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CHEMISTRY OF MODIFIED FLAVONOIDS
17.* IMIDAZOLE ANALOGS OF FLAVONOIDS

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Imidazole analogs of chalcones were synthesized by the reaction of 1-methyl-2-formyl-5-chloroimidazole with o-hydroxyacetophenones. Isomerization and oxidative cyclization of chalcones yielded imidazole analogs of flavonones and flavones. These compounds were used in the synthesis of pyrazolines, pyrazoles, and isoxazoles.

Heterocyclic analogs of the flavonoids exhibit various biological activities, which has evoked interest in compounds of this kind. For example, it was already known in the 1950s that furan and pyridine derivatives of chromone possess spasmolytic, analgesic, and antipyretic activity and the ability to lower blood pressure [2-4]. Moreover, 3-pyridylchromones [5] regulate pituitary functions, influence the activity of the adrenal glands, and exhibit a number of other useful properties. Testing of the pharmacological activity of a number of substituted 2- and 3-hetarylchromones that we have synthesized showed that certain compounds exhibit a significant sugar-lowering effect; others have anabolizing, hepatoprotective, antiinflammatory, and antiblastic effects.

From an analysis of these data the need to produce and investigate the properties of new flavonoids, modified by heterocycles, becomes understandable. In [6] we described imidazole analogs of isoflavones, among which compounds possessing hypolipidemic, antiinflammatory, and hypotensive activity were found. In these compounds the imidazole residue is bonded to the chromone system by the 4-position. Later studies [7, 8] described imidazole analogs of a number of flavonoids: isoflavone, isoflavonone, benzopyran, and 3,4-dihydrobenzopyran; in these compounds the imidazole ring is bonded by the 1-position. The compounds described are active against Gram-positive bacteria and dermatophytes and exhibited antiallergic activity.

Imidazole analogs of chalcone Ia-f were produced by the reaction of 1-methyl-2-formyl-5-chloroimidazole [9] with the corresponding o-hydroxyacetophenone in aqueous alcohol solutions. The chalcones Ia-f are rather high-melting crystalline substances, yellow or orange, readily soluble in organic solvents (see Table 1). Their UV spectra contain two major absorption maxima in the regions 202-225 nm and 350-380 nm, which agrees with the literature data [10].

One of the most important chemical properties of chalcones is their ability for isomerization. The imidazole analogs of chalcones Ia, c, d that we produced were converted to the corresponding imidazole analogs of flavones IIa, c, d by isomerization on the ion exchange resin Amberlite A-21.

2-Hydroxychalcones can also undergo oxidative cyclization, forming flavonones. The best method for this reaction proved to be oxidation of the corresponding propenones Ia-b in boiling dimethyl sulfoxide in the presence of catalytic amounts of iodine [11]. Imidazole analogs of flavones IIIa-d were produced by this method. A different pathway [12] of oxidative cyclization of propenones under the action of selenium dioxide in boiling amyl alcohol can also be used to produce these analogs.

Under the action of alkaline hydrogen peroxide on propenones Ib, d [13] we obtained 3-hydroxychromones IVb, d. Imidazole analogs of chalcones Ia-d were reacted with hydrazine hydrate in alcohol solution. In this case substituted pyrazolines Va-d formed in a short time.

*For Communication 16 see [1].

