*Tetrahedron* Vol. 42, No. 15, pp. 4215 to 4222, 1986
Printed in Great Britain.

0040-4020/86 $3.00+.00
Pergamon Journals Ltd.

# REACTION OF CHROMONES WITH HYDROXYLAMINE IN ANHYDROUS METHANOL A NOVEL ROUTE FOR THE PREPARATION OF CHROMONE OXIMES

VINCE SZABÓ, JÁNOS BORBÉLY, EDIT THEISZ and SÁNDOR NAGY

Department of Applied Chemistry, Kossuth Lajos University of Debrecen, H-4010, Hungary

(*Received in UK* 14 *May* 1986)

Abstract - The reaction of 4H-1-benzopyran-4-one (chromone, 1) and its substituted derivatives with hydroxylamine in aqueous alcohols gives isoxazoles 5 and 10, as the major products, whereas 1a is transformed mainly into 8a with hydroxylamine hydrochloride in anhydrous methanol; compounds 5a, 9a and 10a can be also isolated, and the formation of 6a and 7a has been detected, as well. Depending on the character of the substituent, substituted chromones 1b-g afforded 7,8 or 9 as the isolable major product. Based on the present experiments compound 6, produced in an acid-catalyzed methanol addition on 1, is regarded the key intermediate of the formation of chromone oxime

In previous papers we have reported that nucleophiles ($OH^-$; $EtO^-$[1,2]; $NH_2OH$, $NH_2NHR$[3-5]) attack the chromone ring exclusively at C-2 and the initially formed aldoximes, produced in the reaction with hydroxylamine, subsequently transform in various routes dependent[6] on the substitution pattern and on the reaction conditions. The preparation of chromone oximes with hydroxylamine in aqueous, or anhydrous ethanol earlier[7], but even more recently[8], has been performed by suggesting a C-4 attack of the reagent. Subsequent studies showed, however, that the isolated products were isoxazoles[9] (5) or isoxazole-mixtures[10b,11].

At the same time, Beugelmans and Morin[10a,b] isolated chromone oxime (8a) unambiguously by means of the direct oximation reaction of chromone with dry hydroxylamine hydrochloride in anhydrous methanol. They supposed an initial formation of pyrylium cation 2 from chromone, followed by a C-4 attack of $NH_2OH$, and stabilization of the oxime 8 by the loss of the $C_4$-OH group from the intermediary product.

The procedure of the above authors gave, indeed, oxime 8a in our hands in yields 20-40%, dependent on the reaction time. However, the abs. methanolic reaction mixture contained products the structure of which were not consistent[12] with the chromone oxime formation from a pyrylium cation.

We now explain that the formation of chromone oxime 8 proceeds in several steps, of which the determinant one is neither a C-4 attack at the 2 ⇌ 2' cation, nor the elimination of the $C_4$-OH group.

By comparing the reaction of chromone with hydroxylamine hydrochloride in abs. methanol, dioxane, 1,2-dimethoxyethane and isopropyl ether it has been recognized that 8 is produced only in methanol. In the latter non-protic solvent the sole

procudt is compound 5 (proving an exclusive attack at C-2), although the presence of pyrylium chloride can be supposed in each of the above mixtures. Accordingly, methanol must play a role in the formation of 8 in the sequence 1 → 2 → 6 → 7 → 8 as proposed[12] previously (Scheme 1). In the presence of hydrochloric acid, chromones 1a-g are transformed into 2-methoxychromanone (6) in anhydrous methanol.

NMR investigation of the crude reaction mixture showed that the concentration of both HCl and MeOH is decreased, resulting in the shift of the 1 → 6 equilibrium towards 1 by loss of methanol from compound 6. Therefore, the 6/1 ratios, given in Table 1, are indicative of the relative stability of 6 but not of the degree of the conversion in the methanolic reaction mixture.

The protons of the heterocyclic ring of 6 constitute an ABX system similarly[13] to those of 2-hydroxychromanones, allowing an easy differentiation from the AX proton system of chromone (Table 1).

