CHEMISTRY OF HETEROANALOGS OF ISOFLAVONES.

9.* REACTION OF THIAZOLE ANALOGS OF ISOFLAVONES WITH NUCLEOPHILIC AND ELECTROPHILIC REAGENTS

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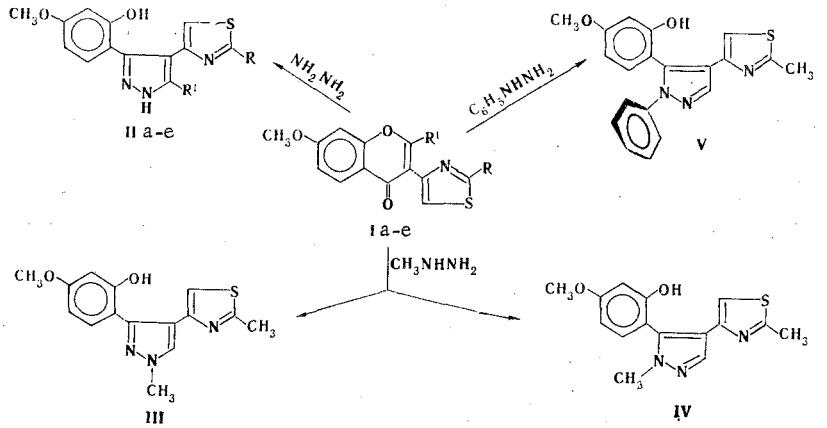
Thiazole analogs of isoflavones and their 4-thioxo derivatives undergo recyclization to pyrazole derivatives and isomeric isoxazoles under the influence of hydrazine, methylhydrazine, phenylhydrazine, and hydroxylamine. A new group enters the 8 position or two groups simultaneously enter the 6 and 8 positions of the chromone ring in electrophilic substitution reactions. Data from the PMR spectra and on the biological activity are presented and discussed.

We have previously shown that derivatives of chromone [2, 3], isoflavone [4], 3-(2-benzofuryl)chromone [5], and 3-(8-quinolyl)chromone [6] are readily recyclized to 3-(2-hydroxyphenyl)pyrazole derivatives under the influence of hydrazine. In the present communication as new examples of nucleophilic reactions in which the carbonyl group and the double bond of the pyrone ring participate we investigated the reaction of thiazole analogs of isoflavones [7, 8] with hydrazine hydrate, methylhydrazine, phenylhydrazine, and hydroxylamine. We found that thiazole analogs of 7-methoxyisoflavone and 2-methyl- and 2-trifluoromethyl-7-methoxyisoflavones (Ia-e) are extremely easily rearranged to (2-hydroxyphenyl)pyrazole derivatives II-IV when they are treated with hydrazine and methylhydrazine; this was proved by chemical reactions and the PMR spectra (Table 1). The reaction of 3-(2-methyl-4-thiazolyl)-7-methoxychromone (Ic) with methylhydrazine gave a mixture of isomeric pyrazoles III and IV, which was separated to give the individual compounds by fractional crystallization and preparative thin-layer chromatography (TLC).



I, II a R=R¹=H; b R=H, R¹=CH₃; c R=CH₃, R¹=H; d R=R¹=CH₃; e R=CH₃, R¹=CF₃

Pyrazoles II-IV are readily soluble in 2 N sodium hydroxide solution, which indicates the presence of a free phenolic hydroxy group in their molecules. Compounds II and III form blue-green chelate complexes with an alcohol solution of ferric chloride as a consequence of the presence of a hydroxy group in the ortho position relative to the nitrogen atom in the pyrazole ring (in the case of pyrazole IV the formation of a colored chelate complex is impossible). A chelate structure makes it possible to explain the 1.0-1.18 ppm shift of the signal

*See [1] for Communication 8.

