Chemistry of Natural Compounds, Vol. 43, No. 4, 2007

REACTION OF NATURAL ISOFLAVONOIDS AND THEIR ANALOGS WITH HYDROXYLAMINE

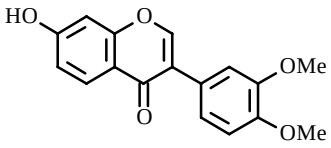
S. P. Bondarenko,[1] M. S. Frasinyuk,[2] and V. P. Khilya[1]

UDC 547.814.5

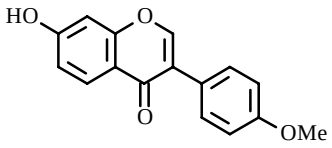
Recyclization of the chromone ring in several natural isoflavonoids and their analogs by reaction with hydroxylamine was studied. It has been found that the most suitable base for carrying out the reaction is N-methylmorpholine. Several derivatives of 4-aryl-5-(2-hydroxyphenyl)isoxazole were synthesized.

Key words: isoflavonoids, isoxazole derivatives, recyclization, hydroxylamine, *N*-methylmorpholine.

In continuation of research on the reactivity of analogs of natural isoflavonoids (cladrin **1a** and formononetin **1b**), we studied their reaction with hydroxylamine.



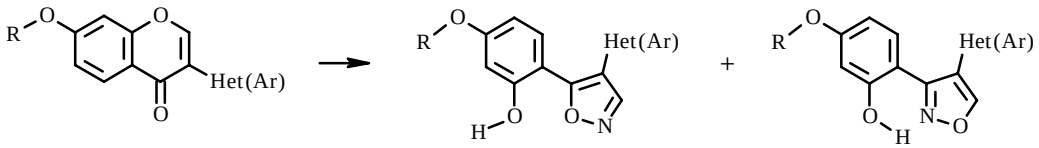
1a



1b

It is known that the products from reaction of chromones, flavones, and isoflavones with hydroxylamine were previously described as oximes [1-3]. Recently it has been shown that products from opening of the chromone ring (mono- and dioximes of ketones and regioisomeric isoxazoles) can be formed in this reaction in addition to oximes [4-6].

The reaction of 3-hetarylchromones with hydroxylamine hydrochloride in pyridine is known to produce derivatives of regioisomeric 4-hetaryl-5-(2-hydroxyphenyl)isoxazoles and 4-hetaryl-3-(2-hydroxyphenyl)isoxazoles [7-10] although 2-methylisoflavones form only one product, derivatives of 4-hetaryl-5-(2-hydroxyphenyl)isoxazole; those unsubstituted in the 2-position, a mixture of isomeric isoxazoles.



In contrast with 3-hetarylchromones with a *N*-containing substituent, the reaction with hydroxylamine of benzodioxole, benzodioxane, and benzodioxepane analogs of isoflavones proceeds much slower and is acompanied by formation of mixtures of recyclization products [11, 12].

Natural isoflavonoids are most often encountered in hydroxylated, methoxylated, or glycosylated forms. The presence in them of several electron-donating groups affects fundamentally the reactivity. Therefore, it seemed interesting to study the reaction of analogs of natural isoflavones with hydroxylamine.

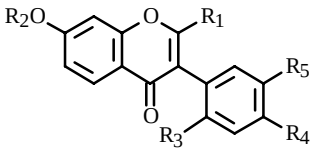
Thus, we selected formononetin, cladrin, and their analogs [13-17] and derivatives of 2′-methoxyisoflavone [18, 19] containing methyl or trifluoromethyl in the 2-position or 2-unsubstituted isoflavones. The starting 7-alkoxy- and

1) Taras Shevchenko Kiev National University, 01033, Ukraine, Kiev, ul. Vladimirskaya, 64; 2) Institute of Bioorganic and Petroleum Chemistry, National Academy of Sciences of Ukraine, 02094, Ukraine, Kiev, ul. Murmanskaya, 1, e-mail: mfras@i.kiev.ua. Translated from Khimiya Prirodnykh Soedinenii, No. 4, pp. 332-336, July-August, 2007. Original article submitted February 8, 2007.