Table 1. $^1$H-NMR data of the product obtained from chromones (1) in HCl-containing boiling anhydrous methanol ( $\delta$, acetone-$d_6$, TMS)

| Starting Chromone | Vinyl protons of 1 | | $C_2$-$OCH_3$ of 6 | ABX system of 6 | | | 6* / 1 |
|---|---|---|---|---|---|---|---|
| | H-2 | H-3 | | A | B | X | |
| 1a | 8.15d | 6.30d | 3.45s | 2.76q | 3.15q | 5.63q | 0.06 |
| 1b | 8.06d | 6.21d | 3.40s | 2.70q | 3.10q | 5.60q | 0.03 |
| 1c | 8.15d | 6.31d | 3.47s | 2.76q | 3.17q | 5.61q | 0.04 |
| 1d | 8.45d | 6.54d | 3.52s | 2.91q | 3.30q | 5.80q | 5.00 |
| 1e | 8.26d | 6.30d | 3.45s | 2.78q | 3.18q | 5.63q | 0.13 |
| 1f | 8.30d | 6.42d | 3.50s | 2.90q | 3.31q | 5.78q | 5.00 |
| 1g | 8.23d | 6.47d | 3.40d | 2.76q | 3.16q | 5.51q | 1.00 |

* calculated from $^1$H-NMR signals of H-2 atoms; s singulet, d doublet, q quartet

From a reaction mixture containing 1a, hydroxylamine hydrochloride and methanol, at 70% chromone conversion[12] (after reflux for 4 hrs) 34% of 8a (calculated for the transformed 1a), 26% of 9a[6] and 13% of 5a were isolated. A sample of the reaction mixture, taken for $^1$H-NMR measurements, contained 15-18% of 7a and traces of 10 and 11 could be also detected by t.l.c. 3 hrs at reflux temperature compound 8b was obtained from 1b in a 63% yield, and the additional components were present in between 2-10%, as determined by $^1$H-NMR spectroscopy.

At the same time, similar transformation of 1c resulted in 5c, 7c and 9c in almost equal quantities and the other components of the mixture (8c, 10c, 6c) were detected by the NMR method. Compound 1e showed the same reactivity as found for 1c, and the presence of 11 could also be detected in the reaction mixture of both chromone derivatives.

Compounds 1f and 1d reacted more readily than the above chromones providing 5f and 5d in 50% and 60% yield, respectively. Moreover, products 7 and 9 (7 < 9) could also be isolated and identified by $^1$H-NMR spectroscopy (Table 2).

Compound 8 was detected only in traces, but significant amounts (cca 3-5 %) of 11f and 11d were found in the mixture by t.l.c. method.

