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FLAVONES, ISOFLAVONES, AND 2- AND 3-HETARYLCHROMONES IN REACTIONS WITH HYDROXYLAMINE. (REVIEW)

V. P. Khilya and V. V. Ishchenko

Published data on the reaction of flavones, isoflavones, and their analogs 2- and 3-hetaryl chromones with hydroxylamine are reviewed, classified, and analyzed. The physicochemical characteristics of the products are discussed and make it possible to determine their structure.

Keywords: 2-hetarylchromones, 3-hetarylchromones, isoxazoles, isoflavones, chromone oximes, 4-thioxochromenes, flavones.

On account of their high biological activity and low toxicity substituted flavones and isoflavones, both natural and synthetic, have found application as drugs in medicine and also as food additives in agriculture and the food industry. Also of interest in this respect are the analogs of these compounds (2- and 3-hetaryl-substituted chromones), the possible uses of which have not yet been fully explored [1-10].

The chemical behavior of flavones, isoflavones, and also 2- and 3-hetarylchromones and their derivatives (in many cases unpredictable and unexpected) is due to their polyfunctional nature. Examples of these types of compounds enter into the most diverse reactions: electrophilic substitution, oxidation, reduction, cycloaddition, condensation, recyclization, and many others. The first papers on the reaction of chromones with nitrogen-containing nucleophiles, e.g., hydrazine, appeared as far back as the nineteenth century, and those on the reactions with hydroxylamine appeared at the beginning of the twentieth century. Now, however, the previously published results have been reexamined and refined, and this has included the discovery of further ways of developing the reaction.

Both the products from reaction at the carbonyl group and the isomeric products from cleavage of the pyrone ring with the subsequent formation of a new heterocycle (isoxazoles, pyrazoles, etc.) can be formed as a result of the treatment of flavones and isoflavones with hydroxylamine, hydrazine, phenylhydrazine, and other similar nucleophiles. This is of special interest in the case of modified flavones and isoflavones, from which compounds difficult to obtain by other synthetic means can be synthesized. The uncertainty of the reactions with nitrogen-containing nucleophiles led to incorrect theories about their mechanism and, consequently, the structure of the intermediate and final products [11-24].

A large number of publications have been devoted to the reaction of flavones, isoflavones, and 2- and 3-hetarylchromones with nucleophiles, but the obtained data have been insufficiently analyzed. There are no reviews on the subject in the literature.

In the present review data (including the authors' own data) on the reaction of flavones (section 1), isoflavones (section 2), and 2- and 3-hetarylchromones (section 3) and also the physicochemical characteristics on the basis of which the structure of the obtained products was determined (section 4) are summarized and

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Taras Shevchenko Kiev National University, Kiev; e-mail: alexish@i.com.ua. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1019-1037, August, 2002. Original article submitted April 4, 2001.

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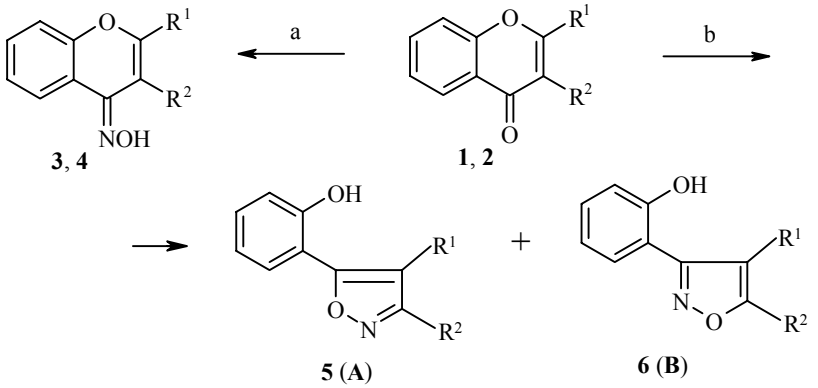
analyzed. In section 1, apart from the transformations of flavones, the reactions involving other chromones not having aryl or hetaryl substituents at positions 2 and 3 are also discussed, since by comparing the results it is possible to form an opinion about the effects of the structure of the initial compounds (e.g., an aryl substituent at position 2 or 3) on their reactivity and the nature of the products.

1. REACTION OF FLAVONES AND CHROMONES NOT CONTAINING ARYL OR HETARYL SUBSTITUENTS AT POSITIONS 2 AND 3 WITH HYDROXYLAMINE

The reactions of flavones and isoflavones with hydroxylamine can take place mainly in two directions, which are illustrated for the case of the unsubstituted flavone **1** and isoflavone **2**. In the first case (path a) the pyrone ring is retained, and the oximes **3** and **4** respectively are formed. In the second case (path b) the ring is opened, and cyclization leading to the isomeric isoxazoles **5** (a structure of type **A**) and **6** (a structure of type **B**) occurs.

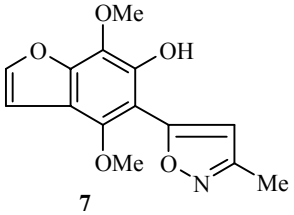


1, **3** R^1 = Ph, R^2 = H; **2**, **4** R^1 = H, R^2 = Ph

Nucleophilic attack at the $C_{(4)}$ atom of the pyrone ring, leading to oximes, seems natural in the investigated and similar reactions. This was indeed the opinion of the authors of the first papers [11-16]. Many researchers over a fairly long period have used the reaction with hydroxylamine to support the structure of the chromones they had synthesized on the assumption that the oximes were formed [17-24]. The synthesis of compounds of such type was also reported in the case of the 4-thio analogs of chromones [14]. The product of the reaction of 3-acetyl-2,6-dimethylchromone with two molecules of hydroxylamine was regarded as a dioxime (with respect to the acetyl and the carbonyl group of the chromone ring) [15].

When the reaction of the flavone **1** with hydroxylamine was reproduced [25], it was found that the product was the isoxazole **5** and not the oxime **3**, as supposed earlier [16]. It should be noted that in the same work [25] the oxime **3** was obtained from 4-thioxoflavone.

Later, the oxime **3** was synthesized from 4,4-dichloro-2-flavene and hydroxylamine in the presence of triethylamine [26]. During the oximation of khellin and visnagin in aqueous pyridine the corresponding isoxazoles **7** (type **A**) and **8** (type **B**) were obtained. The latter was the main product [27].



