salt was precipitated from the mother liquor by the addition of ether. Data on the yields and properties of pyrylium salts I and the results of analysis are presented in Table 1.

Synthesis of Pyridines II from Pyrylium Salts I. A) Pyrylium salt Ia was suspended in glacial acetic acid, a fivefold excess of ammonium acetate was added, and the mixture was refluxed for 1 h. It was then diluted with water and neutralized with NH_4OH. The aqueous mixture was extracted with benzene, the solvent was removed from the extract by vacuum evaporation to dryness, and the residue was recrystallized from heptane.

B) The pyrylium salt (Ib,c) was suspended in C_2H_5OH, 25% ammonium hydroxide was added, and the mixture was allowed to stand for 2 days. It was then extracted with ether, and the ether was removed from the extract by vacuum evaporation to dryness. The residue was recrystallized from alcohol (Table 1).

Synthesis of N-Phenylpyridium Salts III from Pyrylium Salts I. A mixture of equimolar amounts of aniline and pyrylium salt I was refluxed for 1 h in glacial acetic acid (in the case of Ia) or for 1.5-2 h in C_2H_5OH (in the case of Ib,c), after which the mixture was cooled, and the precipitate was removed by filtration. An additional amount of salt III can be precipitated by means of ether. Pyridinium salt III contained crystallization acetic acid from which it can be freed by drying at 160-190°C. Analytically pure samples of pyridium salts III were obtained by recrystallization from alcohol (Table 1).

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CHEMISTRY OF HETEROANALOGS OF ISOFLAVONES.

7.* SYNTHESIS OF THIAZOLE ANALOGS OF ISOMERIC ISOFLAVONES

V. P. Khilya, V. F. Vakulenko, and I. P. Kupchevskaya

UDC 547.814.1'789.1.07

Thiazole analogs of isomeric isoflavones were synthesized from α-(2,4-dimethyl-5-thiazolyl)-2-hydroxyacetophenones, and their reaction with hydrazine hydrate and alkylating and acylating agents was studied. The reaction of thiazole derivatives of 7-hydroxychromone with hydrazine hydrate proceeds with opening of the pyrone ring and subsequent cyclization of the intermediate to o-hydroxyphenylpyrazole derivatives. The reaction of hydrazine hydrate with thiazole derivatives of 5-hydroxychromone, which proceeds with retention of the pyrone ring, leads to hydrazones. The structures of the new compounds were confirmed by the PMR spectra.

Flavonoids are an interesting and unusual group of natural compounds with a broad spectrum of biological activity [2], owing to which they have found application as medicinals. In addition to the utilization of preparations isolated from natural raw material, synthetic products, particularly modified flavonoids, are becoming increasingly valuable. The phenyl group in their molecules is replaced by other groups, including heterocyclic residues with aromatic character.

In the development of research on the synthesis and study of the chemical and biological properties of heterocyclic derivatives of isoflavone as potential physiologically active substances we obtained new thiazole analogs of isomeric isoflavones I-III, as well as compounds of the IV series, and investigated their reactivities with respect to hydrazine hydrate and alkylating and acylating agents. The starting compounds for the synthesis of these

*See [1] for communication 6.

T. V. Shevchenko Kiev State University, Kiev 252017.

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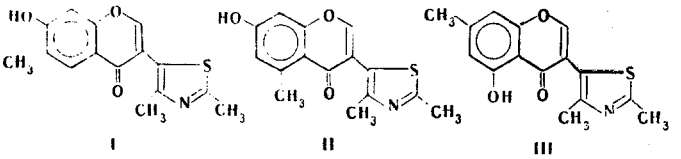
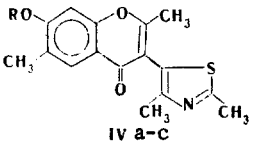


I II III

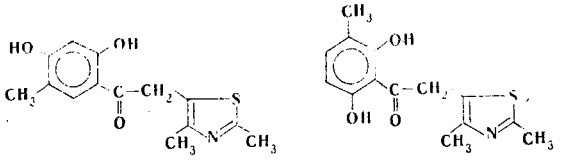


IV a-c

IVa R=H; b R=COCH$_3$; c R=CH$_3$

compounds were α-(5-thiazolyl)-2-hydroxyacetophenones, which were obtained by condensation of 2,4-dimethyl-5-cyanomethylthiazole with 4-methylresorcinol and orcinol [3].