The above experimental data demonstrate that chromone and its derivatives,

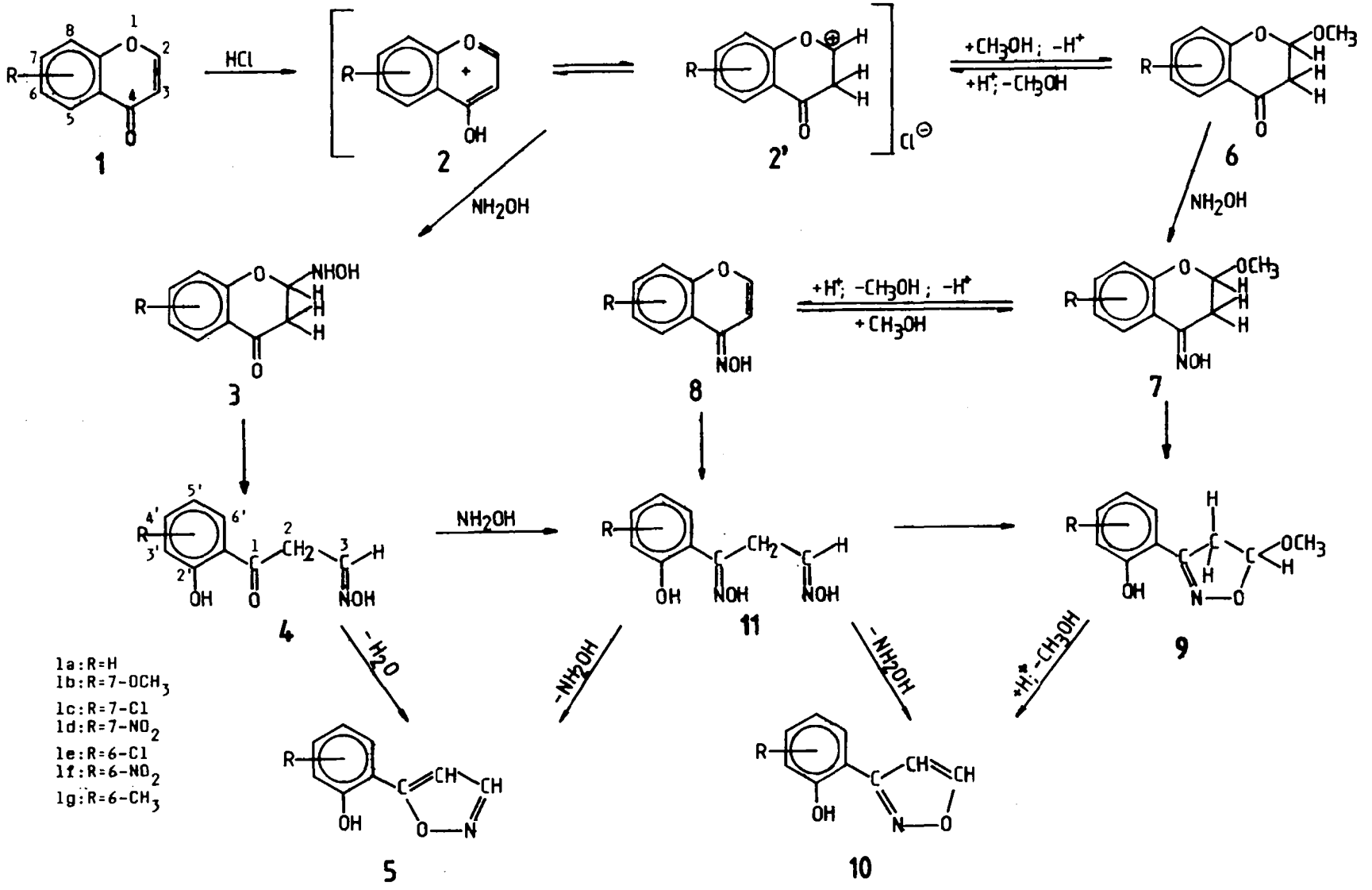
HCl
NH2OH
+CH3OH; -H+
+H+; -CH3OH
+H+; -CH3OH; -H+
+CH3OH
-H2O
-NH2OH
-NH2OH
+H+; -CH3OH
1
2
2'
3
4
5
6
7
8
9
10
11
1a:R=H
1b:R=7-OCH3
1c:R=7-Cl
1d:R=7-NO2
1e:R=6-Cl
1f:R=6-NO2
1g:R=6-CH3

Table 2. $^1$H-NMR data of compounds 7 ($\delta$, acetone-$d_6$, TMS)

| Compound | H-2 | H-3 | 2-OCH$_3$ | NOH |
|---|---|---|---|---|
| 7c | 5.37q | 2.72q ; 3.35q | 3.42s | 10.53s |
| 7e | 5.35q | 2.69q ; 3.31q | 3.40s | 11.08s |
| 7f | 5.39q | 2.66q ; 3.31q | 3.31s | 10.74s |

s singulet; q quartet

substituted at the aromatic ring, create multi-component reaction mixtures when treated with dry hydroxylamine hydrochloride in anhydrous methanol. The observed products can be devided into two main groups (see Scheme 1):

a, products (4,5,11), formed by an initial attack at C-2 of the chromone derivative

b, compounds, produced either by the oxo-reaction of the C-4 carbonyl group of 6 (such as 7), or by the further conversion of the intermediary 7 (8,9,10,11) (see Table 2).

The identification of the structure of 7 by NMR method, as well as the detection of 6 besides 1 in abs. MeOH-hydrochloric acid prove our supposition given on Scheme 1.

According to this, chromone (1) transforms with hydroxylamine hydrochloride in dry methanol into 3 and 6 via cation 2 ⇌ 2' in an acid-catalyzed nucleophylic addition reaction. The process 1 ⇌ (2 ⇌ 2') ⇌ 6 is a pre-equilibrium system, dependent upon the proton concentration, in which 6 can be regarded, indeed, as a saturated aralkyl-ketone. Consequently, an attack of the reagent at C-4 of this latter (just as in the case of chromonone) is considered more probable than that of 1. The NMR spectra, representing the composition of the reaction mixture in the case of 1a has been shown and explained in a previous paper[12]. The present communication documents the spectrum recorded with the mixture obtained from 1c.