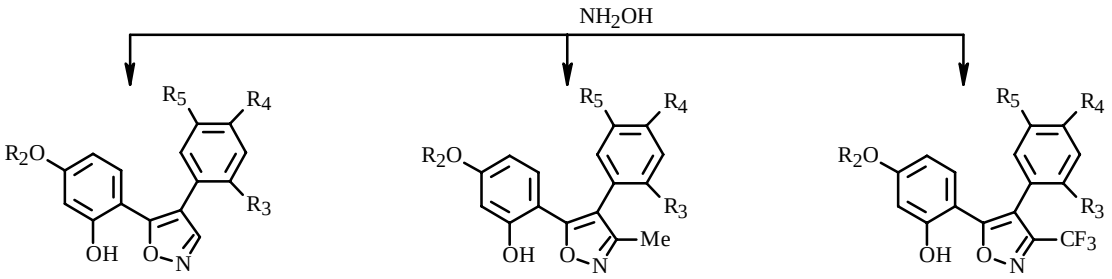
 0009-3130/07/4304-0402

7-benzyloxyisoflavones were synthesized from the corresponding 7-hydroxyisoflavones by alkylation in acetone in the presence of potash [20].

As expected, reaction of 2-methylisoflavones with hydroxylamine hydrochloride in pyridine formed exclusively derivatives of 4-aryl-5-(2-hydroxyphenyl)-3-methylchromones (**17a-c**, **18b**, and **19b**). In contrast with 3-hetarylchromones, recyclization of 2-methylisoflavones containing electron-donating methoxyls in ring B occurred in 2-5 h.



5 - 11



12a - c, 13b, 14b, 15c, 16c **17a - c, 18b, 19b** **20a,b, 21a,b, 22b**

1a - c, **2b**, **3b**, **4c**, **5c:** R_1 = H; **6a - c**, **7b**, **8b:** R_1 = Me; **9a,b, 10a,b, 11b:** R_1 = CF_3
1a - c, **6a - c**, **9a**,**b**, **12a - c**, **17a - c**, **20a,b:** R_2 = H; **2b, 7b, 10a,b, 13b, 18b, 21a,b:** R_2 = Me
3b, 14b: R_2 = Et; **4c, 8b, 11b, 15c, 19b, 22b:** R_2 = $CH_2C(Me)=CH_2$
5c, 16c: R_2 = $CH_2C_6H_4F$-4; **1a, 6a, 9a, 10a, 12a, 17a, 20a, 21a:** R_3 = H, R_4 = R_5 = OMe
1 - 3b, 6 - 14b, 17 - 22b: R_3 = R_5 = H, R_4 = OMe; **1c, 4 - 6c, 12c, 15 - 17c:** R_3 = OMe, R_4 = R_5 = H

Substituted 3-trifluoromethylisoxazoles (**20a** and **b**, **21a** and **b**, and **22b**) were synthesized under analogous conditions. The reactions were complete in this instance after 1-2 h.

The new isoxazole derivatives (**17a-c**, **18b**, **19b**, **20a** and **b**, **21a** and **b**, and **22b**) do not give the characteristic color with alcoholic iron chloride. This is due to peculiarities of their structures and is explained by the inability to form a chelate involving the phenol hydroxyl and the isoxazole N atom. The structures of these compounds were confirmed by PMR spectroscopy. The 2-hydroxyl resonates at 9.60-10.10 ppm in DMSO-d_6 and indicates that there is no intramolecular bond between the phenol hydroxyl and the isoxazole N atom.

Considering the structures of the recyclization products of 2-substituted isoflvaones by hydroxylamine hydrochloride, it can be assumed that nucleophilic attack occured at C-2 of the chromone ring. Evidence for this was the different reaction rates for the 2-trifluoromethyl- and 2-methylisoflavones.

For the 2-unsubstituted isoflavones (**1a-c**, **2b**, **3b**, **4c**, and **5c**), hydroxylamine in pyridine formed a mixture of two isomeric isoxazoles. This was due to nucleophilic attack at C-2 and C-4 of the chromone ring.

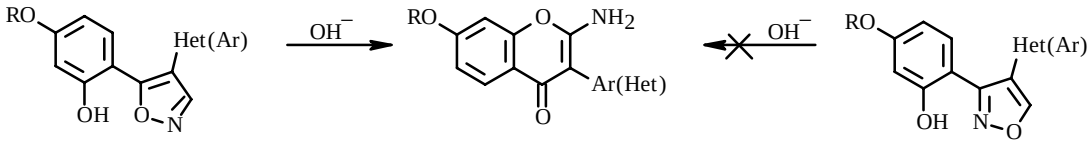
Therefore, our task was to find recyclization conditions for formononetin, cladrin, and their derivatives by hydroxylamine under which the reaction would be regioselective.