One might have expected the formation of two isomeric compounds, V and VI, in the reaction of 2,4-dimethyl-5-cyanomethylthiazole with 4-methylresorcinol.



V VI

Chromatographic analysis showed that virtually one isomer is formed. The selection of its structure was made on the basis of the PMR spectrum of the compound in dimethyl sulfoxide (DMSO). The spectrum of V contains peaks of phenolic hydroxy groups at 10.67 and 12.08 ppm and singlets of protons of the phenolic part of the molecule at 6.36 and 7.76 ppm; this is a confirmation of structure V [4]. In the case of structure VI one might have expected that the signals of the benzene protons would appear in the form of doublets of an AB system, whereas the signals of the OH groups, which alternately form an intramolecular hydrogen bond with the carbonyl oxygen atom, combine to give a single peak.

Ketone V was converted by heating with acetic anhydride in the presence of triethylamine to 2,6-dimethyl-7-acetoxychromone IVb, from which 2,6-dimethyl-7-hydroxychromone IVa was obtained by the action of dilute alkali and brief heating.

The synthesis of the isomeric 3-(5-thiazolyl)chromones I-III, which do not contain substituents in the 2 position, was accomplished by the action of ethyl orthoformate in pyridine solution on the corresponding o-hydroxyacetophenones in the presence of catalytic amounts of piperidine. The rates of formation of the isomeric compounds differed. Thus, in the case

TABLE 1. Thiazole Analogs of Isoflavones

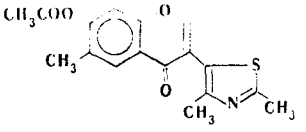
Compound	mp, °C	S found, %	Empirical formula	S calc., %	PMR spectrum, δ, ppm							Yield, %
					protons of the chromone ring					thiazole protons		
					2-R	5-R	6-R	7-R	8-H	2-CH$_3$	4-CH$_3$	
I	282	11.4	$C_{15}H_{13}NO_3S$	11,2	H, 8,43	H, 7,85	CH$_3$, 2,34	OH, 10,95	6,97	2,73	2,46	94
II	295	11,1	$C_{15}H_{13}NO_3S$	11,2	H, 8,32	CH$_3$, 2,73	H, 6,71	OH, 10,68	6,71	2,70	2,42	93
III	155—156	11,0	$C_{15}H_{13}NO_3S$	11,2	H, 7,98	OH, 12,20	H, 6,66	CH$_3$, 2,47	6,75	2,73	2,47	65
IVa	249	10,8	$C_{16}H_{15}NO_3S$	10,6	CH$_3$, 2,31	H, 7,71	CH$_3$, 2,16	OH, 10,80	6,88		2,31	91
IVb	135—136	9,4	$C_{18}H_{17}NO_4S$	9,3	CH$_3$, 2,40	H, 8,06	CH$_3$, 2,30	OCOCH$_3$, 2,45	7,23	2.77	2,35	92
IVc	213—214	10,0	$C_{17}H_{17}NO_3S$	10,2	CH$_3$, 2,38	H, 7,93	CH$_3$, 2,32	CH$_3$O, 4,01	6.83	2.77	2,38	66
VII	168	9.8	$C_{17}H_{15}NO_4S$	9,7	H, 8,52	H, 8,02	CH$_3$, 2,34	OCOCH$_3$, 2,46	7,51	2,72	2,46	76
VIII	160—161	9,7	$C_{17}H_{15}NO_4S$	9.7	H, 7,75	OCOCH$_3$, 2,43 or 2,40	H, 6,75	CH$_3$, 2,48	7,06	2,68	2,40 or 2,43	83
XI*	246	10,6 N, 13,9	$C_{15}H_{15}N_3O_2S$	10,6 N, 13.9	H, 7,72	OH, 12,84	H, 6,24	CH$_3$, 2,26	6,24		2,26	82

*The peak of the 4-H—NH$_2$ grouping is found at 9.22 ppm. The PMR spectra of IVb,c, VII, and VIII were obtained from solutions in deuterochloroform.