Comparison of the two spectra clearly shows the presence of the same materials, and also, a difference -in quantity- of several components (i.e. 5a-5c, 7a-7c, 8a-8c).

The reactivity of the two "reactive" compounds produced from chromone, and thus the ratio of the effective attacks at C-4 and C-2 can be expressed by the ratio of the following products, C-4/C-2=(7+8+9+10)/5 is strongly dependent upon the electronic character of the substituents (see Table 3).

Table 3. Ratio of C-4/C-2 attack after one hundred minutes reaction time

| Starting material | C-4/C-2 |
|---|---|
| 1a | 32.0 |
| 1b | 10.3[M] |
| 1c | 4.4 |
| 1d | 0.5 |
| 1e | 7.0 |
| 1f | 0.4 |
| 1g | 7.0 |

M at 20 minutes is 37

The above results clearly demonstrate that both the primary transformation (1 → 5; 1 → 6 → 7) and the individual partial reactions, shown on Scheme 1, are disparately influenced by the substituents present in the molecules. The presence of a C-7 methoxy group particularly accelerates the conversion of 7 to 8. A chloro substituent slows down this latter transformation, moderately stabilizes structure 7 and en-

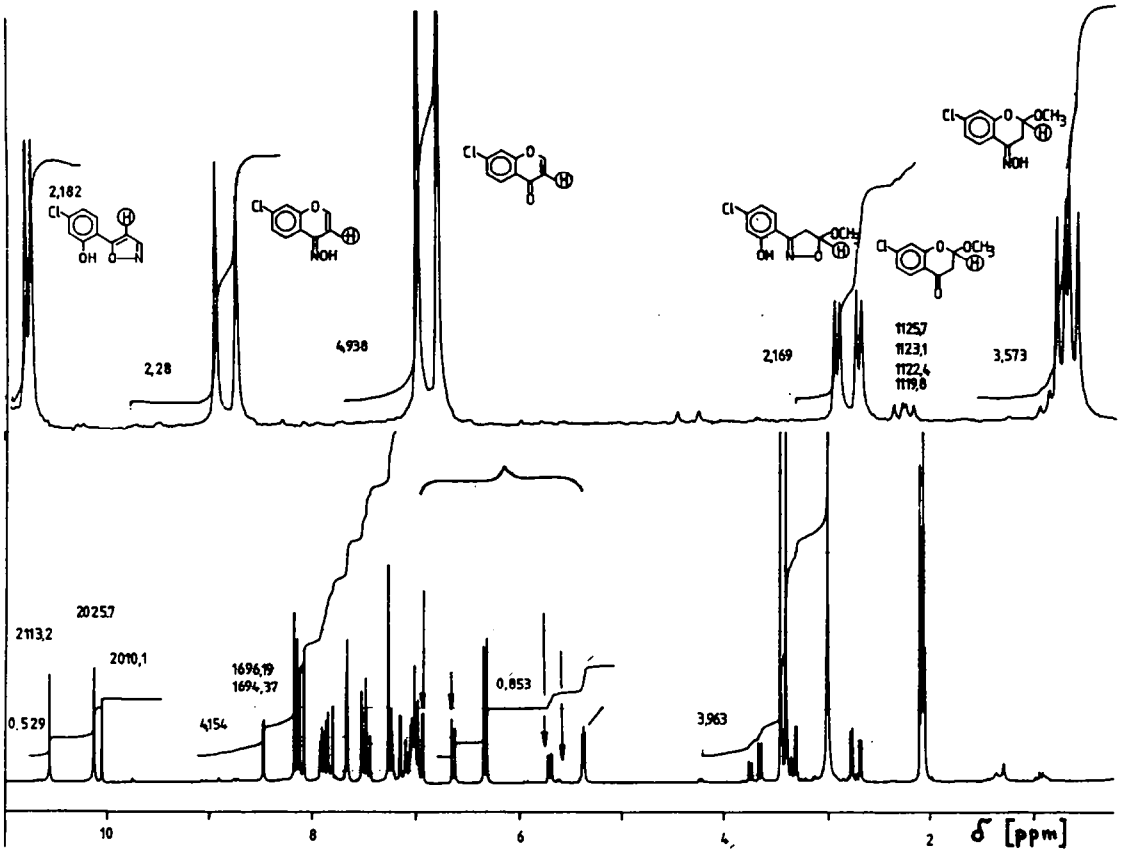


Fig.1. $^{1}$H-NMR spectrum of reaction mixture of 1c and hydroxylamine hydrochloride (δ, acetone-$d_6$, TMS)