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TABLE 1. Products of Cleavage of the Chromone Ring of Thiazole Analogs of Isoflavones (Pyrazoles and Isoxazoles)

Compound	mp, °C	PMR spectrum, ppm									Found, %	Empirical formula	Calc., %	Yield, %
		protons of the phenolic part					thiazole protons		pyrazole or isoxazole protons					
		2-OH	3-H	4-OCH_3	5-H	6-H	2-R	5-H	3(5)-H or 3(5)-CH_3	N—R				
IIa	151—152	12,56	6,43	3,75	6,35	7,05	H 8,85	7,00	7,83	H 9,85	N 15,2 S 11,8	$C_{13}H_{11}N_3O_2S$	N 15,4 S 11,7	95
IIb	225—226	12,40	6,42	3,74	6,25	6,92	H 8,93	7,20	2,33	H 10,28	N 14,5 S 11,2	$C_{14}H_{13}N_3O_2S$	N 14,6 S 11,2	93
IIc	156—157	12,45	6,45	3,76	6,35	7,05	CH_3 2,64	6,72	7,76	H 9,81	N 14,6 S 11,2	$C_{14}H_{13}N_3O_2S$	N 14,6 S 11,2	91
IId	177—178	12,37	6,38	3,76	6,25	6,95	CH_3 2,69	6,98	2,31	H 10,33	N 14,0 S 11,0	$C_{15}H_{15}N_3O_2S$	N 14,0 S 10,6	84
IIe	203—204	13,38	6,42	3,69	6,30	6,93	CH_3 2,61	7,05	—	H 9,93	N 11,9	$C_{15}H_{12}F_3N_3O_2S$	N 11,8	88
III	145—146	9,89	6,54	3,81	6,45	7,20	CH_3 2,73	6,83	8,04	CH_3 3,98	N 14,2 S 10,8	$C_{15}H_{15}N_3O_2S$	N 13,9 S 10,6	33
III*		10,26	6,59	3,88	6,36	7,29	CH_3 2,83	6,98	7,56	CH_3 4,00				
IV	159—160	9,80	6,60	3,85	6,53	7,08	CH_3 2,69	6,47	7,77	CH_3 3,67	S 10,2	$C_{15}H_{15}N_3O_2S$	S 10,6	7
IV*		9,87	6,65	3,74	6,56	7,00	CH_3 2,73	6,75	7,69	CH_3 3,91				
V	185,5	9,82	6,53	4,00	6,46	7,04	CH_3	6,53	8,10	C_6H_5 7,33	N 11,6	$C_{20}H_{17}N_3O_2S$	N 11,6	63
VIIb	135—136	9,99	6,52	3,79	6,47	7,19	H 9,02	7,39	2,47	—	N 9,7 S 11,0	$C_{14}H_{12}N_2O_3S$	N 9,7 S 11,1	75
VIIb*		10,38	6,64	3,79	6,56	7,30	H 8,94	7,35	2,43	—				
VIId	102—103	10,05	6,53	3,79	6,47	7,23	CH_3 2,68	7,16	2,40	—	N 9,4 S 10,8	$C_{15}H_{14}N_2O_3S$	N 9,3 S 10,6	79
VIId*		11,05	6,60	3,87	6,53	7,25	CH_3 2,82	7,05	2,51	—				
VIIe	149—150	10,24	6,57	3,80	6,48	7,27	CH_3 2,69	7,36	—	—	N 7,8	$C_{15}H_{11}F_3N_2O_3S$	N 7,9	82
VIIIb	139—140	9,67	6,55	3,77	6,50	7,16	H 9,06	7,07	2,67	—	N 9,8 S 11,0	$C_{14}H_{12}N_2O_3S$	N 9,7 S 11,1	36,5
VIIIb*		9,66	6,64	3,82	6,35	7,02	H 8,99	7,34	2,49	—				
VIIId	107—108	9,65	6,55	3,84	6,51	7,13	CH_3	6,79		—	N 9,6 S 10,7	$C_{15}H_{14}N_2O_3S$	N 9,3 S 10,6	23,9
VIIId*		9,64	6,55	3,83	6,31	6,99	CH_3 2,83	7,00	2,53	—				

*The PMR spectra of the indicated compounds were obtained from solutions in deuterochloroform, while the PMR spectra of the remaining compounds were obtained from solutions in dimethyl sulfoxide.