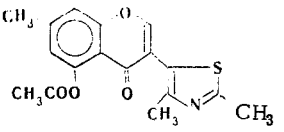
of the preparation of III heating the reaction mixture for 2 h was sufficient, whereas chromones I and II required longer refluxing (6 h).

The signals of the 6-H and 8-H protons virtually coincide in the PMR spectrum (Table 1) of isomeric chromone II. In the spectrum of I both protons of the phenolic portion of the chromone ring appear in the form of narrow singlets, whereas they appear in the form of slightly broadened peaks in the spectrum of isomer III. 5-Hydroxychromone III differs from isomeric I and II with respect to its higher chromatographic mobility and higher solubility in low-polarity and nonpolar organic solvents. The IR spectrum of solid III does not contain absorption of a 5-OH group, and III reacts with an alcohol solution of ferric chloride to give an intensely colored complex. The position of the signal of the hydroxy group in the PMR spectrum is virtually independent of the solvent because of the formation of an intramolecular chelate. All of these peculiarities are useful as evidence for the structure of derivatives of the III series.

The action of acetic anhydride on a pyridine solution of I at room temperature leads to the formation of 7-acetoxy derivative VII, which is converted quantitatively to free 7-hydroxychromone under the influence of 5% sodium hydroxide solution. More severe conditions are required for the acylation of derivative III. This may be associated with the fact that cleavage of the intramolecular hydrogen bond is necessary for the reaction to occur. 5-Acetoxychromone VIII is formed only in the case of prolonged refluxing in acetic anhydride. The end of the reaction is conveniently determined from a negative test with an alcohol solution of ferric chloride.



VII

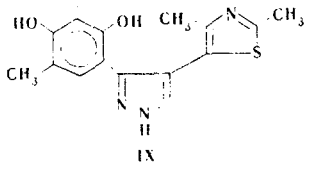


VIII

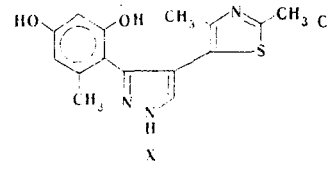
Methylation of the 7-OH group of the chromone ring proceeds smoothly when 7-hydroxychromone IVa is treated with methylating agents in acetone solution in the presence of potassium carbonate. The PMR spectrum of IVc does not contain the signal of the proton of a phenolic hydroxy group; instead, a singlet of a methyl group appears at 4 ppm.

It is known [5, 6] that opening of the pyrone ring occurs in the reaction of hydrazine hydrate with chromones and 4-thiooxochromones that contain CH_3, C_6H_5, and OH groups in the 3 position. Derivatives with a free 3 position form hydrazones.

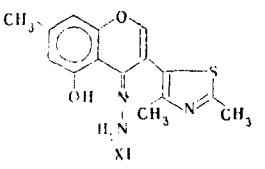
We found that the nature of the products formed in the reaction of thiazole analogs of isoflavones with hydrazine hydrate is determined by their structure. Isomeric chromones I and II are converted to pyrazole derivatives IX and X under the influence of hydrazine hydrate; this is confirmed by their chemical reactions and PMR spectra. Compound IX dissolves readily in 2 N aqueous alkali and reacts with an alcohol solution of ferric chloride to give a blue-green complex because of the presence in the ortho position relative to the heterocyclic nitrogen atom of a hydroxy group that is capable of forming a chelate.



IX



X



XI

The chelate group makes it possible to explain the 1.05-ppm shift of the signal of the 6-H proton in the PMR spectrum of IX to strong field as compared with the position of the peak of the 5-H proton of starting I. The broadened signal of the 5-H proton of the pyrazole ring (spin–spin coupling with the proton attached to the nitrogen atom) and the separately observable singlets of 2-OH and NH groups at 12.92 and 9.85 ppm also constitute evidence for the pyrazole structure of IX.