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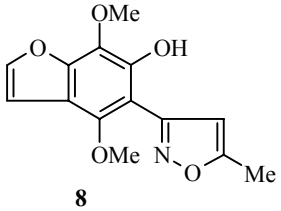

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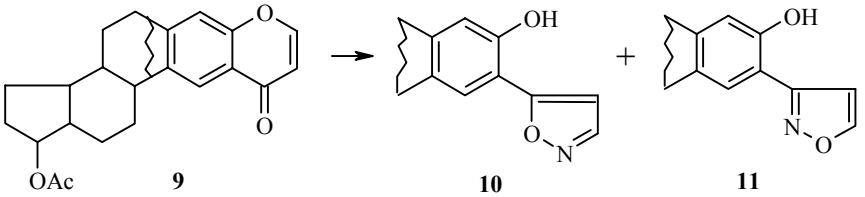
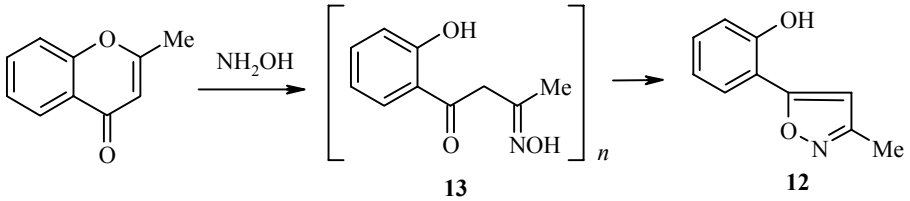
In subsequent papers it was established that isoxazoles were formed as a result of the reaction of flavones with hydroxylamine, but no precise evidence was obtained for the formation of form **A** or **B**.



9 **10** **11**

During the oximation of compound **9** the isoxazoles **10** and **11** were obtained in forms **A** and **B** respectively, and the product **10** predominated (yield 31.4%). The simultaneous formation of compounds **10** and **11** was explained by the ambident nature of hydroxylamine [33]. The assignment of the structure of the obtained isoxazoles and their 1-acetoxy derivatives to forms **A** and **B** was made for the first time on the basis of the ^{1}H NMR spectra by comparison with the spectra of 2- and 3-phenylisoxazoles, which have substantial differences in the chemical shifts of the proton at the position adjacent to the heteroatom (3-H 8.66, 5-H 8.85-ppm).

The formation of the isoxazole **12** (type **A**) and not its isomer, as reported earlier [30], from 2-methylchromone and hydroxylamine was explained by a possible reaction mechanism through the intermediate product **13** [34].



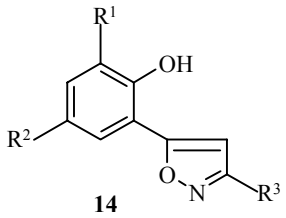
13 **12**

In the same paper it was noted that even in the reaction of 2-methyl- and 2-styryl-4-thioxochromenes isoxazoles are formed together with the oximes.

The structure of the isoxazoles synthesized from chromones and hydroxylamine was demonstrated most convincingly by means of detailed mass-spectrometric investigations in a series of papers by Polish authors [35-41], who refined some of the previously obtained results.

In [24] and [42] the structure of the products was established on the basis of an independent synthesis from dibromochalcones on the assumption that isoxazoles of type **B** are always formed from the latter. In [38, 40] it was shown that this is not always so, particularly if the carbonyl group of the chalcones is attached by an intramolecular hydrogen bond to the 2-hydroxy group of the phenol ring.

Contrary to data in [14] and irrespective of the analogous investigation [34] the authors of [36, 37] obtained derivatives of isoxazole **14** of form **A** with yields of ~90% from 6- or 8-substituted 2-methylchromones and hydroxylamine.

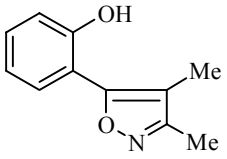


14

R^1 = H, Me; R^2 = Me, H; R^3 = Me

Isoxazoles of the same type are formed during the oximation of 2-ethylchromone and chromone-2-carboxylic acid [38].

Very often the nature of the products from the reaction of hydroxylamine with chromones depends both on the substituent at position 2 of the latter and on the conditions under which the process is conducted. During investigation of the reaction with flavones in dry pyridine it was established that flavone oximes can form at the same time as isoxazoles of type **A** [39, 40]. From 2,3-dimethylchromone and hydroxylamine, both in pyridine with heat and in alkaline solution in the cold, the isoxazole **15** [42] and not the corresponding oxime, as supposed earlier [11], was obtained. In the case of the formation of only isoxazoles from chromones, their isomeric oximes were synthesized from the analogous 4-thioxo derivatives [39, 40].



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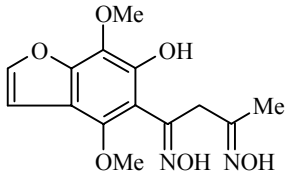


16

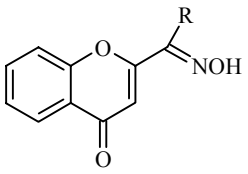
During the oximation of khellin in pyridine the isoxazole **7** and not **8**, as supposed earlier [27], was formed, although the isoxazole **8** and the dioxime **16** were formed in small amounts. The structures of the compounds were supported by the data from the mass spectra [43, 44].

In [44, 45] a method was proposed for the production of chromone oximes in dry methanol with the chromone and hydroxylamine hydrochloride in a ratio of 1:3.

If the conditions of oximation of the unsubstituted chromone (pH, reagent ratio) were varied a mixture of products, among which isomeric isoxazoles of types **A** and **B** predominated, was obtained instead of the expected oxime [46]. The result provides further evidence that the compound obtained in [13, 20] was not the chromone oxime but an isoxazole of type **A**.

It is necessary to mention specially the reactions of hydroxylamine with chromones containing functional groups. If this group is at position 3, attack by the hydroxylamine can take place both at this group and at the $C_{(2)}$ atom of the pyrone ring, leading to the most diverse products.

For example, oximes with structures **17-19**, obtained with yields of 75-82% from the corresponding 2-, 6-, and 8-formylchromones (R = H) or acylchromones (R = Me), were described in [47-50].



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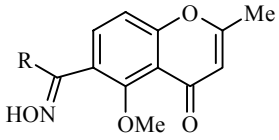

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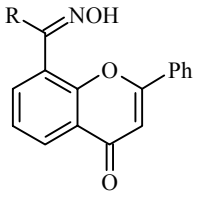

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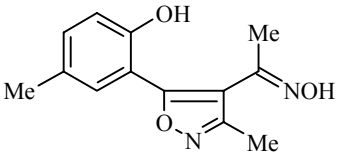
Conversely, in [51] it was shown that the products previously synthesized by the oximation of 3-acetyl-2-methylchromones [15] have the structure of isoxazoles **20** and **21**.