hances the rate of the reaction 1→5. The presence of a $NO_2$ group (particularly at position C-7) inhibits the demethoxylation process 7→8, and 7→9 to a higher degree than does a chloro substituent. (For $^{1}$H-NMR data of compound 9 see Table 4).

It has been observed, in a prolonged reaction, that the ratio of attacks at C-4 and C-2 is decreased by the time to great extent in the case of an electron attracting substituent (1b), whereas it does not change when an electron withdrawing substituent is present (Table 5).

According to preliminary data the different behaviour of the two compounds can be explained by the formation of 11b from 8b, which is present in a high quantity. Compound 11b then can be transformed in anhydrous methanol into 5b to a higher extent than into 9b (via 10b)[12]. The formation and decomposition of dioxime (11) could also be observed with compounds (1c-f) carrying electron attracting groups. However, the amount of dioxime is much less than that of either 7 or 8 (produced from 9) and compounds 11c-f decompose into 10c-f rather than into 5c. As this greater amount of isoxazole 10 is compensated by the formation of the isomeric 5 in reaction 1→5 the C-4/C-2 ratio remains unchanged.

According to the above results it seems that the preparation of oxime 8 via compound 6 is more likely possible from chromones containing hydrogen or electron attracting substituents when the reaction is performed in anhydrous methanol with hydroxylamine hydrochloride. In dry methanolic solutions of chromones substituted at C-3 neither the presence of the "basic compound" 6, nor the formation of chromine oxime can be detected when treated with hydroxylamine hydrochloride under acid conditions.

Table 4. $^1$H-NMR data of compounds 9 ($\delta$, acetone-$d_6$, TMS)

| compound | H-4 | H-5 | 5-$OCH_3$ | 2'-OH |
|---|---|---|---|---|
| 9a | 3.49q<br>3.65q | 5.68q | 3.47s | 9.68s |
| 9b | 3.35q<br>3.63q | 5.62q | 3.45s | ~ |
| 9c | 3.40q<br>3.69q | 5.70q | 3.40$^\phi$ | ~ |
| 9d | 3.60q<br>3.87q | 5.83q | 3.49s | ~ |
| 9e | 3.42q<br>3.71q | 5.65q | 3.47s | ~ |
| 9f | 3.59q<br>3.85q | 5.80q | 3.49s | 10.77s |
| 9g | 3.37q<br>3.65q | 5.65q | 3.47s | ~ |

$\phi$ overlaps with the signal of 4'-$OCH_3$ group; ~ no signal because of the fast exchanging process; s singulet; q quartet

Table 5. Percentages of products starting from 1b and 1c

| reaction time [min] | Percentage of products [%] | | | | | | | ratio of C-4/C-2 |
|---|---|---|---|---|---|---|---|---|
| | 1b | 6b | 7b | 8b | 9b | 10b | 5b | |
| 100 | 50.0 | 1.5 | 8.3 | 30.4 | 1.7 | 2.2 | 4.3 | 10.3 |
| 540 | 2.0 | 0.6 | 9.7 | 63.5 | 3.3 | 6.1 | 16.4 | 4.9 |
| 3000 | 1.7 | - | 10.5 | 15.8 | 12.3 | 23.9 | 36.8 | 1.7 |
| | 1c | 6c | 7c | 8c | 9c | 10c | 5c | |
| 100 | 35.5 | 1.2 | 20.7 | 15.8 | 14.0 | 1.0 | 11.8 | 4.4 |
| 400 | 4.8 | 0.3 | 8.5 | 5.5 | 40.0 | 24.4 | 16.5 | 4.7 |
| 3000 | - | - | - | - | 20.0 | 62.0 | 18.0 | 4.5 |

## EXPERIMENTAL SECTION

Melting points are not corrected. $^1$H-NMR spectra were recorded with a Bruker WP-200 SY instrument. Mass spectra were obtained with a VG 7035 spectrometer.