TABLE 2. Products of Electrophilic Substitution of Thiazole Analogs of Isoflavones

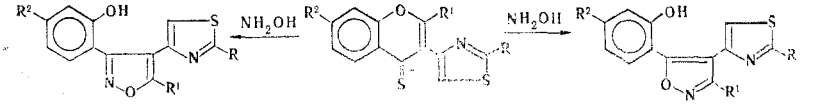
Compound	mp, °C	PMR spectrum,* δ, ppm							Found, %	Empirical formula	Calc., %	Yield, %
		chromone ring protons					thiazole protons					
		2-R	5-H	6-H	7-R	8-R	2-R	5-H				
Ia		H 8,98	8,22	7,01	CH_3O 3,99	H 6,91	H 8,81	8,63				
Ib		CH_3 2,55	8,10	6,90	CH_3O 3,87	H 6,81	H 8,83	7,84				
Ic		H 8,89	8,18	6,97	CH_3O 3,91	H 6,86	CH_3 2,74	8,35				
Id		CH_3 2,49	8,09	6,89	CH_3O 3,87	H 6,82	CH_3 2,73	7,50				
Ie		CF_3	8,07	6,97	CH_3O 3,92	H 6,91	CH_3 2,77	7,31				
VIb		CH_3 2,28	8,47	6,94	CH_3O 3,96	H 6,82	H 8,84	7,38				
VId		CH_3 2,28	8,58	7,01	CH_3O 3,97	H 6,84	CH_3 2,82	7,20				
IXc		H 8,94	8,07	7,02	OH 10,86	H 6,95	CH_3 2,80	8,36				
IXe		CF_3	7,86	7,02	OH 11,05	H 6,95	CH_3 2,75	7,55				
IXf		$COOCH_2CH_3$ 4,36; 1,17	8,00	7,03	OH 10,90	H 6,96	CH_3 2,76	8,09				
Xb	123—124	CH_3 2,68	8,11	6,94	OH 11,69	$CH_2N(CH_3)_2$ 4,12; 2,56	H 8,87	7,92	N 8,9 S 10,2	$C_{16}H_{16}N_2O_3S$	N 8,9 S 10,1	95
Xc	168—169	H 8,73	8,00	6,78	OH 10,57	$CH_2N(CH_3)_2$ 3,97; 2,45	CH_3 2,73	8,23	N 8,9 S 9,7	$C_{16}H_{16}N_2O_3S$	N 8,9 S 10,1	74
XIIe	218—219	CF_3	7,90	7,14	OH 11,83	Br	CH_3 2,71	7,58	Br 20,0	$C_{14}H_7BrF_3NO_3S$	Br 19,7	54
XIIf	220—221	$COOCH_2CH_3$ 4,37; 1,21	7,97	7,14	OH 11,71	Br	CH_3 2,74	8,09	Br 19,0	$C_{16}H_{12}BrNO_5S$	Br 19,5	69
XIIIe	233—234	CF_3	8,09	Br	OH	Br	CH_3 2,71	7,60	Br 33,4	$C_{14}H_6Br_2F_3NO_3S$	Br 32,9	51
XIVb	150	CH_3 2,49	7,66	6,81	OH 11,47	I	H 8,90	7,73	N 3,2 S 8,5	$C_{13}H_8INO_3S$	N 3,6 S 8,3	78
XIVc	211—212	H 8,83	7,93	7,03	OH 11,38	I	CH_3 2,73	8,19	N 3,3 S 8,4	$C_{13}H_8INO_3S$	N 3,6 S 8,3	75

*The PMR spectra of Ib, d, IXc, e, f, XIIe, f, XIIIe, and XIVb, c were measured in DMSO, while the PMR spectra of the remaining compounds were measured in deuterochloroform. We described Ia-e, VIb, d, and IXc, e, f in [7, 8].

of the 6-H proton in the PMR spectra of II-IV to strong field as compared with the position of the peak of the 5-H proton in the spectra of starting chromones I (see Table 2). The peak of the 5-H triazole proton in the spectra of II-IV also experiences a significant diamagnetic shift (1.52-1.88 ppm) as a result of disruption of the coplanarity of the thiazole and chromone rings. In the case of starting 3-(4-thiazolyl)-7-methoxychromones Ia, c there is a strong unbonded interaction of the 5-H proton of the thiazole ring with the carbonyl oxygen atom, since the steric hindrance between the thiazole and chromone rings is not substantial in this case. This interaction gives rise to a paramagnetic shift of the signal of the indicated proton. The broad signal of the 5-H proton of the pyrazole ring (spin–spin coupling with the proton attached to the nitrogen atom) and the separately observed singlets of the 2-OH and NH groups at 12.37-13.38 and 9.81-10.33 ppm also constitute evidence in favor of the pyrazole structure of derivatives II.

