CHEMISTRY OF HETEROANALOGS OF ISOFLAVONES. 8.* REACTION OF BENZOFURAN ANALOGS OF ISOFLAVONES AND THEIR 4-THIOXO DERIVATIVES WITH HYDROXYLAMINE AND HYDRAZINE

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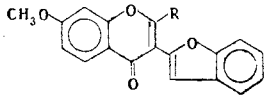
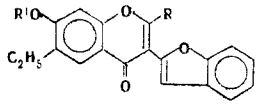
A number of 3-(2-benzofuryl)-6-ethylchromones and their 4-thioxo derivatives were synthesized, and the action of hydroxylamine and hydrazine on them was investigated. Isomeric 3(5)-(o-hydroxyphenyl)isoxazoles were obtained in the reaction with hydroxylamine. The predominant formation of one or the other isomer depends on the character of the substituents in the 2 and 4 positions of the chromone. The reaction of chromones with hydrazine leads to o-hydroxyphenylpyrazoles. The compounds obtained were characterized by their IR, UV, and PMR spectra.

In a previous communication [2] we established that isomeric 5(3)-(2-hydroxy-4-methoxyphenyl)isoxazoles are formed by the action of hydroxylamine on 7-methoxy- and 2-methyl-7-methoxyisoflavones and their 4-thioxo derivatives in solution in pyridine. The predominant formation of one or the other isomers depends on the nature of the substituents in the 2 and 4 positions of the chromone. The isoxazole structure of the products of the reaction of isoflavone and 4-thioxoisoflavone with hydroxylamine in aqueous alcohol solution was proved in [3, 4]. These data are in agreement with reports [5-9] in which it is shown that the reaction of hydroxylamine with substituted chromones leads to isoxazole derivatives rather than to oxides of chromones, as previously assumed.



I, II



III-X

I R=H; II R=CH_3; III R=H, R^1=CH_3; IV R=R^1=CH_3; V R=CF_3, R^1=H; VI R=CF_3, R^1=$COCH_3$; VII R=$COOC_2H_5$, R^1=H; VIII R=$COOC_2H_5$, R^1=$COCH_3$; IX R=R^1=H; X R=H, R^1=$COCH_3$

In the present research we synthesized new benzofuran analogs of isoflavones (III-X) and investigated the reaction of hydroxylamine with them, as well as with the previously obtained [10, 11] chromones I and II. Data on III-X are presented in Table 1.

Compounds XI and XII, which are 5-(2-hydroxyphenyl)isoxazole derivatives, are formed as a result of reactions of hydroxylamine hydrochloride with 2-methylchromones II and IV in solution in pyridine. These compounds are soluble in 2 N sodium hydroxide solution but do not give a color reaction with an alcohol solution of ferric chloride. The formation of XI and XII can be conceived of as being the result of nucleophilic attack by the hydroxylamine molecule on the C_2 atom of chromone, in agreement with the data in [2-6]. (See scheme on following page.) Similarly, 2-methyl-3-(2-benzoylfuryl)-7-hydroxychromone [11] is converted to 3-methyl-4-(2-benzofuryl)-5-(2,4-dihydroxyphenyl)isoxazole (XIII) under the influence of hydroxylamine. We obtained two products in the reactions of thioxochromones XIV [11] and XV with hydroxylamine under the same conditions. Some of these products were identical to XI and XII (in 53 and 42% yields), while others, viz., XVI and XVII (in 33 and 37% yields), give a positive reaction with a solution of ferric chloride, are soluble in 2 N sodium hydroxide solution, and, according to the results of elementary analysis, contain one nitrogen atom. The formation of XVI and XVII, which are 3-(2-hydroxyphenyl)isoxazole derivatives, can be re-

*See [1] for Communication 7.