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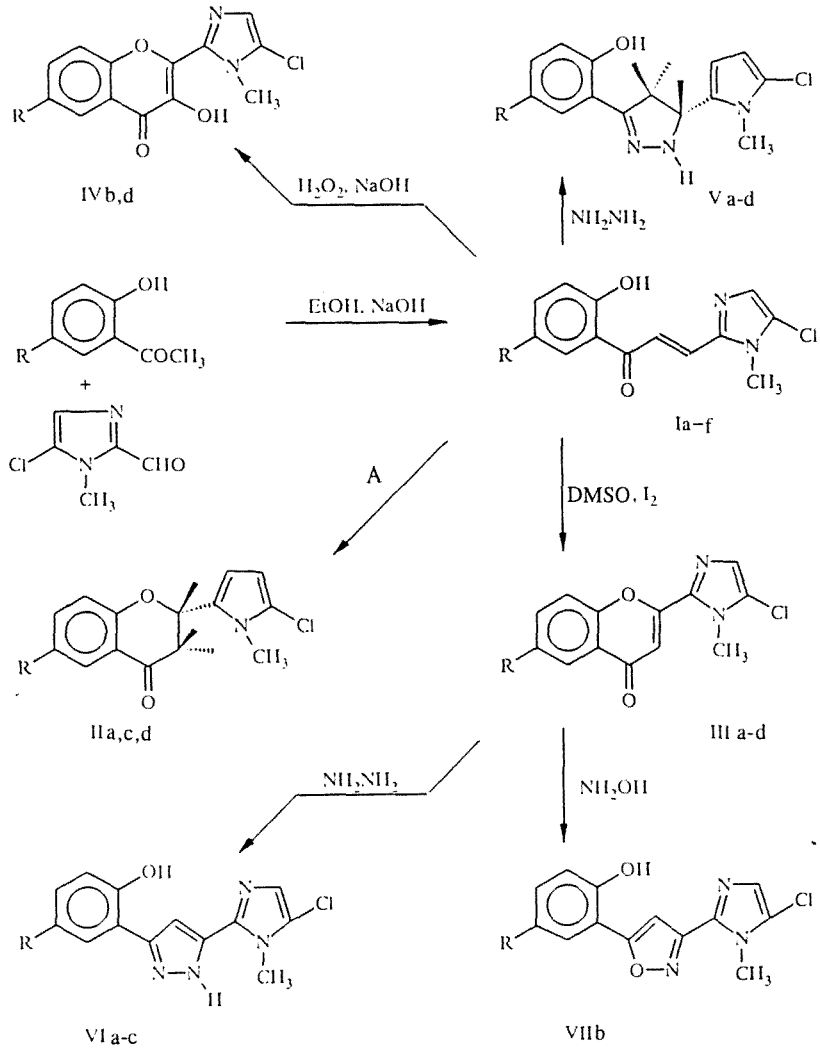

Fig. 1. I–VII a) R = H, b) R = OCH_3, c) R = CH_3 d) R = Cl, e) R = NO_2, f) R = F; A) Amberlite.

Compounds II-V are colorless high-melting crystalline substances. To confirm the structure of compounds I-VII we used ^1H NMR spectroscopy. Doublets of both olefinic protons can be observed separately in the ^1H NMR spectra of compounds Ia-f (Table 2). The spin–spin coupling constants (SSCC) for these protons, equal to 14.5 Hz, indicate a trans-structure of all the imidazole analogs of chalcones obtained. The signals of the olefinic protons appear in the region of 7.9-8.1 and 7.5-7.7 ppm, respectively. Signals in the region of 11.4-13.5 ppm correspond to the hydrogen atoms of the hydroxyl groups in compounds Ia-f, which are involved in the formation of an intramolecular hydrogen bond. The signals of the aromatic protons of the benzene ring appear in the spectrum at 6.5-7.1 (3-H), 7.2-8.4 (4-H), 6.5-7.0 (5-H), and 7.4-8.9 ppm (6-H). The functional groups next to the aromatic protons (except for nitro groups) have only a negligible influence on the chemical shifts of these protons.

In the ^1H NMR spectra of the chromones IIa, c, d (Table 3), the protons of the pyranone ring form the system ABX in the spectrum. The weakly polar doublet of doublets at 5.56-5.62 ppm corresponds to the 2-H_a proton, since this proton reacts with two protons in different steric positions, 3-H_a and 3-H_e. The SSCC are equal to 9 ($^3J_{2\text{-}Ha,3\text{-}Ha}$) and 4 Hz ($^3J_{2\text{-}Ha,3\text{-}He}$); i.e., they agree with the usual values of the SSCC between the axial and equatorial protons in cyclic systems of this type. The second group of signals around 3 ppm takes the form of two doublets and belongs to the 3-CH_2 protons. From this fragment of the spectra we can find the geminal SSCC $^3J_{2\text{-}Ha,3\text{-}Ha}$ and both vicinal SSCC. The values of the last two constants make it possible to draw a conclusion on the orientation of the 2-H proton. If this proton has an equatorial orientation, then the torsional angles between it and the 3-H_a and 3-H_e protons prove to be the same, as is seen on molecular models. Correspondingly, we

TABLE 1. Physicochemical Constants of Propenones Ia-e, Chromanones IIa, c, d, Chromones IIIa-d, IVb, d, Pyrazolines Va-d, Pyrazoles VIa-c, and Isoxazole VIIb