The reaction of phenylhydrazine with chromone Ic in alcohol solution results in the formation of 1-phenylpyrazole derivative V only after refluxing for 4 h. The following facts constitute evidence in favor of structure V. The compound obtained is soluble in dilute sodium hydroxide and does not form a colored complex with an alcohol solution of ferric chloride. The phenolic hydroxy group shows up in the PMR spectrum in the form of a narrow peak at 9.92 ppm, which indicates the absence of an intramolecular interaction between the hydroxy group and the nitrogen atom of the pyrazole ring; the five-proton singlet at 7.37 ppm corresponds to the protons of the phenyl group, and the absence of splitting of the signal of the phenyl group indicates that the benzene ring deviates from the plane of the pyrazole ring.

An oxime structure was assigned to the products of the reaction of chromones, flavones, and isoflavones with hydroxylamine in [9, 10]. These studies were subsequently re-examined. It was found that the products of the reaction of hydroxylamine with chromone and thioxochrome derivatives are not oximes, but rather derivatives of isomeric isoxazoles [11-14]. We determined that the thiazole analogs of 2-methyl- and 2-trifluoromethyl- isoflavones Ib, d, e form isoxazoles with hydroxylamine; exclusively isoxazoles VII are formed from chromones I in most cases, while a mixture of isomeric isoxazoles VII and VIII is formed from thioxochromones VI.



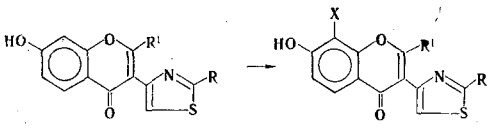
VIIIb, d VI b,d VII b, d

NH_2OH

VI–VIII $R^2 = CH_3O$ I b, d, e

The mixtures of isomeric isoxazoles were separated to give the individual compounds by selective crystallization and TLC. Both types of isoxazoles are readily soluble in 2 N alkali solution. The isomeric isoxazoles can be readily distinguished from one another by reaction with ferric chloride and by means of their chromatographic mobilities: Compounds of the VII type are distinguished by their lower chromatographic mobilities in benzene–ethanol (9 : 1) and do not give a color reaction, whereas compounds of the VIII type form a blue-green chelate through the phenolic hydroxy group and the nitrogen atom of the isoxazole ring. In addition, the isomeric isoxazoles differ from one another with respect to the chemical shift of the phenolic hydroxy group in the PMR spectra measured in deuterochloroform. The 2-OH group of isomers VIII forms an intramolecular hydrogen bond of the chelate type with the nitrogen atom of the isoxazole ring and absorbs at 9.64-9.66 ppm, whereas the same phenolic hydroxy group in isomers VIII participates in the formation of an intramolecular hydrogen bond with involvement of the nitrogen atom of the sterically favorably oriented thiazole ring and absorbs at 10.38-11.05 ppm. If the PMR spectra of isoxazoles VII and VIII are measured in dimethyl sulfoxide (DMSO) (Table 1), the signal of the phenolic hydroxy group is found at 9.67-10.24 ppm, regardless of the nature of the isoxazole. This suggests that the 2-OH group under these conditions participates in the formation of an intermolecular hydrogen bond with the solvent. The absence of a chromone ring in VII and VIII is confirmed by the shift to strong field of the peaks of the 5-H proton of the thiazole ring (0.34-0.77 ppm) and the 6-H proton of the phenolic part of the molecule (0.8-0.9 ppm) as compared with the starting chromones (see Tables 1 and 2).

The reaction of thiazole analogs of 7-hydroxyisoflavones IXb, c with dimethylaminomethane in hot dioxane leads to the formation of Mannich bases Xb, c. The dimethylaminomethyl group enters the 8 position of the chromone ring. The aromatic protons in the 5 and 6 positions show up in the PMR spectra in the form of doublets with a spin–spin coupling constant of 8 Hz. In other electrophilic substitution reactions (bromination and iodination) the halogen atom also enters the 8 position, or two bromine atoms simultaneously enter the 6 and 8 positions of the chromone ring (XIIIe).