Thin layer chromatography was carried out on pre-coated layers Merck DC-Alurolle $F_{254}$. For the separation of the products preparative layer from Merck was used with the following eluent systems: 9:1 benzene-ethanol, 95:5 DKE-MeCOEt or 95:5 isopropyl ether-MeCOEt. Compound 5 was compared with the isoxazole derivative prepared by the cyclization of the suitably substituted 2'-hydroxy-4'-(5')-R-phenyl-propanedione-aldoxime.

Investigation of tranformation 1→6 Chromone derivatives 1a-1g 10 mg were dissolved in anhydrous methanol (10 ml) containing 1mM of hydrochloric acid. The equilibrium 1⇌6 was found to develop within 5-10 min. at reflux temperature and within 40-60 min. at room temperature. After removal of methanol and hydrochloric acid at reduced pressure, the residue was coevaporated with acetone (to make it free

of methanol) and then dissolved in acetone-$d_6$ for the NMR measurements. The data are given in Table 1.

Chromone oxime (8a) A solution of chromone (1.02g, 7.0mM) and dry hydroxylamine hydrochloride (1.96g, 28mM) in abs. methanol (56 ml) was refluxed for 4h. The homogeneous solution was concentrated to 25 ml and diluted with water (50 ml). The produced emulsion was extracted several times with hexane for the removal of 9a. From the aqueous methanolic layer, 8a was obtained along with small amounts of 1a and 5a by extraction with ethyl acetate solution and was concentrated to give 0.6g of yellow syrup wich was dissolved in benzene (6 ml) and purified by preparative layer chromatography using isopropyl ether as the eluent. Pure 8a was obtained by dissolving the layer-zone with ether followed by evaporation. The isolated colourless crystals were washed with hexane and dried on air, to obtain 0.212 g (19%), mp: 130°C (lit.[3] mp: 127°C). $^1$H-NMR (ppm, acetone-$d_6$): 6.65 (d, H-3), 7.2 (d, H-2). By elution with ethanol cca-50mg of 5a (mp: 181°C, lit.[14] mp: 184°C) was also isolated and compounds 1a and 9a were also detected.

5-Methoxy-3-(2'-hydroxyphenyl)-isoxazoline (9a) The hexane extract of the above reaction mixture was dried ($MgSO_4$) and the partly solid residue was dissolved in benzene. After application into a preparative silicagel layer (development with 95:5 DKE-MeCOEt) the fractions were eluted with ether.

9a: 0.195 g; mp: 85°C (lit[8] mp: 84-85°C). The $^1$H-NMR data see Table 4.
8a: 23 mg
5a: 35 mg

7-Methoxychromone oxime (8b) To a solution of chromone 1b (1.0 g, 5.7 mM) in abs. methanol (50 ml) hydroxylamine hydrochloride (2.3 g, 33.5 mM) was added and the solution was boiled under reflux for 3h. It was then evaporated and the separated crystals were filtered and washed with benzene and water. Crystallization from 1:1 benzene-ethanol gave 0.68 g (63%), mp: 210-212°C; $^1$H-NMR (ppm, acetone-$d_6$): 6.60 (d, H-3), 7.20 (d, H-2).

Conversion of 6-nitrochromone into 5f, 7f and 9f Compound 1f (0.382 g, 2 mM) and dry hydroxylamine hydrochloride (0.56 g, 8mM) were dissolved in abs. methanol (16 ml). After boiling under reflux for 80 min. the homogeneous solution was poured onto ice-water (50 ml) and the solution, containing crystals, was kept in the refrigerator for 16 h. The filtered crystals (0.34 g), containing large quantity of 5f, were exhaustively washed with benzene (16 ml) and then filtered to obtain 0.15 g of 5f, mp: above 253°C (charred); $^1$H-NMR (ppm, acetone-$d_6$): 7.00 (d, H-4), 8.50 (d, H-3). The mp. and the layer chromatographic $R_f$ value of 5f were in good agreement with that of isoxazole prepared from 1-(2'-hydroxy-5'-nitrophenyl)-propandione-aldoxime.