Because different bases can substantially affect the nucleophilicity of hydroxylamine hydrochloride, addition of them to the reaction mixture can change the direction of the nucleophilic attack. Taking this into account, we recyclized the chromone ring in the presence of tertiary amines (triethylamine, *N*-methylmorpholine, DBU), potash, and potassium acetate in various solvents commonly used to synthesize oximes (pyridine, propan-2-ol, ethanol).

As it turned out, reaction of 2-unsubstituted isoflavones with hydroxylamine hydrochloride in ethanol in the presence of *N*-methylmorpholine formed exclusively 4-aryl-5-(2-hydroxyphenyl)isoxazoles (**12a-c**, **13b**, **14b**, **15c**, and **16c**). Use of *N*-methylmorpholine as the base causes hydroxylamine to attack selectively at the 2-position of the chromone ring and enables one of the isomeric isoxazoles of the natural isoflavones and their analogs to be produced preparatively.

The synthesized isoxazoles (**12a-c**, **13b**, **14b**, **15c**, and **16c**) had typically less chromatographic mobility in toluene:ethanol (9:1) than their regioisomers and the starting isoflavones (**1a-c**, **2b**, **3b**, **4c**, and **5c**). This provided a qualitative analysis of the reaction mixtures.

The action of base on 4-hetaryl-5-(2-hydroxyphenyl)isoxazoles is known to form 2-amino-3-hetarylchromone derivatives [21]. In order to confirm the proposed recyclization pathway of the chromone ring by hydroxylamine and the structures of the synthesized substituted isoxazoles, we studied their reaction with base using **12c** as an example. Thus, **12c** was converted by NaOH solution (4 N) into 2-aminoisoflavone (**23**), the structure of which was confirmed by PMR spectroscopy. The PMR spectrum of **23** exhibited a 2H singlet for an amino group at 6.44 ppm and a resonance for H-5 of the chromone ring at 7.73 ppm, in contrast with that at 7.01 ppm for the starting isoxazole.



Thus, conversion of substituted isoxazole **12c** into **23** further proves that hydroxylamine attacks in the presence of *N*-methylmorpholine at the C-2 position of the chromone ring and forms 4-aryl-5-(2-hydroxyphenyl)isoxazole derivatives.

We studied the reactivity of the synthesized 5-(2-hydroxyphenyl)isoxazoles by alkylating and acylating the phenol hydroxyl of **12c**. This formed 2-chlorobenzyl and furyl derivatives **24** and **25**, respectively. Their structures were confirmed by PMR spectroscopy and elemental analysis.

Thus, the natural isoflavones cladrin and formononetin and their analogs were used as examples to study the reaction of isoflavones with hydroxylamine. We found the conditions for a regioselective reaction that enabled substituted 4-aryl-5-(2-hydroxyphenyl)isoxazoles to be preparatively produced. They can be synthesized only by this route.

EXPERIMENTAL

The course of reactions and the purity of products were monitored by TLC on Sorbfil UV-254 (Russia) and Merck (Germany) plates with elution by $CHCl_3$:CH_3OH (19:1 and 9:1) or toluene:ethanol (9:1). PMR spectra in DMSO-d_6 were measured on a VXR-300 (Varian, 300 MHz) instrument relative to TMS (internal standard) on the δ-scale. Elemental analyses of all compounds agreed with those calculated.

General Method for Synthesizing 7-Alkoxyisoflavones 2b, 3b, 4c, 5c, 7b, 8b, 10a and b, and 11b. A hot solution of the appropriate 7-hydroxyisoflavone (**1a-c**, **6a-c**, **9b** and **c**, 10 mmol) in absolute acetone (30 mL) was treated with freshly calcined potash (2.1 g, 15 mmol), stirred, boiled, and treated with the appropriate alkylhalide (12 mmol). The reaction mixture was stored for 1-4 h (end of reaction determined by TLC) and poured into acidified icewater (100 mL). The resulting precipitate was filtered off and crystallized from a suitable solvent.

3-(2-Methoxyphenyl)-7-[(4-fluorobenzyl)oxy]-4*H*-chromen-4-one (5c). $C_{23}H_{17}FO_4$, yield 89%, mp 190-192°C (propan-2-ol). PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 3.72 (3H, s, OMe-2′), 5.26 (2H, s, $ArCH_2O$-7), 7.00, 7.09, 7.26, 7.38, 7.57 (9H, 5m, H-8, H-3′, H-4′, H-5′, H-6′, FC_6H_4), 7.15 (1H, dd, ^3J = 8.0, ^4J = 2.0, H-6), 8.00 (1H, d, ^3J = 8.0, H-5), 8.26 (1H, s, H-2).