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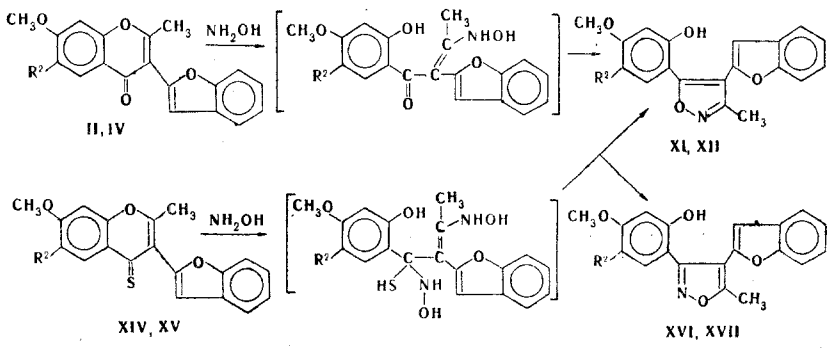
TABLE 1. 3-(2-Benzofuryl)-6-ethylchromones and Their Derivatives

Compound	mp, °C	UV spectrum λ_{max}, nm (log ε)	PMR spectrum, δ, ppm						Found, %		Empirical formula	Calc, %		Yield, %
			protons of the phenolic part					benzofuran 3-H	C	H		C	H	
			2-H or 2-CH_3	5-H	6-CH_2CH_3	7-OH or 7-OCH_3	8-H							
III	200	285 (4,57); 296 (4,53)	8,50	8,02	2,72; 1,25	3,92	6,76	7,76	75,4	5,4	$C_{20}H_{16}O_4$	75,0	5,0	52
IV	159	235 (4,46); 285 (4,54)	2,71	7,97	2,74; 1,26	3,94	6,75	7,39	75,0	5,6	$C_{21}H_{18}O_4$	75,4	5,4	78
V	278		—	7,79		11,13	7,00	7,23	F 15,5		$C_{20}H_{13}F_3O_4$	F 15,2		67
VI	136								F 13,8		$C_{22}H_{15}F_3O_5$	F 13,7		70
VII	203			7,92		11,12	7,03	7,53	69,5	4,6	$C_{22}H_{18}O_6$	69,8	4,8	97
VIII	162								68,2	5,0	$C_{24}H_{20}O_7$	68,6	4,8	71
IX	262	285 (4,68); 295 (4,67)							74,0	5,0	$C_{19}H_{14}O_4$	74,5	4,6	90
X	186								72,1	4,9	$C_{21}H_{16}O_5$	72,4	4,6	75
XV	209		2,36	8,38	2,76; 1,26	3,97	6,79	6,91	S 9,4		$C_{21}H_{18}O_3S$	S 9,2		80
XX	174		8,42	8,42	2,74; 1,26	3,92	6,72	8,22	S 9,2		$C_{20}H_{16}O_3S$	S 9,5		58

[a]The PMR spectra of III, IV, XV, and XX were obtained from solutions in deuterochloroform, while those of V and VII were obtained from solutions in dimethyl sulfoxide.

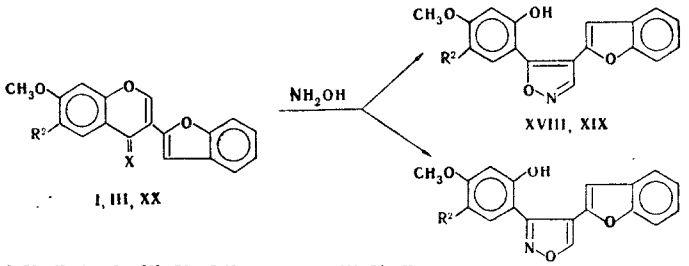


II, IV — XI, XII — XIV, XV — XVI, XVII

II, XI, XIV, XVI $R^2 = H$; IV, XII, XV, XVII $R^2 = C_2H_5$

garded as being the result of nucleophilic attack by the hydroxylamine molecules on the C_2 and C_4 atoms, which leads to opening of the γ-pyrone ring with subsequent cyclization of the intermediate to o-hydroxyphenylisoxazoles.

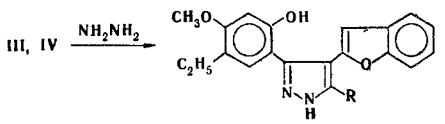
The reaction of 7-methoxy-3-(2-benzoylfuryl)chromones I and III with hydroxylamine under the conditions described above leads to isoxazoles with structures XVIII and XIX. Only one isoxazole (XXI, in 25% yield), which gives a positive reaction with an alcohol solution of ferric chloride, and chromone III (in 25% yield) were isolated in a similar reaction with 4-thioxochromone XX.