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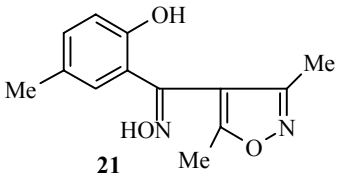
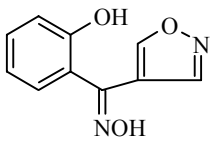


21

The reaction of 3-formylchromones with hydroxylamine hydrochloride has been studied by many authors. It was shown that the reaction of 3-formylchromone and hydroxylamine under various conditions (pH, ratio of substrates) gives a mixture of compounds, the main components of which are compounds **22**-**24** [52, 53].



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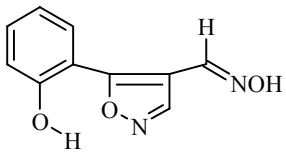

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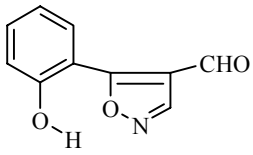
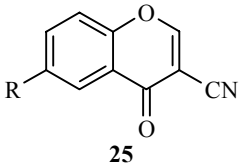


24

When this reaction was conducted in an acidic medium, the nitrile **25** and isoxazole **26** were obtained [10, 54]. Such a transformation of the formyl group to a nitrile group is widely used for the synthesis of 3-tetrazolyl- and 3-imidazolylchromones.



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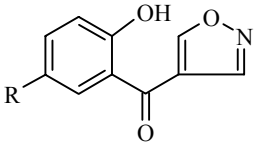

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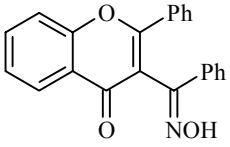
25, **26** R = H, Me



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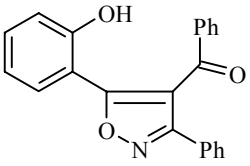
3-Cyanoflavone, the oxime **27**, and the isoxazoles **28** and **29** were obtained from 3-benzoylflavone under the indicated conditions [55].



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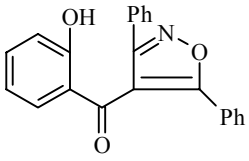

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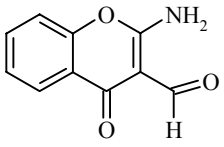
2-Amino-3-formylchromone (**30**) was obtained from 2-aminochromone through the intermediate oxime in an alkaline medium. The action of hydroxylamine hydrochloride on compound **30** led to the oxime **31** [56].



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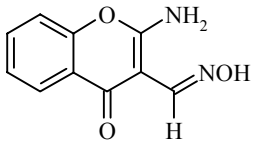
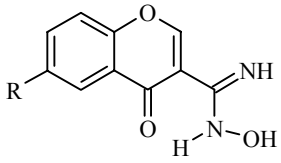


31

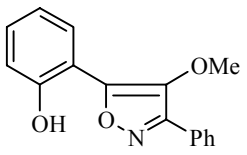
Products with structure **32** were synthesized from 6-R-3-cyanochromones and hydroxylamine [57].



32

R = H, Me, Et

The inertness of 3-hydroxy- and 3-methoxyflavones toward hydroxylamine under various conditions (in pyridine, in weakly acidic, neutral, and alkaline media) was reported [42]. The authors explained the absence of activity in 3-γ-hydroxyflavones by the conjugation of the electron pair of the 3-OH group. The donating effect of the methoxy group is fairly strong and prevents opening of the pyrone ring by the hydroxylamine – a weak nucleophilic reagent (does not react in pyridine). During evaluation of the reactivity of 3-methoxyflavones toward hydroxylamine in a strongly alkaline medium, in which the pyrone ring is opened under the influence of OH^- ions (e.g., in boiling ethanol in the presence of sodium hydroxide), a product that was the isoxazole **33** according to the analytical and spectral characteristics was obtained [42].



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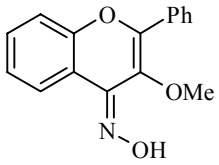

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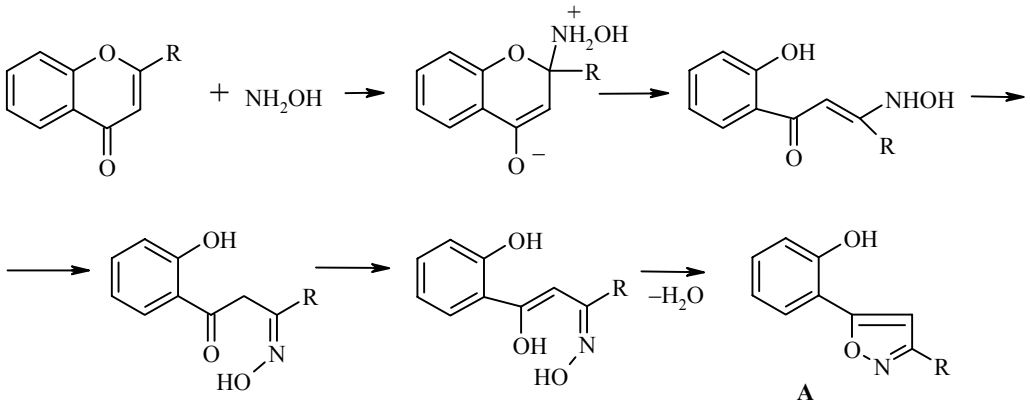
It was only possible to obtain 3-methoxyflavone oxime **34** from 3-methoxy-4-thioxoflavene and hydroxylamine in pyridine [42]. The synthesis of compounds **33** and **34** is the first example of the indirect production of isoxazole and oxime in the flavonol series.

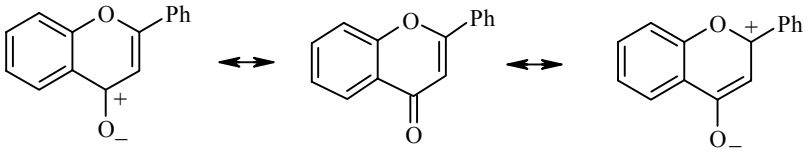
It can be concluded on the basis of the foregoing that the reaction of chromone and its derivatives with hydroxylamine leads, irrespective of the nature of the substituent at the $C_{(2)}$ atom (electron-donating or electron-withdrawing), to the formation mainly of isoxazoles of type **A** and takes place according to the previously proposed scheme [40]:



A

The reaction begins with nucleophilic attack by the hydroxylamine at the $C_{(2)}$ atom of the chromone ring, followed by cleavage of the pyrone ring and the formation of a new heterocycle with the release of a water molecule. It is this that determines the form A for the obtained isoxazole.