IX b, c, e, f Xb, c XIIe, f, XIVb, c

IX, XII f R=CH_3, R^1=$COOC_2H_5$; X X=$CH_2N(CH_3)_2$; XII X=Br; XIV X=I

In order to search for medicinal preparations among heterocyclic analogs of isoflavones for the treatment of diseases of the cardiovascular system we investigated some of the compounds obtained for their hypolipidemic activity. As a result of the tests we observed that under the conditions of hyperlipidemia developed under the influence of Triton WR-1339, injection of the animals with VIb, Xb, XIc, and XIVc impedes the development of hyperlipidemia and decreases the amounts of cholesterol and triglycerides (Table 3). The biological studies were made in comparison with tsetamifen in male rats weighing 200-300 g afflicted with experimentally induced hyperlipidemia. The investigated compounds were injected intraperitoneally in doses of 25-150 mg/kg 24 h prior to the use of Triton and simultaneously with it. The LD_{50} values were determined in experiments with mice by intraperitoneal injection.

EXPERIMENTAL

The individuality of the compounds obtained and the course of the reactions were monitored by TLC on Silufol with elution with chloroform–methanol (9 : 1) or benzene–ethanol (9 : 1). The PMR spectra were measured with a ZKR-60 spectrometer relative to tetramethylsilane as the internal standard. The constants and yields of the compounds obtained are given in Tables 1 and 2.

3-(2-Hydroxy-4-methoxyphenyl)-4-(2-R-4-thiazolyl)pyrazoles (IIa-e). A 12-ml (24 mmole) sample of a 2 N alcohol solution of hydrazine hydrate was added to a hot solution of 2 mmole of chromone I or thioxochromone VI in the minimum amount of alcohol. After 5-10 min, the reaction mixture was diluted with 200 ml of water, and the resulting precipitate was removed by filtration and crystallized from aqueous alcohol to give the product in the form of colorless needles.

1-Methyl-3-(2-hydroxy-4-methoxyphenyl)-4-(2-methyl-4-thiazolyl)pyrazole (III) and 1-Methyl-4-(2-methyl-4-thiazolyl)-5-(2-hydroxy-4-methoxyphenyl)pyrazole (IV). A 2-ml (40 mmole) sample of methylhydrazine was added to a warm solution of 2.73 g (10 mmole) of chromone Ic in 180 ml of alcohol. After 5 min, the mixture was evaporated to a volume of 50 ml, and the resulting precipitate was removed by filtration and washed with alcohol to give 1.51 g (50%) of a mixture of isomers III and IV. Crystallization from alcohol gave 1 g (33%) of pyrazole III. The mother liquor after isolation of III was evaporated, and the residue was chromatographed on plates with silica gel (with a layer thickness of 1 mm) in benzene–ethanol (9 : 1). Desorption with alcohol gave 0.21 g (7%) of pyrazole IV.

1-Phenyl-4-(2-methyl-4-thiazolyl)-5-(2-hydroxy-4-methoxyphenyl)pyrazole (V). A mixture of 0.55 g (2 mmole) of chromone Ic and 0.25 ml of phenylhydrazine in 30 ml of alcohol was refluxed for 4 h, after which it was poured into 100 ml of water, and the reaction product was removed by filtration and crystallized from aqueous alcohol. The yield was 0.46 g.

3-R^1-4-(2-R-4-Thiazolyl)-5-(2-hydroxy-4-methoxyphenyl)isoxazoles (VIIb, d, e). A mixture of 2 mmole of chromone Ib, d, e and 6 mmole of hydroxylamine hydrochloride in 10 ml of dry pyridine was heated at 110-115°C for 1-3 h, after which the hot solution was poured into 150 ml of water. The resulting precipitate was removed by filtration and crystallized from aqueous alcohol.

TABLE 3. Effect of 3-(4-Thiazolyl)-7-hydroxychromone Derivatives on Hyperlipidemia in Rats Induced by the Injection of Triton WR-1339*

Compound	Amounts of cholesterol and triglycerides in the blood serum of the rats, mg %				LD_{50}, mg/kg	Dose, mg/kg
	cholesterol	% decrease	triglycerides	% decrease		
VIb	259,0±2,8	−11,7	344,0±3,1	−16,5	3000	150
XIVc	247,0±1,7	−15,8	342,0±1,5	−17,0	3000	150
Control	293,5±3,3		412,0±4,1			
Xb	264,2±3,5	−13,0	343,0±1,7	−18,7	500	25
XIc	267,5±2,4	−11,2	345,2±2,0	−18,2	1000	50
Control	303,6±4,6		422,0±4,5			
Tsetamifen	251,1±5,5	−17,3	299,2±5,6	−29,1		200

*With respect to six animals for each substance ($P < 0.001$).