I, III, XX — XVIII, XIX — XXI

I $R^2 = H$, X = O; III $R^2 = C_2H_5$, X = O; XVIII $R^2 = H$; XIX–XXI $R^2 = C_2H_5$; XX X = S

From previous publications [4, 7-9, 12] it is known that chromones do not give the normal carbonyl reaction with hydrazine hydrate or hydroxylamine but undergo recyclization to o-hydroxyphenylpyrazole derivatives. Compounds XXII and XXIII are formed by the action of hydrazine hydrate on alcohol solutions of chromones III and IV:



XXII R = H; XXIII R = CH_3 XXII, XXIII

They are readily soluble in a warm 2 N solution of sodium hydroxide and give a blue coloration with an alcohol solution of ferric chloride, which constitutes evidence for the development of a phenolic hydroxy group in their molecules.

To confirm the structures of XI-XIII, XVI-XIX, and XXI-XXIII we recorded their UV, PMR, and IR spectra. The forms of the absorption curves of the UV spectra are almost identical for all of the isoxazoles and differ clearly from the absorption curves of chromones. If the reactions presented above had proceeded with retention of the pyrone ring, the form of the absorption curves of the products should have reproduced the absorption curves of the chromones themselves. The structures of the isoxazoles and pyrazoles obtained are also in agreement with the data from the PMR spectra (Table 2). The signals of the 5-H protons of the chromones and 4-thioxochromones experience paramagnetic shifts under the influence of the adjacent carbonyl group. The signals of the 6-H protons of the phenolic part of the isoxazoles and pyrazoles are shifted 0.82-0.97 and 0.95-1.06 ppm, respectively, to strong field as compared with the signals of the 5-H protons of the starting chromones. This is the result of disruption of the planar structure of the molecules due to the benzofuran ring and its ring currents. Narrow singlets of hydroxy groups appear at 9.62-10.42 ppm.

TABLE 2. 3(5)-(o-Hydroxyphenyl)isoxazoles and 3-(o-Hydroxyphenyl)pyrazoles

Compound	mp, °C	IR spectrum, ν, cm^{-1}		UV spectrum λ_{max}, cm^{-1}	PMR spectrum,[a] δ, ppm							Found, %			Empirical formula	Calc., %			Yield, %
					protons of the phenolic part					isoxazole or pyrazole protons									
		OH	C=N		2-OH	3-H	4-OCH_3 or 4-OH	5-H or 5-CH_2CH_3	6-H	3(5)-H or 3(5)-CH_3	benzofuran 3-H	C	H	N		C	H	N	
XI	169	3145	1652	257 (4,44); 292 (4,33)	9,95	6,50	3,77	6,55	7,12—7,70	2,48	6,82	70,7	4,8	4,3	$C_{19}H_{15}NO_4$	71,0	4,7	4,4	75
XII	173,5			260 (4,40); 293 (4,28)	9,75	6,55	3,89	2,58; 1,15	7,15	2,59	6,84			4,0	$C_{21}H_{19}NO_4$			4,0	96
XIII	175	3090, 3350	1650	260 (4,37); 293 (4,26)	10,03	6,56	10,03	6,50	7,26—7,83		6,93	70,8	4,5	4,6	$C_{18}H_{13}NO_4$	70,4	4,3	4,6	95
XVI	138	3160	1638	278 (4,32); 290 (4,31); 302 (4,19)	9,74	6,50	3,81	6,48	7,24	2,78		70,7	4,9	4,3	$C_{19}H_{15}NO_4$	71,0	4,7	4,4	33
XVII	124			291 (4,33); 300 (4,24)	9,62	6,52	3,85	2,56; 1,1	7,05	2,08	6,57			4,1	$C_{21}H_{19}NO_4$			4,0	37
XVIII	151	3175	1650	259 (4,29); 289 (4,25); 310 (4,23)	10,42	6,81		6,80	7,35—7,90	9,3	7,02	70,6	4,5	4,6	$C_{18}H_{13}NO_4$	70,4	4,3	4,6	93
XIX	182			285 (4,16); 315 (4,28); 330 (4,16)										4,3	$C_{20}H_{17}NO_4$			4,2	55
XXI	138			288 (4,35); 300 (4,31)	10,12	6,48	3,93		7,05	9,85	6,63			4,3	$C_{20}H_{17}NO_4$			4,2	25
XXII[b]	185				9,63	6,50	3,87		7,07	7,99	6,62			8,3	$C_{20}H_{18}N_2O_3$			8,4	91
XXIII[c]	189				9,97	6,52	4,03		6,91		6,65			8,1	$C_{21}H_{20}N_2O_3$			8,0	80

[a]The PMR spectra were recorded from solutions in dimethyl sulfoxide. [b]The spectrum also contains a peak at 12.86 ppm (pyrazole N–H). [c]The spectrum also contains a peak at 12.65 ppm (pyrazole N–H).