7-Methoxy-3-(3,4-dimethoxyphenyl)-2-trifluoromethyl-4*H*-chromen-4-one (10a). $C_{19}H_{15}F_3O_5$, yield 76%, mp 184-185°C (ethanol). PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 3.66, 3.78, 3.81 (9H, 3s, OMe-7, OMe-3′, OMe-4′), 6.82 (1H, dd, ^3J = 8.0, ^4J = 2.0, H-6), 6.91 (1H, d, ^4J = 2.0, H-8), 7.03 (1H, d, ^3J = 8.0, H-5′), 7.28 (1H, dd, ^3J = 8.0, ^4J = 2.0, H-6′), 7.54 (1H, d, ^4J = 2.0, H-2′), 8.06 (1H, d, ^3J = 8.0, H-5).

7-[(2-Methylprop-2-enyl)oxy]-3-(4-methoxyphenyl)-2-(trifluoromethyl)-4*H*-chromen-4-one (11b). $C_{21}H_{17}F_3O_4$, yield 68%, mp 88-89°C (ethanol). PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 1.80, 4.70, 5.02, 5.11 [3H, s, 2H, s, 2H, 2s, $MeC(=CH_2)CH_2O$-7], 3.81 (3H, s, OMe-4′), 7.00 (2H, d, ^3J = 8.0, H-3′, H-5′), 7.18 (1H, dd, ^3J = 8.0, ^4J = 2.0, H-6), 7.20 (2H, d, ^3J = 8.0, H-2′, H-6′), 7.29 (1H, d, ^4J = 2.0, H-8), 7.99 (1H, d, ^3J = 8.0, H-5).

General Method for Synthesizing 5-(2-Hydroxyphenyl)isoxazoles 12a-c, 13b, 14b, 15c, and 16c. A solution of the appropriate isoflavone (**1a-c**, **2b**, **3b**, **4c**, and **5c**, 5 mmol) in ethanol (25 mL) was treated with hydroxylamine hydrochloride

(0.7 g, 10 mmol) and *N*-methylmorpholine (1 mL). The reaction mixture was boiled for 6-8 h (end of reaction determined by TLC) and poured into water (100 mL) acidified with dilute HCl until the pH was 6. The resulting precipitate was filtered off and crystallized from methanol.

4-[4-(3,4-Dimethoxyphenyl)isoxazol-5-yl]benzene-1,3-diol (12a). $C_{17}H_{15}NO_5$, yield 63%, mp 205-207°C (methanol). PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 3.61, 3.73 (6H, 2s, OMe-4′ and OMe-4′), 6.34 (1H, dd, ^3J = 8.0, ^4J = 2.0, H-6), 6.45 (1H, d, ^4J = 2.0, H-2), 7.09 (1H, d, ^3J = 8.0, H-5), 6.88-6.98 (3H, m, H-2′, H-5′, and H-6′), 8.69 (1H, s, isoxazole H-3), 9.82 (2H, 2s, OH-1 and OH-3).

4-[4-(4-Methoxyphenyl)isoxazol-5-yl]benzene-1,3-diol (12b). $C_{16}H_{13}NO_4$, yield 80%, mp 125°C (methanol). PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 3.73 (3H, s, OMe-4′), 6.33 (1H, dd, ^3J = 8.0, ^4J = 2.0, H-6), 6.42 (1H, d, ^4J = 2.0, H-2), 6.90 (2H, d, ^3J = 8.0, H-3′, H-5′), 7.06 (1H, d, ^3J = 8.0, H-5), 7.30 (2H, d, ^3J = 8.0, H-2′, H-6′), 8.90 (1H, s, isoxazole H-3), 9.79 (2H, s, OH-1 and OH-5).

4-[4-(2-Methoxyphenyl)isoxazol-5-yl]benzene-1,3-diol (12c). $C_{16}H_{13}NO_4$, yield 54%, mp 196-198°C (methanol). PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 3.70 (3H, s, OMe-2′), 6.27 (1H, dd, ^3J = 8.0, ^4J = 2.0, H-6), 6.37 (1H, d, ^4J = 2.0, H-2), 7.01 (1H, d, ^3J = 8.0, H-5), 6.85, 7.03, 7.09, 7.26 (4H, 4m, H-3′, H-4′, H-5′, and H-6′), 8.69 (1H, s, isoxazole H-3), 9.70, 9.72 (2H, 2s, OH-1 and OH-3).