The formation of the flavone oximes can be explained by the M-effect of the phenyl group on the $C_{(2)}$ atom and by the existence of the flavones in three resonance forms [39].

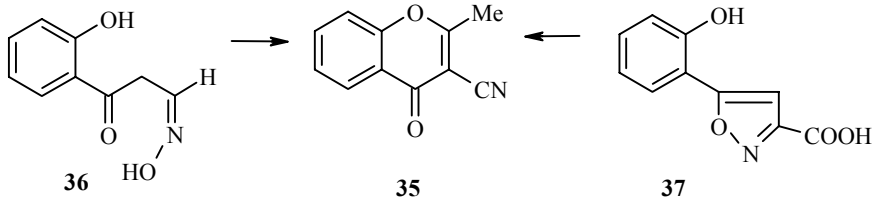


There is a view that attack by a nucleophile on the carbonyl carbon of chromone takes place only in an absolutely dry medium [43, 44].

It was shown that oximes are also formed from polyfluorinated chromones by the action of hydroxylamine as a result clearly of the enhanced electrophilicity of the carbonyl group, due to the presence of the polyfluoroaromatic ring and the ethoxycarbonyl group [58, 59].

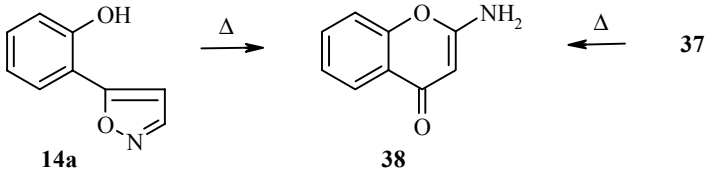
More intensive investigations into the oximation of the chromone ring showed that the final products of this reaction may be not only oximes and isoxazoles. This is due to the previously discovered sensitivity of the isoxazole ring to the action of nucleophilic reagents [60]. For example, the transformation of 5-phenylisoxazole-3-carboxylic acid by heat into cyanoacetophenone, but not with a very high yield, has been described [61]. In turn 2-hydroxybenzoylacetonitrile is capable of being transformed thermally into 2-aminochromone [62].

There is also a new example of the Kostanetskii–Robinson synthesis in the formation of 3-cyano-2-methylchromone (**35**) during the action of heat on the aldoxime **37** in acetic anhydride with pyridine or with sodium acetate [60].

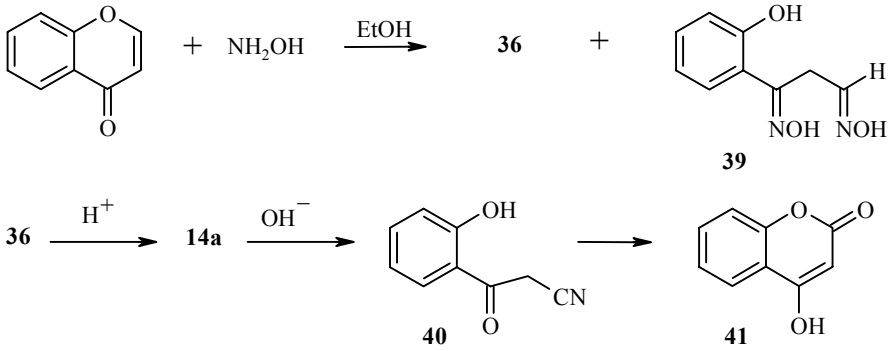


By this synthesis it is possible to obtain the difficultly obtainable 2,3-disubstituted derivatives of chromone.

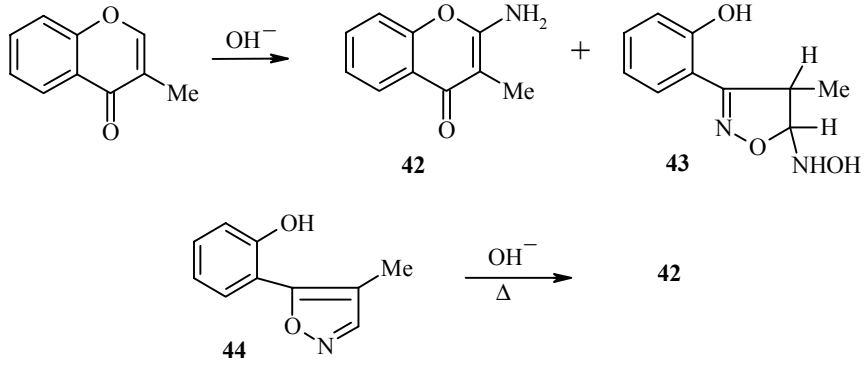
New rearrangements of the substituted isoxazoles formed during oximation into derivatives of coumarins or chromones were reported in [38, 62]. For example, the isoxazole **14a** ($R^1 = R^2 = R^3 = H$) obtained from unsubstituted chromone and also the carboxylic acid **37** rearrange when heated above the melting point into one and the same substance, which was identified on the basis of the IR and UV spectra as 2-aminochromone (**38**), previously synthesized by other methods [62-64].



During the oximation of unsubstituted chromone in aqueous ethanol a mixture of the monoxime **36** and the dioxime **39** in a ratio depending on the concentration of the nucleophilic reagent was obtained. In acetic acid or neutral solutions compound **36** was quickly transformed into the isoxazole **14a**, which isomerized in an alkaline medium to the nitrile **40**. The latter in turn was converted during acid hydrolysis into the coumarin **41** [65].



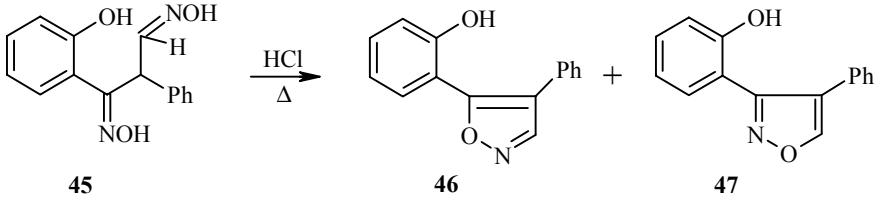
3-Methylchromones were transformed into 4-hydroxycoumarins in a similar way [66]. Later it was shown that three products are formed from 3-methylchromone and hydroxylamine, depending on the conditions [67]. For example, in an alkaline medium with a threefold excess of hydroxylamine at room temperature the familiar 2-amino-3-methylchromone (**42**) [64, 66] and 5-hydroxylamino-3-(2-hydroxyphenyl)-4-methyl-2-oxazoline (**43**) were obtained. The structure of the latter was established on the basis of mass-spectroscopic data. According to data in [66], compound **42** is formed as a result of isomerization of the isoxazole **44** by the action of the alkali or heat.