Compound	Structural formula	Tmp, °C	Yield, %
Ia	$C_{13}H_{11}ClN_2O_2$	169...170	86
Ib	$C_{14}H_{13}ClN_2O_3$	167	82
Ic	$C_{14}H_{13}ClN_2O_2$	155...156	75
Id	$C_{13}H_{10}Cl_2N_2O_2$	156	97
Ie	$C_{13}H_{10}ClN_3O_4$	171...172	93
If	$C_{13}H_{10}ClFN_2O_2$	151...152	93
IIa	$C_{13}H_{11}ClN_2O_2$	120...121	37
IIc	$C_{14}H_{13}ClN_2O_2$	158...159	37
IId	$C_{13}H_{10}Cl_2N_2O_2$	187...188	35
IIIa	$C_{13}H_{9}ClN_2O_2$	171	76
IIIb	$C_{14}H_{11}ClN_2O_3$	194	71
IIIc	$C_{14}H_{11}ClN_2O_2$	208	65
IIId	$C_{13}H_{8}Cl_2N_2O_2$	214	70
IVb	$C_{14}H_{11}ClN_2O_4$	231	70
IVd	$C_{13}H_{8}Cl_2N_2O_3$	178...279	79
Va	$C_{13}H_{13}ClN_4O$	145...147	57
Vb	$C_{14}H_{15}ClN_4O_2$	159	80
Vc	$C_{14}H_{15}ClN_4O$	180...181	82
Vd	$C_{13}H_{12}Cl_2N_4O$	193...194	75
VIa	$C_{13}H_{11}ClN_4O$	251	65
VIb	$C_{14}H_{13}ClN_4O_2$	231	76
VIc	$C_{14}H_{13}ClN_4O$	268...269	73
VIIb	$C_{14}H_{12}ClN_3O_3$	257	80

TABLE 2. Parameters of the ^1H NMR Spectra of Chalcones Ia-f

Compound	Chemical shifts, ppm							
	olefinic protons	protons of the phenolic portion					protons of imidazole	
		2-OH	3-H	4-H	5-R	6-H	N-CH_3	4-H
Ia	8.10, 7.67	12.75	6.89	7.51	7.01	7.98	3.74	7.16
Ib	8.02, 7.56	12.37	6.91	7.20	3.86	7.37	3.76	7.13
Ic	8.08, 7.65	12.57	6.91	7.31	2.31	7.76	3.73	7.16
Id	7.99, 7.67	12.65	6.96	7.44	—	7.96	3.75	7.18
Ie	8.08, 7.77	13.48	7.11	8.37	—	8.91	3.78	7.23
If	7.96, 7.68	12.46	6.92	7.25	—	7.64	3.75	7.18

should also expect equal values of the vicinal SSCC for these protons. If the proton 2-H has an axial orientation, then, as it follows from calculation according to the Karplus formula for a molecular model optimized by the method of molecular mechanics, the vicinal SSCC with the 3-H_a and 3-H_e protons are 5.0 and 9.6 Hz, which is correlated with the experimental values. Thus, the 2-H proton in compounds II is in an axial position. Among the 3-CH_2 protons, the one for which a large vicinal SSCC is observed is axial. The most profitable conformation of II molecules is the half-chair.

In the ^1H NMR spectra of the chromones IIIa-d (Table 4), the signal of the proton 5-H (7.6-8.2 ppm), adjacent to the carbonyl group, appears in the weakest field. The 3-H and 8-H protons give signals at 6.9-7.0 and 6.9-7.5, respectively, in the spectrum, and the proton 7-H at 7.0-7.5 ppm. The protons of the benzene ring form the system ABX. The narrow singlet at 6.9-7.2 ppm in the spectra of compounds I-VII belongs to the 4-H proton of the imidazole ring; the protons of the N-CH_3 group appear in the form of a three-proton singlet at 3.4-3.9 ppm.