5-Methoxy-2-[4-(4-methoxyphenyl)isoxazol-5-yl]phenol (13b). $C_{17}H_{15}NO_4$, yield 85%, mp 130°C (methanol). PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 3.72, 3.76 (6H, 2s, OMe-5, and OMe-4′), 6.52 (2H, 2m, H-4 and H-6), 6.90 (2H, d, ^3J = 8.0, H-3′, H-5′), 7.20 (1H, d, ^3J = 8.0, H-3), 7.29 (2H, d, ^3J = 8.0, H-2′, H-6′), 8.93 (1H, s, isoxazole H-3), 10.03 (1H, s, OH-1).

2-[4-(4-Methoxyphenyl)isoxazol-5-yl]5-ethoxyphenol (14b). $C_{18}H_{17}NO_4$, yield 56%, mp 140-142°C (methanol). PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 1.34, 4.02 (3H, t, 2H, q, OEt-5), 3.73 (3H, s, OMe-4′), 6.49 (1H, dd, ^3J = 8.0, ^4J = 2.0, H-4), 6.50 (1H, d, ^4J = 2.0, H-6), 6.90 (2H, d, ^3J = 8.0, H-3′, H-5′), 7.17 (1H, d, ^3J = 8.0, H-3), 7.30 (2H, d, ^3J = 8.0, H-2′, H-6′), 8.92 (1H, s, isoxazole H-3), 9.79 (1H, s, OH-1).

5-[(2-Methylprop-2-enyl)oxy]-2-[4-(2-methoxyphenyl)isoxazol-5-yl]phenol (15c). $C_{20}H_{19}NO_4$, yield 55%, mp 122-124°C (methanol). PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 1.76, 4.44, 4.96, 5.05 [3H, s, 2H, s, 2H, 2s, $MeC(=CH_2)CH_2O$-5], 3.68 (3H, s, OMe-2′), 6.46 (1H, dd, ^3J = 8.0, ^4J = 2.0, H-4), 6.47 (1H, d, ^4J = 2.0, H-6), 7.11 (1H, d, ^3J = 8.0, H-3), 6.86, 7.06, 7.08, 7.27 (4H, 4m, H-3′, H-4′, H-5′, and H-6′), 8.79 (1H, s, isoxazole H-3), 9.91 (1H, s, OH-1).

2-[4-(2-Methoxyphenyl)isoxazol-5-yl]-5-[(4-fluorobenzyl)oxy]phenol (16c). $C_{23}H_{18}FNO_4$, yield 60%, mp 159-161°C (methanol). PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 5.06 (4H, m, 2H, s, $ArCH_2O$-5), 3.68 (3H, s, OMe-2′), 6.51 (1H, d, ^4J = 2.0, H-6), 6.53 (1H, dd, ^3J = 8.0, ^4J = 2.0, H-4), 7.21 (1H, d, ^3J = 8.0, H-3), 6.82-7.54 (8H, 4m), 8.72 (1H, s, isoxazole H-3), 9.96 (1H, s, OH-1).

General Method for Synthesizing 5-(2-Hydroxyphenyl)isoxazoles 17a-c, 18b, 19b, 20a and b, 21a and b, and 22b. A solution of the appropriate isoflavone (**6a-c**, **7b**, **8b**, **9a** and **b**, **10a** and **b**, and **11b**, 5 mmol) in dry pyridine (10 mL) was treated with hydroxylamine hydrochloride (0.7 g, 10 mmol), heated at 80-90°C for 1-5 h (end of reaction determined by TLC), and poured into water (100 mL) acidified with dilute HCl until the pH was 6. The resulting precipitate was filtered off and crystallized from methanol.

4-[3-Methyl-4-(3,4-dimethoxyphenyl)isoxazol-5-yl]benzene-1,3-diol (17a). $C_{18}H_{17}NO_5$, yield 73%, mp 102-104°C (methanol). PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 2.27 (3H, s, isoxazole Me-3), 3.62, 3.74 (6H, 2s, OMe-3′ and OMe-4′), 6.25 (1H, dd, ^3J = 8.0, ^4J = 2.0, H-6), 6.36 (1H, d, ^4J = 2.0, H-2), 6.78 (1H, dd, ^3J = 8.0, ^4J = 2.0, H-6′), 6.83 (1H, d, ^4J = 2.0, H-2′), 6.92 (1H, d, ^3J = 8.0, H-5′), 6.96 (1H, d, ^3J = 8.0, H-5), 9.66 (2H, 2s, OH-1 and OH-3).