EXPERIMENTAL

The purity of the compounds obtained and the course of the reactions were monitored by thin-layer chromatography (TLC) on Silufol; a mixture of chloroform and methanol (9 : 1) or a mixture of benzene and ethanol (9 : 1) was used as the eluent. The UV spectra of alcohol solutions of the compounds ($0.2 \cdot 10^{-5}$ mole) were recorded with a Specord UV-vis spectrophotometer. The PMR spectra of the compounds were recorded with a ZKR-60 spectrometer relative to tetramethylsilane as the internal standard. The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer.

α-(2-Benzofuryl)-2,4-dihydroxy-5-ethylacetophenone (XXIV). A solution of 3.06 g (0.02 mole) of 4-ethylresorcinol and 1.36 g (0.01 mole) of freshly calcined zinc chloride in 12 ml of absolute ether was added with stirring to a solution of 3.14 g (0.02 mole) of 2-benzofurylacetonitrile in 17 ml of absolute ether, and the mixture was cooled to 0-3°C and saturated with stirring with dry hydrogen chloride for 3-4 h, after which it was allowed to stand overnight at 0°C. The ether was decanted from the resulting viscous yellow-orange oil, and the latter was washed with ether and treated with 100-150 ml of hot water. The aqueous mixture was refluxed for 1 h. It was then poured over ice, and the resulting yellow precipitate was removed by filtration and washed with water until the wash waters had pH 6. This procedure gave 5.8 g (89%) of crude product. Recrystallization from 40% alcohol gave 5 g (77%) of needles with mp 151°C. PMR spectrum (in DMSO): 4.63 (CH_2), 11.92 (2-OH), 6.43 (3-H), 10.50 (4-OH), 7.75 (6-H), and 6.80 ppm (benzofuran 3-H). Found: C 72.8; H 5.6%. $C_{18}H_{16}O_4$. Calculated: C 72.9; H 5.8%.

α-(2-Benzoyuryl)-2-hydroxy-4-methoxy-5-ethylacetophenone (XXV). A solution of 9.5 g (32 mmole) of ketone XXIV in 160 ml of absolute benzene and 4.45 g (35 mmole) of dimethyl sulfate was refluxed with stirring with 16 g (116 mmole) of freshly calcined potassium carbonate for 3.5 h. The inorganic precipitate was removed by filtration, and the filtrate was acidified with three to five drops of glacial acetic acid. The solvent was removed by evaporation to dryness, and the residue was crystallized from alcohol to give 4.7 g (77%) of needles with mp 91°C. PMR spectrum (in DMSO): 4.74 (CH_2), 12.04 (2-OH), 6.60 (3-H), 7.83 (60H), and 6.85 ppm (benzofuran 3-H). Found: C 73.1; H 5.7%. $C_{19}H_{18}O_4$. Calculated: C 73.5; H 5.8%.

3-(2-Benzofuryl)-6-ethyl-7-methoxychromone (III). A mixture of 4.5 g (14 mmole) of ketone XXV, 14.4 ml of freshly distilled ethyl orthoformate, 14.4 ml of dry pyridine, and 30-35 drops of dry piperidine was refluxed at 120-130°C for 4-5 h. It was then cooled, and the precipitate was removed by filtration and washed with a small amount of pyridine, alcohol, and ether to give 2.8 g (60%) of needles of III (from n-butanol).

2-Methyl-3-(2-benzofuryl)-6-ethyl-7-methoxychromone (IV). A mixture of 3.11 g (10 mmole) of ketone XXV, 4.98 g (40 mmole) of acetic anhydride, and 3.03 g (30 mmole) of triethylamine was heated at 120°C for 2-3 h, after which the solution was poured into 300 ml of water containing 8 ml of concentrated hydrochloric acid, and the precipitate was removed by filtration and washed thoroughly with water to give 3.2 g (96.5%) of needles of IV (from alcohol).