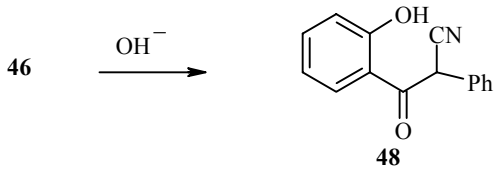
2. REACTION OF ISOFLAVONES WITH HYDROXYLAMINE

Study of the reaction of isoflavones with hydroxylamine was started by Hungarian investigators, who did not avoid the usual error and assumed in the first publications [68, 69] that the reaction led to isoflavone oxime. However, in the course of further investigations into the reactivity of the obtained products the same authors found that the reaction with hydroxylamine in an alkaline medium led to opening of the pyrone ring of the isoflavones and subsequent cyclization of the intermediate compounds to derivatives of isomeric isoxazoles (mainly isoxazoles of type **A**) or 4-hydroxycoumarins [66, 70, 71].

In the reaction of the 4-thioxo analog of isoflavone and hydroxylamine the stable dioxime **45** was obtained as the main product (yield 62%) with a small amount of the isoxazole **46** (yield 12%) [72]. Boiling of the dioxime **45** in hydrochloric acid solution led to the formation of the isomeric isoxazoles **46** and **47** with an overall yield of 47%.

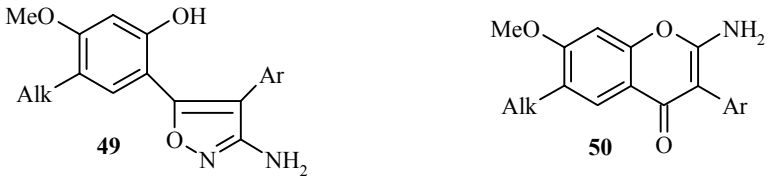


In alkaline solution at room temperature the isoxazole **46** was converted into the nitrile **48**, whereas the isoxazole **47** remained unchanged.



Thus, the difference in structure has an appreciable effect on the stability and reactivity of the isomeric isoxazoles, which creates possibilities for their structural assignment.

The reaction of substituted isoflavones and their 4-thioxo analogs with hydroxylamine was studied in greater detail by Khilya and coauthors. In their papers [73, 74] it was shown that the direction of this reaction depends on the presence and the nature of substituents at position 2 of the chromone ring. Thus, isoxazoles of type **A** are nearly always formed in the reaction of 2-methyl- and 7-methoxy-2-trifluoromethylisoflavones with hydroxylamine in pyridine [73]. In the case of the 4-thioxo analog of these isoflavones both types of isoxazoles are formed with an overall yield of 91% [74]. As a rule the reaction of hydroxylamine with isoflavone derivatives not containing substituents at position 2 leads to a multicomponent mixture of structurally different products, among which in addition to both types of isoxazoles 3-aminoisoxazole **49** (yield 15%) and 2-aminochromone **50** (yield 24%) were isolated.



49 **50**

Alk = Me, Et, Pr; Ar = Ph, 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-$O_2NC_6H_4$

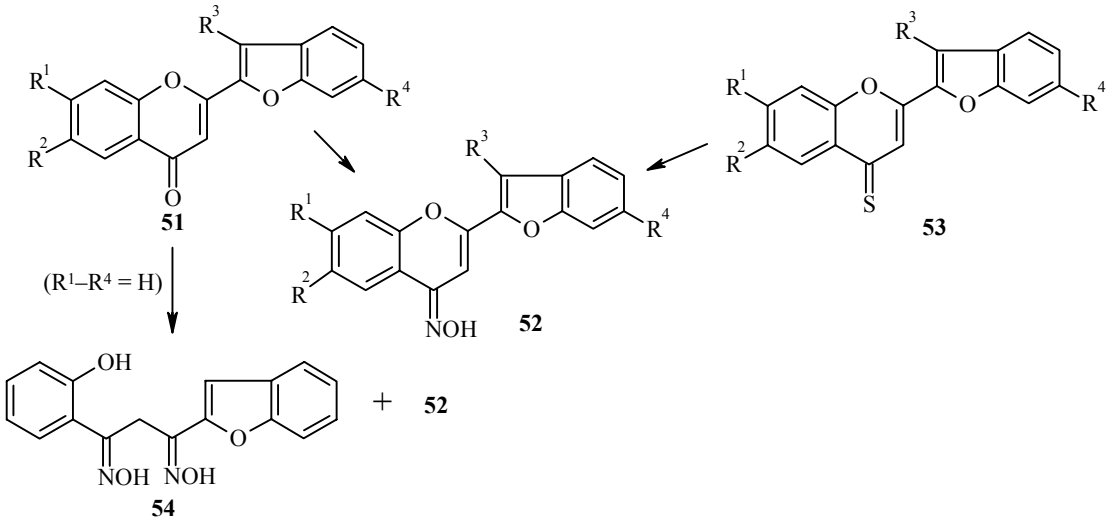
Thus, neither isoflavones nor their thioxo analogs form chromone oximes in reaction with hydroxylamine under various conditions. This distinguishes them from flavones, from which in very rare cases it is possible to obtain such derivatives in absolutely dry solvents [74, 75].

3. REACTIONS OF 2- OR 3-HETARYLCHROMONES WITH HYDROXYLAMINE

Intensive investigations into the reaction of 2- and 3-hetarylchromones (modified flavones and isoflavones) with hydroxylamine began at the beginning of the eighties.

Already in the early papers [76-78] it had been shown that the course of the reaction and the nature of the obtained products depended both on the substituents in the benzopyrone fragment and on the nature of the 2- or 3-hetaryl.

Thus, the reaction of methyl-substituted 2-benzofurylchromones **51** with hydroxylamine hydrochloride in pyridine leads to the chromone oximes **52** (yield 91%). The same products are formed with yields of 85-90% from the corresponding 4-thioxochromenes **53** [79].