The ^1H NMR spectra of pyrazolines Va-d confirm their structure. The appearance of the spectra depends greatly on the solvent used (see Table 5). Thus, in dimethyl sulfoxide the 4-CH_2 and 5-H protons of the pyrazoline ring form the system ABX with SSCC values characteristic of rings with this structure. The spectral parameters of these signals were determined using the PANIC iteration calculation program, included in the system of mathematical support for the Bruker spectrometers. The signal of the NH proton of this ring is greatly broadened and is observed close to the region of absorption of the aromatic

TABLE 3. Parameters of the ^1H NMR Spectra of Chromanones IIa, c, d

Compound	Chemical shifts, ppm (SSCC, Hz)							
	protons of chromanone fragment						protons of imidazole	
	2-H d.d	3-H_a d 3-H_e d	5-H d	6-R	7-H	8-H	1-CH_3	4-H
IIa	5,60 (10,3; 3,9)	3,08, 3,55 (17,1; 3,9) (17,1; 10,3)	7,94 d.d (7,8; 2,5)	7,06 m	7,49 m	7,06 m	3,73	6,94
IIc	5,56 (9,0; 4,0)	3,06; 3,54 (17,0; 4,0) (17,0; 9,0)	7,73 (2,5)	2,30 s	7,30 d.d (9,0; 2,5)	6,88 d (9,0)	3,71	6,93
IId	5,62 (9,0; 4,2)	3,09; 3,53 (16,5; 4,2) (16,5; 9,0)	7,89 (2,5)	—	7,42 d.d (9,0; 2,5)	6,93 d (2,5)	3,72	6,93

TABLE 4. Parameters of the ^1H NMR Spectra of Chromones IIIa-d and IVb, d

Compound	Chemical shifts, ppm						
	chromone protons					imidazole protons	
	3-H	5-H	6-R	7-H	8-H	N-CH_3	4-H
IIIa	7,00	8,21	7,50	7,71	7,40	3,98	7,15
IIIb	6,97	7,56	3,90	7,26	7,43	3,96	7,13
IIIc	6,99	7,99	2,45	7,50	7,37	3,96	7,14
IIId	7,01	8,18	—	7,64	7,45	3,97	7,17
IVb		7,5 d (2,5)	3,88	7,38 d.d (2,5, 9,0)	7,64 d (9,0)	3,88	7,33
IVd		8,05	—	7,79	7,79	3,89	7,36

protons. In deuterochloroform the protons of the pyrazoline ring form the spin system A_2MX, in which the methylene protons 4-CH_2 prove equivalent, and the signal of NH appears in the form of a slightly broadened doublet with ^3J = 2.5 Hz. In deuterobenzene the protons of the pyrazoline ring form the system ABMX, in which the protons of the 4-CH_2 group are nonequivalent. We explain the observed effects by an increase in the mobility of the pyrazoline ring in nonsolvating solvents. In deuterochloroform, where solvation effects are absent or minor, there is a rapid inversion of the tetrahedral cyclic nitrogen atom $N_{(1)}$ and, as a result, an averaging of the signals of the protons of the 4-CH_2. With increasing solvating properties of the solvent (deuterobenzene, dimethyl sulfoxide), inversion does not occur and the signals of the protons of the 4-CH_2 group are observed separately. The presence of solvation also affected the rates of proton exchange and, correspondingly, the shape of the signal of the NH proton. The signals of the protons of the phenolic hydroxyls of pyrazoline derivatives involved in the formation of an intramolecular hydrogen bond appear in the region of 10.6-11.1 ppm. The signals of all the aromatic protons form a complex multiplet in the spectra. Interesting changes occur in the spectra of pyrazolines in deuterotrifluoroacetic acid. Directly after dissolution, the protons of the pyrazoline ring form the spin system ABX (the signal of the NH proton is absent in the spectrum on account of deuteroexchange). However, after a few minutes the signals of a different ABX spin system, differing somewhat in values of the chemical shifts, appear in the spectrum. After 4-6 h the spectrum corresponds to an equimolar mixture of the two products, containing signals of the same multiplicity but with different chemical shifts. We believe that these changes occur on account of the possibility of protonation of the pyrazoline ring at one of the two nonequivalent heterocyclic nitrogen atoms. The $N_{(2)}$ nitrogen atom is protonated first, as the more basic, and later a mixture of forms protonated at the $N_{(2)}$ or $N_{(1)}$ nitrogen atom is formed.

In a continuation of [15-18], in order to study the properties of imidazole analogs of flavone, we investigated the products of their reaction with hydrazine and hydroxylamine. As a result of multihour (10-20 h) boiling of alcohol solutions of the chromones IIIa-c with hydrazine hydrate, compounds VIa-c — derivatives of o-hydroxyphenylpyrazole — are formed. These colorless, high-melting crystalline compounds give a blue-green color in an alcohol solution of ferric chloride and dissolve in a warm 2 N solution of sodium hydroxide, which is evidence of the presence of a phenolic hydroxyl group in the molecule.