3-Methyl-4-(2-thiazolyl)-5-(2-hydroxy-4-methoxyphenyl)isoxazole (VIIb) and 5-Methyl-3-(2-hydroxy-4-methoxyphenyl)-4-(2-thiazolyl)isoxazole (VIIIb). A mixture of 2.89 g (10 mmole) of thioxochromone VIb and 2.1 g (30 mmole) of hydroxylamine hydrochloride in 10 ml of dry pyridine was heated at 100-105°C for 1-2 h, after which it was poured into 150 ml of water, and the resulting precipitate was removed by filtration and washed with water. The yield of the mixture of isomeric isoxazoles VIIb and VIIIb was 2.3 g (80%). The mixture of products was refluxed in hexane, and the hot suspension was filtered to remove the undissolved material (VIIb). The hexane solution was cooled to give acicular crystals of VIIIb containing a very small amount of VIIb. Recrystallization of VIIIb successively from hexane and aqueous alcohol gave 1.05 g (36.5%) of pure product in the form of colorless needles with mp 139-140°C. Recrystallization of VIIb from aqueous alcohol gave 1.02 g (35.4%) of pure reaction product in the form of shiny plates with mp 135-136°C. Isoxazole VIIIb proved to be identical to the substance obtained in a similar reaction from chromone Ib.

3-Methyl-4-(2-methyl-4-thiazolyl)-5-(2-hydroxy-4-methoxyphenyl)isoxazole (VIId) and 5-Methyl-3-(2-hydroxy-4-methoxyphenyl)-4-(2-methyl-4-thiazolyl)isoxazole (VIIId). The reaction of 2.1 g (7 mmole) of thioxochromone VId and 1.5 g (21 mmole) of hydroxylamine hydrochloride under the conditions for the preparation of VIIb and VIIIb gave 1.68 g (80.4%) of a mixture of isomeric isoxazoles VIId and VIIId. Crystallization from aqueous alcohol in the presence of activated charcoal gave 1.2 g of a substance in the form of cubic prisms, which was found to be a mixture of isoxazoles by means of TLC. Preparative TLC on silica gel with a layer thickness of 1 mm in benzene–ethanol (9 : 1) gave 0.5 g (23.9%) of VIIId in the form of needles with mp 107-108°C (from alcohol) and 0.3 g (14.4%) of VIId in the form of plates with mp 102-103°C (from aqueous alcohol).

3-(2-R-4-Thiazolyl)-7-hydroxy-8-dimethylaminomethylchromones (Xb, c). A mixture of 20 mmole of chromone VIb, c, 10 ml of bis(dimethylamino)methane, and 70 ml of dioxane was refluxed for 1-2 h, after which the solvent was removed by vacuum distillation (with a water aspirator) to give a substance that was soluble in water and methanol. Mannich base Xb was crystallized from heptane–benzene (4 : 1), while Xc was crystallized from isopropyl alcohol.

3-(2-Methyl-4-thiazolyl)-7-hydroxy-8-dimethylaminomethylchromone Hydrochloride (XIc). Dry hydrogen chloride was bubbled into a solution of 0.32 g (1 mmole) of Xc in dry chloroform for 30 min, and the resulting precipitate was removed by filtration, washed with chloroform and ether, and crystallized from dioxane to give 0.33 g (94%) of a product with mp 239-240°C. Found: Cl 10.3%. $C_{16}H_{16}N_2O_3S \cdot HCl$. Calculated: Cl 10.1%.

3-(2-Methyl-4-thiazolyl)-7-hydroxy-8-iodochromone (XIVc). A mixture of 0.52 g (2 mmole) of chromone IXc and 0.74 g (3 mmole) of crystalline iodine in 10 ml of dimethyl sulfoxide (DMSO) was maintained at 20°C for 3 days, after which it was poured into 100 ml of water, and the resulting precipitate was removed by filtration and washed with 5% sodium sulfite solution to give 0.58 g (75%) of product, which was crystallized from n-butanol. Compound XIVb was similarly obtained.