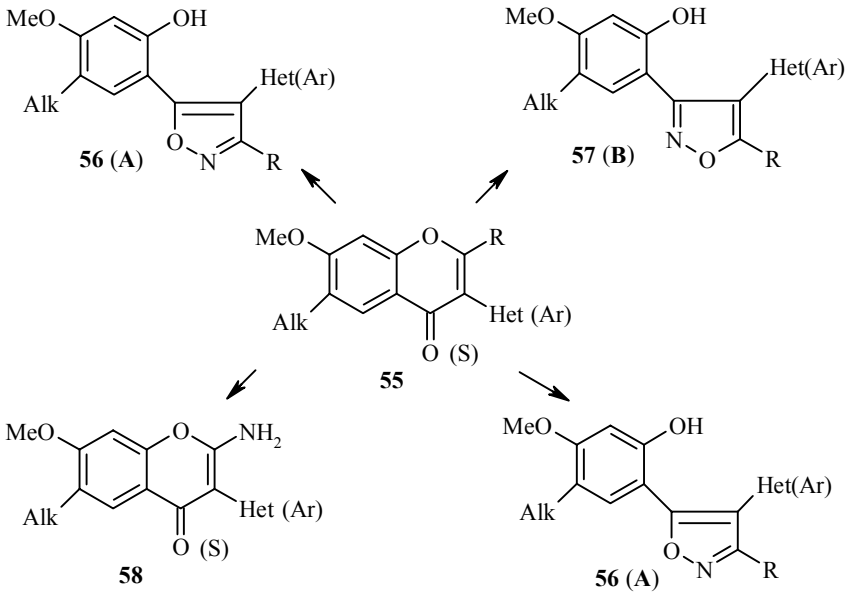


R^1 = Me, R^2 = H, R^3 = R^4 = Me; R^1 = H, R^2 = Me, R^3 = R^4 = Me; R^1 = OMe, R^2 = H, R^3 = R^4 = H

In the case of the unsubstituted 2-(2-benzofuryl)chromone **51** (R^1-R^4 = H), however, in the same paper two products were obtained, i.e., its oxime **52** (R^1-R^4 = H) (yield 32%) and dioxime **54** (yield 49%).

In the reaction of the chromone **51** with hydroxylamine hydrochloride on absolute methanol under the conditions of [45] only the corresponding oxime **52** is formed.

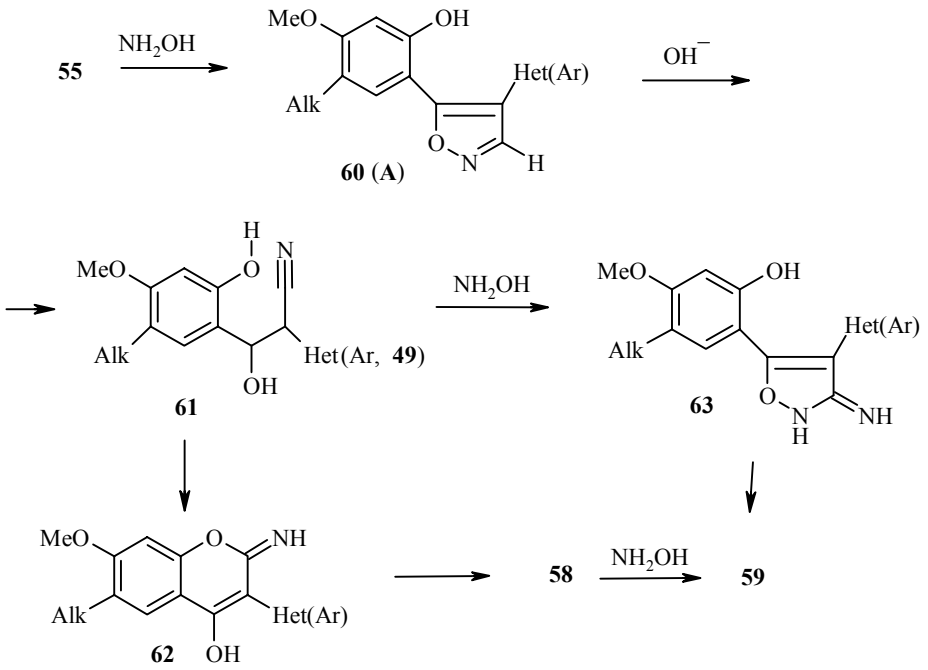
In papers devoted to study of the reaction of derivatives of 2-methyl- and 2-trifluoromethyl-7-methoxy-3-hetaryl(aryl)chromones **55** (Alk = Me, Pr, Bu) with quinoline [76, 80], thiazole [77, 78, 81], furan [75], and benzofuran [79, 82] residues (Het) or with Ar = C_6H_5, 4-BrC_6H_4, 4-$O_2NC_6H_4$, and 4-$CH_3OC_6H_4$ it was shown that in most cases the isoxazoles **56** (form **A**) are formed exclusively, whereas a mixture of the regioisomers **56** and **57** (form **B**) is formed from their 4-thioxo analogs.



In the case of isoflavones and 3-hetarylchromones not having substituents at position 2 (R = H) different products are formed. Thus, the reaction of 3-hetaryl-7-methoxychromones (Het = 2-isoxazolyl, 2-thiazolyl, 2-furyl, 2-benzothiazolyl) with hydroxylamine with heating in dry pyridine takes place unusually selectively and leads to the exclusive formation of derivatives of 2-amino-3-hetarylchromones **58** with high yields (70-90%) [77, 78, 81, 83-85]. From 3-(2-pyridyl)- or 3-(2-quinolyl)chromones mixtures of products containing, together with the isoxazoles **56** (yield ~60%), derivatives of compounds **58** (~25%) and 3-aminoisoxazoles **59** (9-12%) were obtained with overall yields of 70-80% [2].

The formation of 2-amino-3-hetaryl(aryl)chromones **58** can be represented as the result of successive recyclizations and isomerizations. For example, in the isoxazole derivative **60** formed from compound **55** by the action of hydroxylamine the heterocycle is opened under the influence of the base and is converted into the intermediate nitrile **61**. Intramolecular attack by the oxygen atom of the phenolic hydroxyl on the carbon atom of the nitrile group in compound **61** results in the formation of 4-hydroxycoumarinimine **62**, which isomerizes to the more stable 2-aminochromone **58**. In addition to the intramolecular process there can also be an intermolecular process, involving addition of a molecule of hydroxylamine to the nitrile group of the intermediate **61** and subsequent cyclization to compound **63** with isomerization to 3-aminoisoxazole **59**. It is not impossible that the latter may also be formed as a result of secondary cyclization of 2-aminochromone **58** under the influence of the hydroxylamine [83, 86, 87].