TABLE 5. Parameters of the ^1H NMR Spectra of Pyrazolines Va-d in Dimethyl Sulfoxide

Compound	Chemical shifts, ppm (SSCC, Hz)									
	protons of phenolic portion					pyrazoline protons			imidazole protons	
	2-OH	3-H	4-H	5-R	6-H	1-H	4-CH_2	5-H	1-CH_3	4-H
Va*	10,85	6,9	7,3	6,9	7,3	6,22 d (3,3)	3,55 (9,7)	5,02 d.t. (9,7; 3,3)	3,63	6,88 s
Va**	11,36	6,6	7,2	6,7	7,2	5,50 d (2,9)	3,05; 2,69 d.d (16,6; 9,3) (16,6; 11,7)	4,18 m	2,57 s	6,86 s
Va	11,05	6,8	7,4	6,8	7,4	7,70	3,74; 3.47 d.d (17,1; 7,8) (17,1; 11,2)	5,05 d.d (11,2; 7,8)	3,63 s	6,93 s
Vb	10,58	6,85 s	6,85 s	3,73 s	6,90 d (2,0)	7,90	3,83; 3,46 d.d. (17,5; 11,2) (17,5; 8,3)	5,05 d.d. (11,7; 8,3)	3,6 s	6,91 s
Vc	10,82	6,80 d (8,0)	7,07 d. d (8,0; 2,0)	2,25	7,18 d (2,0)	7,84 c	3,72; 3,42 d.d (17,1; 11,2) (17,1; 7,8)	5,02 d.d. (11,2; 7,8)	3,6 s	6,90 s
Vd	11,10	6,93 d (8,5)	7,26 d.d. (8,5; 2,6)	–	7,42 d (2,6)	7,99 s	3,74; 3,46 d.d (17,8; 11,2) (17,1; 7,8)	5,07 d.d (11,2; 7,8)	3,6 s	6,91 s

*$CDCl_3$
**C_6D_6

TABLE 6. Parameters of the ^1H NMR Spectrum of Pyrazoles VIa-c (solvent DMSO-D_6)

Compound	Chemical shifts, ppm (SSCC, Hz)								
	protons of phenolic portion					pyrazole protons		imidazole protons	
	2-OH S	3-H d	4-H d.d.	5-R	6-H d	1-H, S	4-H, S	1-CH_3, S	4-H, S
VIa	10,35	6,86	7,14 m	6,98	7,71 (7,8)	13,16	7,10	3.90	7,02
VIb	9,89	6,92 (8,5)	6,81 (3,5; 2,5)	3,76	7,32 (2,5)	13,19	7,23	3,92	7,12
VIc	10,11	6,85 (8,3)	7,01 (8,3; 2,0)	2,27	7,54 (2,0)	13,12	7,15	3,91	7,10

The structure of the pyrazoles VIa-c obtained is unambiguously confirmed by their ^1H NMR spectra (see Table 6). At 13.1-13.2 ppm a broadened signal of the NH group is observed; at 9.9-10.4 ppm a narrower signal of the OH groups is observed; instead of the signal of the 5-H proton of the chromone ring at 7.6-8.2 ppm, the spectra contain a signal at 7.3-7.7 ppm, corresponding to the 6-H proton of the phenolic portion of the pyrazole molecule. The strong-field shift of the signal may be associated with the noncoplanarity of the pyrazole and phenol fragments and, consequently, with weakening of the influence of the unshared electron pair of the pyrazole nitrogen atom on the chemical shift of the signal of the 6-H proton in comparison with the influence of the unshared electron pair of the chromone carbonyl in the original chromone on the signal of the 5-H proton.

Under the action of strongly acidic hydroxylamine on the chromone IIIb in pyridine, there is a cleavage of the chromone ring, which leads to the formation of a derivative of 2-hydroxyphenylizoxazole VIIb, which is a high-melting colorless crystalline substance that does not give a color reaction with a solution of ferric chloride and dissolves in 2 N sodium hydroxide solution, which agrees with the literature data [19, 20].

Thus, imidazole analogs of chalcones have been synthesized by alkaline condensation of 1-methyl-2-formyl-5-chloroimidazole, and their cyclization to the corresponding flavone and flavonone analogs has been studied. The conformation of the flavonones and the configuration of the olefinic fragment of the chalcones were established; the products of the reaction of imidazole analogs of flavonoids with hydrazine and hydroxylamine were investigated.