Pyrazole X, formed from chromone II, does not give a color reaction with an alcohol solution of ferric chloride, since in this case the formation of a chelate complex is impos-

sible because of steric hindrance on the part of the 6-CH_3 group of the phenolic portion of the molecule. This hindrance gives rise to an 0.88-ppm diamagnetic shift of the peak of the indicated group as compared with starting II, since the methyl group is found in the region of shielding by the aromatic ring currents of the pyrazole ring, whereas the carbonyl oxygen atom has the opposite effect on it in the case of starting chromone II.

Compound III behaves in a different way under the influence of hydrazine hydrate. The pyrone ring is not opened, and the reaction product is hydrazone XI. Two singlets corresponding to the OH and NH_2 groups, of which the two-proton singlet lies at stronger field (9.22 ppm) than the one-proton peak (12.84 ppm), are observed in the PMR spectrum of this compound. In the case of a pyrazole structure of the IX and X type the signal of two equivalent hydroxy groups would be found at weaker field (~13 ppm).

We assume that the reason for the different behavior of I and II, on the one hand, and III, on the other, in the reaction with hydrazine hydrate is stabilization of the hydrazone structure of XI due to the formation of a chelate.

EXPERIMENTAL

The course of the reactions and the purity of the compounds obtained were monitored by thin-layer chromatography on Silufol-254. A mixture of benzene and ethanol (95:5) or a mixture of chloroform and methanol (9:1) was used as the eluent. The PMR spectra of solutions of the compounds in DMSO and deuterochloroform were recorded with a ZKR-60 spectrometer relative to tetramethylsilane (as the internal standard).

Compounds I-V and VII were obtained by the method in [3].

α-(2,4-Dimethyl-5-thiazolyl)-2,4-dihydroxy-5-methylacetophenone (V). This compound, with mp 226°C (from alcohol), was obtained in 71% yield. PMR spectrum: 4.52 (CH_2); protons of the phenolic portion, 12.08 (2-OH), 6.36 (3-H), 10.67 (4-OH), 2.16 (5-CH_3), 7.76 (6-H); thiazole protons, 2.31 ppm (4-CH_3). Found: S 11.5%. $C_{14}H_{15}NO_3S$. Calculated: S 11.6%.

3-(2,4-Dimethyl-5-thiazolyl)-5-acetoxy-7-methylchromone (VIII). A mixture of 1 mmole of chromone III and 3 ml of acetic anhydride was refluxed for 3 h, after which it was cooled, and the precipitate was crystallized from alcohol or benzene.

3-(2-Hydroxyphenyl)-4-(2,4-dimethyl-5-thiazolyl)pyrazoles (IX, X) and 3-(2,4-Dimethyl-5-thiazolyl)-4-hydrazono-5-hydroxy-7-methylchromone (XI). A 6-ml sample of a 2 N solution of hydrazine hydrate in alcohol was added to a hot solution of 1 mmole of chromone in ethanol or propanol. After 5-10 min, the mixture was diluted with water to a volume of 100-120 ml, and the resulting precipitate was removed by filtration. When no precipitate formed upon dilution of the mixture, the solvent was removed by distillation, and the residue was crystallized from aqueous ethanol. Compound IX, with mp 228°C, was obtained in 91% yield. PMR spectrum: protons of the phenolic portion, 12.92 (2-OH), 6.45 (3-H), 9.38 (4-OH), 2.00 (5-CH_3), 6.80 (6-H); protons of the pyrazole ring, 9.85 (NH), 7.72 (5-H); thiazole protons, 2.58 (2-CH_3) and 2.18 ppm (4-CH_3). Found: N 13.8%. $C_{15}H_{15}N_3O_2S$. Calculated: N 13.9%. Compound X, with mp 264-265°C, was obtained in 85% yield. PMR spectrum: protons of the phenolic portion, 12.69 (2-OH), 6.23 (3-H), 9.19 (4-OH), 6.23 (5-H), and 1.85 (6-CH_3); protons of the pyrazole ring, 9.30 (NH) and 7.76 (5-H); thiazole protons, 2.52 (2-CH_3) and 2.29 ppm (4-CH_3). Found: N 14.0; S 10.6%. $C_{15}H_{15}N_3O_2S$. Calculated: N 13.9; S 10.6%.

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