The formation of 2-amino-3-hetaryl(aryl)chromones **58** was confirmed by spectral methods and chemical transformations [2, 74, 83, 86] (see also section 4).



4. THE CHEMICAL AND PHYSICOCHEMICAL CHARACTERISTICS OF THE PRODUCTS OF THE REACTION OF FLAVONES, ISOFLAVONES, AND 2- AND 3-HETARYLCHROMONES WITH HYDROXYLAMINE MAKING IT POSSIBLE TO DETERMINE THE STRUCTURE OF THESE PRODUCTS

The variety of the products obtained as a result of the reaction of flavones, isoflavones, their 4-thioxo analogs, and particularly 2- and 3-hetarylchromones with hydroxylamine created the problem of determining their structure. The main chemical and physicochemical characteristics of the obtained compounds (oximes of chromones, substituted isoxazoles, 2-amino-3-hetarylchromones) that make it possible to identify them during analysis of the reaction products are examined below.

The differences in the chemical characteristics make it possible to reach a preliminary conclusion about the affiliation of the obtained product to one of the above-mentioned groups of compounds. Chromone oximes, 2-amino-3-hetarylchromones, and oxazoles of type **A** give a negative reaction with an alcohol solution of ferric chloride [2, 35, 39, 50, 51]. Conversely, isoxazoles of type **B** form a colored complex with $FeCl_3$ (a weak hydrogen bond between the hydroxyl group and the nitrogen atom of the isoxazole ring) [2, 36, 39, 67, 73]. In our opinion, however, the statement by the authors in [38] that isoxazoles of type **A** do not enter into reaction with ferric chloride on account of a strong intramolecular hydrogen bond with the oxygen atom of the isoxazole ring is erroneous, since such a bond cannot be formed by virtue of the unfavorable orientation of the free electron pair of this atom in space. In contrast to the isoxazoles, the indicated oximes and aminochromones dissolve in acids and do not dissolve in a 2 N solution of alkali or sodium carbonate either in the cold or on heating. Moreover, when the flavone oximes are boiled in acidified methanol they are converted into the corresponding flavones, indicating that the chromone structure is retained [2, 35, 39, 50, 51, 58, 59, 71, 82]. It should also be noted that unlike isoxazoles of both types **A** and **B**, which are readily acetylated at the phenolic hydroxyl, 2-aminochromone cannot be acetylated at the amino group [83].

As a rule data from the IR spectra are used for the determination of structure only in conjunction with other methods. The direction of the reactions with hydroxylamine examined in the review (toward the formation of the corresponding isoxazole or oxime and also 2-amino-hetarylchromone) can be established on the basis of

data from the UV spectra. The absorption curves of the oximes of chromones and aminochromones repeat the form of the absorption curves of the initial chromones and also their 4-thioxo analogs and differ clearly from the absorption curves of isoxazoles, which have almost identical forms [2, 59, 74, 78, 80-82 (88-90)].

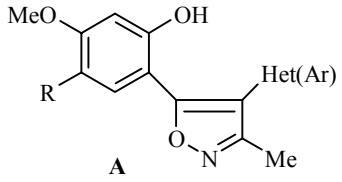
The structure of the isoxazoles synthesized from chromones and hydroxylamine has been proved convincingly by detailed mass-spectrometric investigations in a series of papers [35-41, 43, 44], where the main fragmentation paths of isoxazoles are presented.

The NMR spectra, particularly the ^{1}H NMR spectra, are the most informative for interpreting the structure of the obtained products.

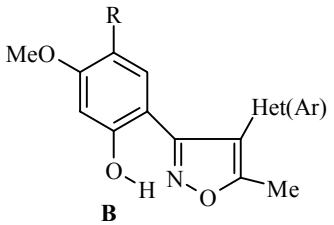
Previously, there was the view that the structure of the products obtained in the reaction of modified flavones and isoflavones with hydroxylamine can only be proved by means of the mass spectra [35-41, 43-45]. However, Khilya and coauthors [2, 74-76, 78, 79, 81] established on the basis of a systematic study of the ^{1}H NMR spectra of the isomeric isoxazoles synthesized by recyclization of 3-hetarylchromones and synthetic isoflavones by the action of hydroxylamine that opening of the pyrone and closure of the isoxazole ring are always accompanied by a significant diamagnetic shift for the protons of the phenol part and the heterocyclic residues, positioned in direct proximity to the isoxazole ring. The diamagnetic shift for the 6-H proton of the phenol part and for the corresponding protons of the heterocyclic rings (5-H of thiazole [81], 3-H of furan [79], benzofuran [75], pyridine, quinoline [88]) amounts on the average to 1 ppm in comparison with the corresponding protons of the initial chromones. Such diamagnetic shifts of the indicated protons result from loss of the coplanarity of the heterocyclic rings in the molecules of the isoxazoles.

One of the clearest and most reliable signs of difference in the isoxazole regioisomers is the chemical shift of the proton of the phenolic hydroxyl 2-OH in the ^{1}H NMR spectra, recorded in deuterochloroform [74, 75, 79, 81, 88]. The hydrogen atom of the 2'-OH group in isomers **B** forms an intramolecular bond of the chelate type with the nitrogen atom of the isoxazole ring and absorbs at 9.0-9.6 ppm. Conversely, the hydrogen atom of the same 2'-OH group in the **A** isomers cannot form such a hydrogen bond and therefore absorbs in the upfield region (6.5-7.0 ppm), i.e., in the region characteristic of the absorption of monohydric phenols.

TABLE 1. The Chemical Shifts of the Protons of the 2'-OH Group in Isomers **A** and **B** of 4-Het(Ar)-substituted Isoxazoles (in Deutero-chloroform)



A



B

4-Hetaryl or 4-aryl	δ, ppm, 2'-OH group	
	Isomer **A**	Isomer **B**
2-Furyl	6.92	9.16
2-Benzofuryl	6.58	9.30
Phenyl	7.04	9.64
4-Methoxyphenyl	7.04	9.65
4-Thiazolyl	10.38	9.66
2-Methyl-4-thiazolyl	11.05	9.64
2-Pyridyl	12.60	12.58
2-Quinolyl	13.47	13.45

The observed differences in the chemical shifts of the protons in the phenolic hydroxyl 2'-OH of compounds of types **A** and **B**, exceeding 2 ppm, are always retained if the aromatic or heterocyclic substituents at position 4 of isoxazole do not have basic characteristics [74, 83, 88].