4-[3-Methyl-4-(4-methoxyphenyl(isoxazol-5-yl]benzene-1,3-diol (17b). $C_{17}H_{15}NO_4$, yield 66%, mp 178-180°C (methanol). PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 2.23 (3H, s, isoxazole Me-3), 3.74 (3H, s, OMe-4′), 6.23 (1H, dd, ^3J = 8.0, ^4J = 2.0, H-6), 6.34 (1H, d, ^4J = 2.0, H-2), 6.90 (2H, d, ^3J = 8.0, H-3′, H-5′), 6.95 (2H, d, ^3J = 8.0, H-3′, H-5′), 7.16 (2H, d, ^3J = 8.0, H-2′, H-6′), 9.63, 9.67 (2H, 2s, OH-1 and OH-3).

4-[3-Methyl-4-(2-methoxyphenyl)isoxazol-5-yl]benzene-1,3-diol (17c). $C_{17}H_{15}NO_4$, yield 68%, mp 204-205°C (methanol). PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 2.08 (3H, s, isoxazole Me-3), 3.69 (3H, s, OMe-2′), 6.17 (1H, dd, ^3J = 8.0, ^4J = 2.0, H-6), 6.31 (1H, d, ^4J = 2.0, H-2), 7.05 (1H, d, ^3J = 8.0, H-5), 6.86, 6.88, 7.02, 7.30 (4H, 4m, H-3′, H-4′, H-5′, and H-6′), 9.60 (2H, 2s, OH-1 and OH-3).

5-Methoxy-2-[3-methyl-(4-methoxyphenyl)isoxazol-5-yl]phenol (18b). $C_{18}H_{17}NO_4$, yield 87%, mp 80°C (methanol). PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 2.24 (3H, s, isoxazole Me-3), 3.72, 3.74 (6H, 2s, OMe-5 and OMe-4′), 6.42 (1H, dd,

^3J = 8.0, ^4J = 2.0, H-4), 6.44 (1H, d, ^4J = 2.0, H-6), 6.91 (2H, d, ^3J = 8.0, H-3′, H-5′), 7.08 (1H, d, ^3J = 8.0, H-3), 7.16 (2H, d, ^3J = 8.0, H-2′, H-6′), 9.87 (1H, s, OH-1).

2-[3-Methyl-4-(4-methoxyphenyl)isoxazol-5-yl]-5-[(2-methylprop-2-enyl)oxy]phenol (19b). $C_{21}H_{21}NO_4$, yield 75%, mp 126-128°C (methanol). PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 1.74, 4.40, 4.94, 5.02 [3H, s, 2H, s, 2H, 2s, MeC(=CH_2)CH_2O-5], 2.23 (3H, s, isoxazole Me-3), 3.72 (3H, s, OMe-4′), 6.42 (1H, dd, ^3J = 8.0, ^4J = 2.0, H-4), 6.43 (1H, d, ^4J = 2.0, H-6), 6.90 (2H, d, ^3J = 8.0, H-3′, H-5′), 7.05 (1H, d, ^3J = 8.0, H-3), 7.15 (2H, d, ^3J = 8.0, H-2′, H-6′), 9.92 (1H, s, OH-1).

4-[4-(3,4-Dimethoxyphenyl)-3-(trifluoromethyl)isoxazol-5-yl]benzene-1,3-diol (20a). $C_{18}H_{14}F_3NO_5$, yield 77%, mp 206-208°C (methanol). PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 3.63, 3.75 (6H, 2s, OMe-3′ and OMe-4′), 6.26 (1H, dd, ^3J = 8.0, ^4J = 2.0, H-6), 6.39 (1H, d, ^4J = 2.0, H-2), 6.80 (1H, dd, ^3J = 8.0, ^4J = 2.0, H-6′), 6.86 (1H, d, ^4J = 2.0, H-2′), 6.97 (1H, d, ^3J = 8.0, H-5′), 7.03 (1H, d, ^3J = 8.0, H-5), 9.93 (2H, 2s, OH-1 and OH-3).

4-[4-(4-Methoxyphenyl)-3-(trifluoromethyl)isoxazol-5-yl]benzene-1,3-diol (20b). $C_{17}H_{12}F_3NO_4$, yield 81%, mp 170-172°C (methanol). PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 3.76 (3H, s, OMe-4′), 6.25 (1H, dd, ^3J = 8.0, ^4J = 2.0, H-6), 6.36 (1H, d, ^4J = 2.0, H-2). 6.95 (2H, d, ^3J = 8.0, H-3′, H-5′), 7.00 (2H, d, ^3J = 8.0, H-3′, H-5′), 7.19 (2H, d, ^3J = 8.0, H-2′, H-6′), 9.88, 9.94 (2H, 2s, OH-1 and OH-3).