2-Trifluoromethyl-3-(2-benzofuryl)-6-ethyl-7-hydroxychromone (V). A 0.84-g (4 mmole) sample of trifluoroacetic anhydride was added dropwise to a cooled (to 0-3°C) solution of 0.59 g (2 mmole) of XXIV in 3 ml of dry pyridine, and the mixture was allowed to stand overnight at room temperature. It was then poured over ice, and the resulting mixture was acidified. The white precipitate was removed by filtration to give 0.7 g (95%) of needles of V (from benzene or aqueous alcohol).

2-Ethoxycarbonyl-3-(2-benzofuryl)-6-ethyl-7-hydroxychromone (VII). This compound was obtained from 0.59 g (2 mmole) of XXIV and 0.546 g (4 mmole) of ethoxyalyl chloride under the conditions used for the preparation of V. Workup gave 0.74 g (97%) of needles of VII (from aqueous alcohol).

3-(2-Benzofuryl)-6-ethyl-7-hydroxychromone (IX). This compound was obtained from 0.95 g (3.2 mmole) of XXIV, 3.2 ml of ethyl orthoformate, 3.2 ml of pyridine, and five drops of piperidine under the conditions used to prepare III. Workup gave 0.9 g (94%) of a crude product, which was purified through the acetyl derivative.

3-(2-Benzofuryl)-6-ethyl-7-acetoxychromones (VI, VIII, and X). A 4-mmole sample of acetic anhydride was added to a solution of 1 mmole of chromone in the minimum amount of dry pyridine, and the mixture was allowed to stand at 0°C for 24 h. The precipitate was removed by filtration, washed with a small amount of pyridine and ether, and crystallized from benzene.

3-(2-Benzofuryl)-4-thioxo-7-methoxychromones (XV and XX). A well-ground mixture of 7 mmole of

chromone IV or III and 1.5 g (7 mmole) of phosphorus pentasulfide in 40 ml of absolute pyridine was heated at 100°C for 2 h, after which it was added to 200-250 ml of water, and the solid material was removed by filtration and washed on the filter with water to give bright-red or yellow-orange needles (from n-butanol).

4-(2-Benzofuryl)-5-(2-hydroxy-4-methoxyphenyl)isoxazoles (XI-XIII, XVIII, and XIX). A mixture of 1 mmole of 3-(2-benzofuryl)chromone and 3 mmole of hydroxylamine hydrochloride in 3-8 ml of dry pyridine was heated at 100-105°C for 0.5-6 h, after which the hot solution was added to 100 ml of water. The liberated oil gradually began to solidify, and the solid was recrystallized from alcohol or aqueous alcohol.

3-(2-Hydroxy-4-methoxyphenyl)-4-(2-benzofuryl)-5-methylisoxazoles (XVI and XVII) and 3-Methyl-4-(2-benzofuryl)-5-(2-hydroxy-4-methoxyphenyl)isoxazoles (XI and XII). A mixture of 1 mmole of thioxochromone XIV or XV and 3 mmole of hydroxylamine hydrochloride in 3-10 ml of dry pyridine was heated at 115-120°C for 45-60 min, after which it was added to 100 ml of water. The solidified oil was removed by filtration, air dried, and treated with hot carbon tetrachloride. The solid material that was insoluble in hot CCl_4 was XI or XII. The carbon tetrachloride mother liquor was evaporated to dryness, and the XVI or XVII was recrystallized from alcohol. In addition to these compounds, a compound that did not give a reaction with a solution of ferric chloride and was only very slightly soluble in alcohol was isolated from the reaction mixture. The structure of this compound could not be established.

3-(2-Hydroxy-4-methoxy-5-ethylphenyl)-4-(2-benzofuryl)isoxazole (XXI). This compound was obtained by a method similar to that used to prepare XVI and XVII.

3-(2-Hydroxy-4-methoxy-5-ethylphenyl)-4-(2-benzofuryl)pyrazoles XXII and XXIII. A 6-ml (12-mmole) sample of a 2 N solution of hydrazine hydrate in alcohol was added to a hot solution of 1 mmole of chromone in the minimum amount of alcohol, and, after 5-10 min, the mixture was added to 100-120 ml of water. The precipitate was removed by filtration and crystallized from alcohol to give colorless needles of the product.

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