The dependence of the chemical shifts of the proton of the 2'-OH group in isomers **A** and **B** on the nature of the substituent at position 4 of the isoxazole ring [74, 75, 79, 81, 88] is shown in Table 1.

With increase in the basicity of the 4-hetaryl in the molecules of isoxazoles of type **A** the possibility of the formation of a hydrogen bond between the 2'-OH hydrogen atom and the nitrogen atom of the heterocyclic substituent at position 4 and not the nitrogen atom of the isoxazole ring appears. The appearance of such a bond with the nitrogen atom of the thiazole, pyridine, or quinoline ring is the reason for the above-mentioned significant paramagnetic shift in isoxazoles of type **A**.

The presence in the ^{1}H NMR spectra (DMSO) of a signal for the 5-H proton of the chromone fragment in the region of 7.7-8.0 ppm indicates retention of this system (the formation of the oximes of chromones or 2-aminochromones). During opening of the pyrone ring with the formation of isoxazoles this signal is absent from the spectra of the latter, but in the region of 7.1-7.3 ppm there is a signal for the 6'-H proton of the phenolic substituent of the isoxazole. A narrow singlet for the hydroxyl group of the substituent is observed in the region of 9.4-10.1 ppm [2, 50, 51, 58, 59, 71, 82]. The flavone oximes are characterized by a signal for the 3-H proton of the chromone fragment in the region of 7.0-7.6 and also by a signal for the =NOH group in the region of about 11.2 ppm [73, 79]. A distinguishing feature of the spectra of 2-amino-3-hetarylchromones is the presence of a broad two-proton singlet at 8.2-10.0 ppm, which disappears on dilution with heavy water. It belongs to the 2-NH_2 group, which forms an intramolecular hydrogen bond with the nitrogen atom of the heterocyclic residue [83, 84]. In derivatives of 3-aminoisoxazoles, where such a bond is impossible, the signal for the protons of this group is at 6.5-6.6 ppm [83]. In the case of 3-aminooxazoles the protons of the NH_2 group are also exchanged readily with heavy water, but their signals are in the region of 5.3-5.4 ppm [74].

NMR spectroscopy at ^{13}C, ^{14}N, and ^{15}N nuclei was used to obtain evidence for the formation of 2-amino-3-hetarylchromones **58** and not the corresponding 4-hydroxycoumarin imines **62** (see section 3) [83]. The spectra of the obtained products were compared with the spectra of model 4-hydroxy-3-hetarylcoumarins [91] and the initial 3-hetarylchromones, e.g., 3-(3-isoxazolyl)chromones. Analysis and comparison of the ^{13}C NMR spectra enabled the authors of the present review to discover the characteristic regions of the ^{13}C chemical shifts for the fragments of 3-hetaryl-substituted chromone, 2-aminochromone, and 4-hydroxycoumarin (Table 2) [84-86].

Such an assignment of the chemical shifts agrees with the data in [92, 93]. The significant diamagnetic shift of 20-30 ppm for the signal of the $C_{(3)}$ atom in 2-aminochromones **58** and the model 4-hydroxy-3-hetarylcoumarins compared with the initial chromones **55** is due to the strong electronic effect of the adjacent 2-NH_2 and 4-OH groups. The $C_{(2)}$ and $C_{(4)}$ carbon atoms in the molecules of 2-aminochromones **58** and the initial chromones **55** absorb in one and the same region, which rules out the 4-hydroxycoumarin structure **62** for the obtained 2-amino-3-hetaryl(aryl)chromones. Such a conclusion is not contradicted by the chemical shifts in the ^{15}N NMR spectra (92.2-93.00 ppm in relation to NH_3) or by the form of the signal of the nitrogen atom of the 2-NH_2 group. For compound **58** enriched with ^{15}N isotopes this signal appears in the form of a distinct doublet at 92.9 ppm with spin–spin coupling constant $J_{15N,1H}$ = 90.33 ppm [93]. (In the case of the tautomer **62** the signal of the imine nitrogen atom has the form of a doublet and lies in the region of 300-360 ppm.)

TABLE 2. The Regions of the Chemical Shifts of the Atoms in 3-Hetaryl-substituted Chromones, 2-Aminochromones, and 4-Hydroxycoumarins

Compound	^{13}C, NMR, δ, ppm		
	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$
Chromone	154-156	116-117	172-174
2-Aminochromone	152-158	85-94	172-173.5
4-Hydroxycoumarin	161-162	93-94	153-154

TABLE 3. The Principal Characteristics of the Products from the Reaction of Flavones, Isoflavones, and 2- and 3- Hetarylchromones with Hydroxylamines

Products	Characteristics	IR spectrum, cm^{-1}	^1H NMR spectrum, ppm (DMSO)
Oximes of chromones	Does not form colored complex with $FeCl_3$	1630-1650 (C=N), 1615-1645 (C=C), 1120-1125 (C–O–C), 3000-3300 (OH)	11.0-11.3 (N–OH), 6.8-7.2 (3-H), 7.8-8.2 (5-H), 7.3-7.6 (8-H)
	Does not dissolve in alkalies		
	Dissolves in acids		
	Is transformed into flavone		
Substituted isoxazoles	**A**: Does not form colored complex with $FeCl_3$	1610-1615 (C=N, C=C), 1270-1275 (C–O–N), 3100-3170 (OH)	10.2-10.8 (OH), **A**: 7.3-7.5 (4-H), **B**: 7.4-7.8 (4-H), 6.9-7.3 (6-H)
	B: Forms colored complex with $FeCl_3$		
	Dissolves in alkalies		
	Does not dissolve in acids		
	Is not transformed into flavone		
2-Amino-3-hetaryl(aryl) chromones	Does not form colored complex with $FeCl_3$	3060-3180, 3270-3330 (NH_2), 1640-1660 (C=O)	7.7-8.0 (5-H), 9-10.5 (NH_2)
	Does not dissolve in alkalies		
	Dissolves in acids		
	Is not transformed into flavone		

The most important data examined in section 4 are summarized briefly in Table 3.

Thus, the various directions in the reaction of flavones, isoflavones, their 4-thioxo analogs, and 2- and 3-hetarylchromones with hydroxylamine have been discussed on the basis of a study of the published data. Physicochemical and chemical criteria for distinguishing between the products were discovered, and the prospects for the use of chromone derivatives in the synthesis of new chemically active and biologically useful 2-amino-3-hetarylchromones, 3-hetaryl-4-hydroxycoumarins, and 3-aryl-4-hetarylisoxazoles inaccessible by other methods were indicated.

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