formed — formyl derivatives — and the target chromones do not give this reaction, was utilized. Formyl derivatives are located on the chromatogram above the target chromones. Deformylation of the formyl derivatives during heating leads to the end products XII-XVIII.

General Procedure for the Production of 2-Trifluoromethyl-(4-methyl-2-thiazolyl)-6-alkyl-7-hydroxychromones (XIX-XXI). To a solution of 10 mmoles of the ketone I, IV, or VI in a minimum volume of pyridine, 2.8 ml (20 mmoles) of trifluoroacetic anhydride was added dropwise with cooling. After 18 h of standing at room temperature the reaction mixture was poured out into 100 ml of water; the precipitate that formed was filtered off and crystallized from acetic acid.

General Procedure for the Production of 3-(4-Methyl-2-thiazolyl)-6-alkyl-7-(1-methyl-1-ethoxycarbonyl)-methoxychromones (XXII-XXVIII). To a hot mixture of 0.025 mole of the corresponding 3-(4-methyl-2-thiazolyl)-6-alkyl-7-

hydroxychromone XII-XVIII and 10.3 g (0.075 mole) of freshly prepared potash in absolute acetone or dioxane, 5.2 ml (0.04 mole) of the ethyl ester of α-bromopropionic acid was added dropwise, and the mixture was heated with mixing for 2.5-6 h. The hot solution was filtered off from the inorganic precipitate, the solvent was distilled off, and the end products were crystallized from alcohol.

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