5-Methoxy-2-[4-(3,4-dimethoxyphenyl)-3-(trifluoromethyl)isoxazol-5-yl]phenol (21a). $C_{19}H_{16}F_3NO_5$, yield 64%, mp 159-161°C (methanol). PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 3.64, 3.72, 3.75 (9H, 3s, OMe-5, OMe-3′, and OMe-4′), 6.45 (1H, dd, ^3J = 8.0, ^4J = 2.0, H-4), 6.47 (1H, d, ^4J = 2.0, H-6), 6.80 (1H, dd, ^3J = 8.0, ^4J = 2.0, H-6′), 6.87 (1H, d, ^4J = 2.0, H-2′), 6.97 (1H, d, ^3J = 8.0, H-5), 7.17 (1H, d, ^3J = 8.0, H-5′), 10.17 (2H, 2s, OH-1 and OH-3).

5-Methoxy-2-[4-(4-methoxyphenyl)-3-(trifluoromethyl)isoxazol-5-yl]phenol (21b). $C_{18}H_{14}F_3NO_4$, yield 76%, mp 106-108°C (methanol). PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 3.73, 3.76 (6H, 2s, OMe-5 and OMe-4′), 6.45 (1H, dd, ^3J = 8.0, ^4J = 2.0, H-4), 6.48 (1H, d, ^4J = 2.0, H-6), 6.96 (2H, d, ^3J = 8.0, H-3′, H-5′), 7.15 (1H, d, ^3J = 8.0, H-3), 7.20 (2H, d, ^3J = 8.0, H-2′, H-6′), 10.18 (1H, s, OH-1).

5-[(2-Methylprop-2-enyl)oxy]-2-[4-(4-methoxyphenyl)-3-(trifluoromethyl)isoxazol-5-yl]phenol (22b). $C_{21}H_{18}F_3NO_4$, yield 58%, mp 104-105°C (methanol). PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 1.75, 4.44, 4.96, 5.04 [3H, s, 2H, s, 2H, 2s, MeC(=CH_2)CH_2O-5], 3.77 (3H, s, OMe-4′), 6.45 (1H, dd, ^3J = 8.0, ^4J = 2.0, H-4), 6.48 (1H, d, ^4J = 2.0, H-6), 6.96 (2H, d, ^3J = 8.0, H-3′, H-5′), 7.15 (1H, d, ^3J = 8.0, H-3), 7.20 (2H, d, ^3J = 8.0, H-2′, H-6′), 10.18 (1H, s, OH-1).

2-Amino-7-hydroxy-3-(2-methoxyphenyl)-4*H*-chromen-4-one (23). A solution of **12c** (1.4 g, 5 mmol) in ethanol (30 mL) was treated with NaOH solution (2.5 mL, 10 mmol, 4 N), boiled for 5 h, diluted with water (50 mL), and neutralized until the pH was 7 with dilute HCl. The resulting precipitate was filtered off and crystallized from ethanol. $C_{16}H_{13}NO_4$, yield 43%, mp 264-266°C (ethanol). PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 3.72 (3H, s, OMe-2′), 6.44 (2H, s, NH_2-2), 6.64 (1H, d, ^4J = 2.0, H-8), 6.73 (1H, dd, ^3J = 8.0, ^4J = 2.0, H-6), 7.73 (1H, d, ^3J = 8.0, H-5), 6.94, 6.99, 7.11, 7.28 (4H, 4m, H-3′, H-4′, H-5′, and H-6′), 10.19 (1H, s, OH-7).

3-Methyl-5-{4-methoxy-2-[(2-chlorobenzyl)oxy]phenyl}-4-(4-methoxyphenyl)isoxazole (24). A hot solution of **12c** (1.4 g, 5 mmol) in absolute acetone (30 mL) was treated with freshly calcined potash (1.05 g, 7.5 mmol), stirred, boiled, treated with 2-chlorobenzylchloride (0.7 mL, 5.5 mmol), stored for 2 h, and poured into acidified icewater (100 mL). The resulting precipitate was filtered off and crystallized from ethanol. $C_{25}H_{22}ClNO_4$, yield 82%, mp 125-127°C (ethanol). PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 2.45 (3H, s, isoxazole Me-3), 3.74, 3.78 (6H, 2s, OMe-4 and OMe-4′), 6.64 (1H, dd, ^3J = 8.0, ^4J = 2.0, H-5), 6.68 (1H, d, ^4J = 2.0, H-3), 6.85 (2H, d, ^3J = 8.0, H-3′, H-5′), 7.04-7.46 (7H, m).