The benzene mother-liquor of 1f was concentrated to 8 ml and applied onto a silicagel preparative layer. The layers, developed with i-propylether and giving materials with $R_f$=0.85 (yellow colour with $FeCl_3$) and $R_f$=0.62 (dark red-violet reaction with $FeCl_3$) were eluted with actone.

Compound with $R_f$=0.85: 7f (40 mg), mp: 168-169°C, for NMR data see Table 2. Anal. Calcd. for $C_{10}H_{10}N_2O_3$ (222,2): N, 12,60; Found: N, 12.2 %

Compound with $R_f$=0,62: 9f (30 mg), mp: 159-160°C, for NMR data see Table 4. Anal. Calcd. for $C_{10}H_{10}N_2O_5$ 222,2: N, 12.60; Found: N, 12,40%

Conversion of 7-chlorochromone into 5c, 7c, 8c, and 9c A solution of 7-chlorochromone (360 mg, 2 mM) and hydroxylamine hydrochloride (840 mg) in abs. methanol (16 ml) was boiled under reflux for 2h and then 16 ml of water was added. The solution containing a small quantity of crystals was shaken with a mixture of hexane (32 ml) and benzene (8 ml) and the crystals separated at the boundary surface of the two layers were filtered to obtain 40 mg of 5c, mp: 214-215°C, $^1$H-NMR (ppm, acetone-$d_6$): 6.92 (d, H-4) and 8.47 (d, H-3).

The benzene-hexane solution was concentrated until the separation of crystals and it was applied on a preparative layer. The elution and work-up were carried out as described at the conversion of 6-nitrochromone.

9c, $R_f$=0.65 (eluted with $CHCl_3$), gives dark violet-blue reaction with $FeCl_3$. For $^1$H-NMR data see Table 4.

Mixture of 7c and 8c: (~8:2, eluted with $CHCl_3$), and separated by repeated preparative layer chromatography with i-propylether.

7c, $R_f$=0.90 (yellow colour reaction with $FeCl_3$), for $^1$H-NMR data see Table 2.

8c, $R_f$=0.94; $^1$H-NMR data (ppm, acetone-$d_6$) 6.61 (d, H-2), 7.20 (d,H-3), 10.8 (s, N-OH).

Using the similar method 1e was converted into 7e and 9e (for $^1$H-NMR data see Table 2 and 4., respectively) and also a very small amount of 8e was also isolated; $^1$H-NMR (ppm, acetone-$d_6$): 6.64 (d, H-3), 7.2 (d, H-2) and 10.60 (s, N-OH).

## REFERENCES

1. Szabó, V.; Zsuga, M.: Acta Chim. Hung., 85, 179 (1975).
2. Szabó, V.; Zsuga, M.: React. Kinet. Catal. Lett., 5, 229 (1976).
3. Szabó, V., Borda, J., Losonczy, L.: Acta Chim. Hung., 97, 69 (1978).
4. Szabó, V., Borda, J., Végh, V.: Acta Chim. Hung., 98 457 (1978).
5. Szabó, V., Borda, J., Theisz, E.: Magy. Kém. Foly., 84, 134 (1978). (in hunga-

rien); Acta Chim. Hung., 103, 271 (1980).
6. Szabó, V., Borbély, J., Borda, J., Theisz, E., Janzsó, G.: Tetrahedron, 40, 413 (1984).
7. Wittig, G., Bangert, F.: Chem. Ber., 588, 2636 (1925).
8. Moon, M.W.: Sharp, J.C.: Ger Offen., 2 513 652
9. Basinski, W., Jerzmanowska, Z.: Rocz. Chem., 48, 2217 (1974).
10. Beugelmans, R., Morin, C.: Tetrahedron Letters 1976, 2145; J. Org. Chem., 42, 1356 (1977).
11. Chantegrel, B., Nadi, A.I., Gelin, S.: J.Org. Chem., 49, 4419 (1984).
12. Szabó, V., Borbély, J., Theisz, E., Janzsó, G.: Tetrahedron Letters 1982, 5347
13. Borbély, J., Szabó, V., Sohár, P.: Tetrahedron 37, 2307 (1981).
14. Szabó, V., Nemes, S., Borbély, J.: to be published