EXPERIMENTAL

The purity of the compounds obtained and the course of the reactions were monitored by thin-layer chromatography on Silufol UV-254 plates. A mixture of benzene and ethanol (9:1) was used as the eluent. The ^1H NMR spectra were recorded on a Bruker WP100-SY spectrometer. The chemical shifts were determined relative to TMS (internal standard).

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

1-(2-Hydroxyphenyl)-3-(1-methyl-5-chloroimidazolyl-2)propenones (Ia-f). To a hot solution of 20 mmoles of the corresponding 2-hydroxyacetophenone in alcohol we added 20 mmoles of 1-methyl-2-formyl-5-chloroimidazole and 6 ml of a 50% sodium hydroxide solution. The reaction mixture was kept at room temperature for 20-40 h. Then the precipitate was suspended in water and acidified to a neutral pH with acetic acid. It was filtered off and crystallized from alcohol.

2-(1-Methyl-5-chloroimidazolyl-2)chromanones (IIa, c, d). A suspension of 10 mmoles of compound Ia, c, d and 3.5 g of the resin Amberlite A-21 in 60 ml of methanol was boiled with mixing for 5-7 h. Then the mixture was filtered off, and part of the solvent was evaporated until the chromanone crystallized. The products IIc, d were recrystallized from alcohol, and IIa was preliminarily purified by column chromatography on silica gel, with eluent: chloroform–ethyl acetate (9:1).

2-(1-Methyl-5-chloroimidazolyl-2)chromones (IIIa-d). A mixture of 15.6 mmoles of the propenone Ia-d in 80 ml of dimethyl sulfoxide in the presence of catalytic amounts of iodine was boiled for 2 h. The mixture was cooled, diluted with water, filtered off, washed on the filter with water and with a 10% solution of sodium thiosulfate, then once again with water, and crystallized from ethyl acetate.

2-(1-Methyl-5-chloroimidazolyl-2)-3-hydroxychromones (IVb, d). To a suspension of 10 mmoles of the propenone Ib, d in 40 ml of methanol we added 75 ml of a 4 N sodium hydroxide solution and 34 ml of a 36% hydrogen peroxide solu-

tion. The reaction mixture was kept at room temperature for 10-12 h. The precipitate was filtered off, suspended in water and acidified to a neutral pH with acetic acid, filtered off, and crystallized from alcohol.

3-(2-Hydroxyphenyl)-5-(1-methyl-5-chloroimidazolyl-2)-4,5-dihydropyrazoles (Va-c). To a solution of 10 mmoles of the propenone Ia-d in 50 ml of alcohol we added 1 ml of an 80% solution of hydrazine hydrate and boiled for 20 min. Then the reaction mixture was diluted with water, the precipitate was filtered off, and it was washed on the filter with water. The product was crystallized from alcohol.

3-(2-Hydroxyphenyl)-5-(1-methyl-5-chloroimidazolyl-2)pyrazoles (VIa-c). To a hot solution 5 mmoles of the chromone IIIa-c and 50 ml of alcohol we added 0.5 ml of an 80% solution of hydrazine hydrate and boiled for 10-20 h. The reaction mixture was diluted with water; the precipitate that formed upon cooling was filtered off, washed on the filter with water, and crystallized from alcohol.

5-(2-Hydroxy-5-methoxyphenyl)-3-(1-methyl-5-chloroimidazolyl-2)isoxazole (VIIb). A solution of 6 mmoles of the chromone IIIb and 18 mmoles of hydroxylamine hydrochloride in 15 ml of absolute pyridine was heated at 110-115°C for 10 h. Then the reaction mixture was diluted with water. The precipitate formed was filtered off, washed on the filter with water, and crystallized from ethyl acetate. PMR spectrum (DMSO-D_6): protons of the phenolic portion 11.00 (1H, c, 2-OH), 7.38 (1H, d, ^3J = 9.0 Hz, 3-H), 7.11 (1H, d. d, ^3J = 9, ^4J = 3 Hz, 4-H), 3.8 (3H, c, 5-OCH_3), 7.30 (1H, d, ^4J = 3 Hz, 6-H); imidazole protons 3.87 (3H, c, 1-CH_3), 7.09 (1H, c, 4-H); isoxazole protons 7.21 (1H, c, 4-H).

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