5-Methoxy-2-[4-(4-methoxyphenyl)-3-methylisoxazol-5-yl]phenyl-2-furate (25). A solution of **12c** (1.4 g, 5 mmol) in dry pyridine (10 mL) was treated with 2-furylchloride (0.54 mL, 5.5 mmol), stored at room temperature for 36 h (end of reaction determined by TLC), and poured into acidified icewater (100 mL). The resulting precipitate was filtered off, washed with water, and crystallized from ethanol. $C_{23}H_{19}NO_6$, yield 75%, mp 96-97°C (ethanol). PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 2.18 (3H, s, isoxazole Me-3), 3.77, 3.81 (6H, 2s, OMe-4 and OMe-4′), 6.94 (1H, dd, ^3J = 8.0, ^4J = 2.0, H-4), 7.94 (1H, d, ^4J = 2.0, H-6), 6.90 (2H, d, ^3J = 8.0, H-3′, H-5′), 7.11 (2H, d, ^3J = 8.0, H-2′, H-6′), 7.30 (1H, d, ^3J = 8.0, H-3); furyl protons: 6.75 (1H, dd, ^3J = 3.6, ^3J = 1.7, H-4), 7.27 (1H, dd, ^3J = 3.6, ^4J = 0.9, H-3), 8.05 (1H, dd, ^3J = 1.7, ^4J = 0.9, H-5).

REFERENCES

1. P. Venturella and A. Bellino, *Ann. Chim.*, **58**, No. 2, 145 (1968).
2. M. W. Moon and J. C. Sharp, Ger. Pat. No. 2,513,652, Oct. 9, 1975; *Chem. Abstr.*, **84**, 30890s (1976).
3 W. Basinski and Z. Jerzmanowska, *Rocz. Chem.*, **48**, 989 (1974).
4. W. Basinski and Z. Jerzmanowska, *Pol. J. Chem.*, **53**, 229 (1979).
5. V. Szabo, J. Borda, and L. Losonczi, *Magy. Kem. Foly.*, **83**, No. 6, 278 (1977).
6. L. G. Grishko, I. P. Kupchevskaya, and V. P. Khilya, *Dokl. Akad. Nauk Ukr. SSR, Ser. B*, **6**, 518 (1978).
7. I. P. Kupchevskaya and V. P. Khilya, *Dokl. Akad. Nauk Ukr. SSR, Ser. B*, **2**, 119 (1979).
8. V. P. Khilya, V. F. Vakulenko, and I. P. Kupchevskaya, *Khim. Geterotsikl. Soedin.*, **1**, 25 (1979).
9. V. P. Khilya, L. G. Grishko, and T. L. Davidkova, *Khim. Geterotsikl. Soedin.*, **7**, 892 (1980).
10. V. P. Khilya, I. P. Kupchevskaya, I. L. Kazakov, and T. M. Tkachuk, *Khim. Geterotsikl. Soedin.*, **3**, 321 (1982).
11. V. P. Khilya, A. Aitmambetov, and G. M. Golubushina, *Khim. Prir. Soedin.*, 633 (1994).
12. M. Sree Rama Murthy and E. Venkata Rao, *Indian J. Chem., Sect. B*, **24**, No. 7, 667 (1985).
13. A. Pelter and S. Foot, *Synthesis*, **5**, 326 (1976).
14. A. Levai, *J. Chem. Res. Synop.*, **5**, 163 (1992).
15. V. G. Pivovarenko, V. P. Khilya, and S. A. Vasil′ev, *Khim. Prir. Soedin.*, 639 (1989).
16. A. S. Kukla and T. R. Seshadri, *Indian J. Chem.*, **1**, 343 (1963).
17. S. P. Bondarenko, M. S. Frasinyuk, and V. P. Khilya, *Khim. Prir. Soedin.*, 273 (2003).
18. A. Levai, W. Adam, R. T. Fell, R. Gessner, T. Patonay, A. Simon, and G. Toth, *Tetrahedron*, **54**, 13105 (1998).
19. M. S. Frasinyuk, S. P. Bondarenko, and V. P. Khilya, *Khim. Prir. Soedin.*, 117 (2006).
20. S. P. Bondarenko, M. S. Frasinyuk, and V. P. Khilya, *Khim. Prir. Soedin.*, 277 (2003).
21. A. L. Kazakov, V. P. Khilya, V. V. Mezheretskii, and D. Litkei, *Natural and Modified Isoflavonoids* [in Russian], Izd. RGU, Rostov-on-Don (1985).