2-R'-3-(2-Methyl-4-thiazolyl)-7-hydroxy-8-bromochromones (XIIe, f). A solution of 0.32 g (2 mmole) of bromine in 4 ml of glacial acetic acid was added gradually with stirring and heating (70-80°C) to a suspension of 2 mmole of chromone IXe, f in 6 ml of glacial acetic acid, after which stirring was continued for 4 h. The resulting precipitate was removed by filtration and crystallized from aqueous alcohol.

2-Trifluoromethyl-3-(2-methyl-4-thiazolyl)-7-hydroxy-6,8-dibromochromone (XIIIe). A solution of 0.32 g (2 mmole) of bromine in 4 ml of glacial acetic acid was added gradually to a refluxing solution of 1 mmole of chromone IXe in 5 ml of glacial acetic acid, after which heating was continued for 8 h. The resulting precipitate was removed by filtration and crystallized from aqueous methanol. The yield was 0.19 g.

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SYNTHESIS OF cis- AND trans-PERHYDROTHIENO[3,4-d]IMIDAZOLE-2-THIONE 5,5-DIOXIDES

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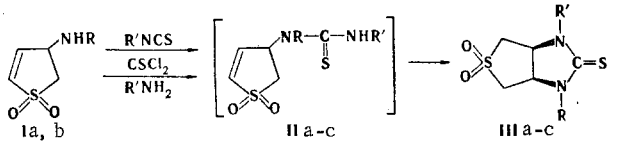
It is shown that the cis and trans isomers of perhydrothieno[3,4-d]imidazole-2-thione 5,5-dioxides can be obtained in good yields from the accessible derivatives of thiolane and 2-thiolene 1,1-dioxides.

In the course of developing research on the synthesis of new two-ring compounds with potential biological activity from derivatives of thiolane and 2-thiolene 1,1-dioxides [1] we synthesized a number of perhydrothieno-[3,4-d]imidazole-2-thione 5,5-dioxides.

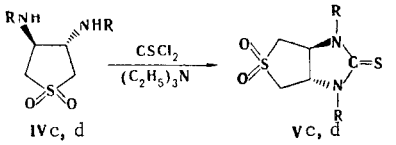
We established that sulfones Ia, b react with isothiocyanates or with thiophosgene and amines to give thioureas IIa-c, which undergo cyclization in the same way as ureas [2, 3] to give two-ring compounds IIIa-c:



Ia, b IIa-c IIIa-c

Ia R=C_6H_5; b R'=$C_6H_5CH_2$; II, III a R=R'=C_6H_5; b R=C_6H_5, R'=$C_6H_5CH_2$; c R=R'=$C_6H_5CH_2$

It has previously been demonstrated [1, 2] that the intramolecular cyclization of N-(1,1-dioxo-2-thiolen-4-yl)ureas and N-monosubstituted 1,1-dioxo-2-thiolen-4-yl esters of dithiocarbamic acids leads to cis-fused two-ring compounds. The reaction under consideration in this paper proceeds similarly, and we therefore assigned a cis structure to IIIa-c. We obtained their trans isomers by the action of thiophosgene on trans-3,4-diaminothiolane 1,1-dioxides IVc, d (obtained by the method in [4]) in the presence of tertiary amines.



IVc, d Vc, d

IV, V c R=$C_6H_5CH_2$; d R=CH_3

A melting-point depression is observed for a mixture of IIIc and Vc, and the IR (Table 1) and PMR spectra of these compounds differ: The α protons of the 1,1-dioxothiolane rings of IIIa, c give multiplets with widths of, respectively, 8 Hz (3.48 ppm, trifluoroacetic acid) and 13 Hz (3.4 ppm, deuteropyridine). A group of signals from 2.75 to 3.8 ppm is observed for the α protons of the 1,1-dioxothiolane ring of Vc in deuteropyridine. It has been reported that similar differences are observed in the spectra of cis- and trans-perhydrothieno[3,4-d]-imidazol-2-one 5,5-dioxides [2, 5] and cis and trans 3,4-disubstituted thiolane 1,1-dioxides [6]. Taking these data into account, we assigned cis and trans structures to III and V, respectively.

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