Tetrahedron Vol 40, No 2, pp 413 to 417, 1984
Printed in Great Britain

0040-4020/84 $3.00 + .00
Pergamon Press Ltd

THE REACTIONS OF CHROMONE AND 2-HYDROXYCHROMANONE WITH HYDROXYLAMINE†

VINCE SZABÓ, JÁNOS BORBÉLY,* EDIT THEISZ, JENŐ BORDA and GÉZA JANZSÓ
Department of Applied Chemistry, Kossuth Lajos University, H-4010 Debrecen, 10, Hungary

(*Received in the UK 3 December 1982*)

Abstract—Chromone and 2-hydroxychromanone react with hydroxylamine to give several products through attack at Ca2. The aldoxime **2** is transformed to dioxime **4** or to isoxazole **3**. The dioxime exists as a tautomer mixture; it reacts in several ways, giving chromoneoxime **8**, isoxazole **10** and a new isoxazoline **9**.

We earlier reported that chromone **1** and 2-hydroxychromanone **1a** reacted with hydroxylamine to give **2**, **3**, **10**, **13**, **14** and **4**, the product distribution depending on the pH and temperature.

Polish authors recently reported[2,3] that **1** or **1a** was transformed to **5**. The melting point and chemical behaviour of this compound were the same as described for **4** from our laboratories. In this report we describe studies performed to attempt to clarify this contradiction. They described **1b** as 1-(2-hydroxyphenyl)-2-formylacetophenone, but the structure is 2-hydroxychromanone.[4,5]

1 reacts slowly with hydroxylamine in an acidic water-ethanol mixture pH 0.5-2. In alkaline solution the increase of pH in initially increases the rate of formation of **2** and **4**. In 2 N NaOH the conversion of **1** to **4** is quantitative. Since 2-hydroxychromanone is more sensitive to nucleophilic reagents than the corresponding chromones,[7] **1a** gives **2** and **4** at a higher rate than **1**.

The reaction with O-methylhydroxylamine is slow in alkaline solution. The oxime-ether formation is acid-catalysed and especially fast from **1a**. The ^{1}H-NMR spectra in DMSO-d_6 and in pyridine-d_5 clearly shows the open-chain structure of **2**, **4**, **15** and **16** (Table 1). The double doublets, the double triplets and also the number of phenolic and oxime-hydroxyl protons of reveal that these compounds are not homogeneous stereochemically as was claimed earlier,[1] but exist as syn/anti isomer mixture.

In an acetone or methanol solution of **4** another set of lines appears in addition to the above mentioned signals, corresponding to the open-chain-ring structure. A double quartet and a multiplet for the ABX system, an NH and an OH-group proton appear (Fig. 1). Comparison of the coupling constants of the ABX system with those of **1a** seems to indicate the presence of a five-membered ring (Table 1).[8] This new set of lines assigned to structure **5**. The ^{1}H-NMR spectra also suggest that the product from **1** or **1a** in nucleophilic solution is best described as **4**, whilst in protic or polar aprotic solvents an isomeric mixture of **4**⇌**5** is formed. It may be noted that the 3-phenyl-5-hydroxyisoxazoline described by Auwers and Wunderling[9] is also a **4**⇌**5** type isomer mixture.

4 is stable in alkaline aqueous or aprotic solutions at room temperature but in hot solution it forms **10**. The transient formation of **9** and **12** too is observed. In protic solution **4** decomposes to a mixture of **9** and **12**.

In hot acidic ethanol **4** gives **3** and **10**. These products are the results of partial hydrolysis and solvolysis of **4** (giving **2** or **6**) and subsequent cyclization.

In cold acidic water-ethanol or acetone mixtures the main product of decomposition is the known **12**.[3] From this reaction mixture a new product was also isolated, which was formed faster than **12**. On the evidence of the analytical data (IR, ^{1}H-NMR) this new product was best formulated as **7** or **9**. Without information on the anisotropy caused by the C=N–OH group in **7**, the differences in the coupling constants J_{AX} and J_{BX} for this new compound and **1a** which are observed in the case of five- and six-membered rings[8] are not sufficient enough to make a definite assignment to either **7** or **9**.

It was possible, however to compare the H-5 and H-6' signals (the distance between H-5 or H-6' atom and the nearest aromatic proton–in $CDCl_3$–are put in brackets as $\Delta\delta$ value) of **1** (0.30), **8** (0.56), chromanone (0.48) and chromanoneoxime (0.61).

For **12** and the **9** product the H-6' signals are not separated from those of the other aromatic protons. These data suggest that the new compound is not **7** but **9**. **9** was transformed to the corresponding methyl ether in high yield. **11** and **9** gave the corresponding acetates **17** and **18**. The six-membered **1a** gave no similar stable derivatives.

There are two plausible mechanisms for the formation of **9**: (i) **5** is protonated and loses hydroxylamine to give cation **9a**, which is hydrolysed to **9**; (ii) a more probable mechanism is that **4** is hydrolysed to **6** and cyclized to **9**. The second reaction route is also favoured by the observation that **8**[11,12] appeared in these hydrolysis mixtures.

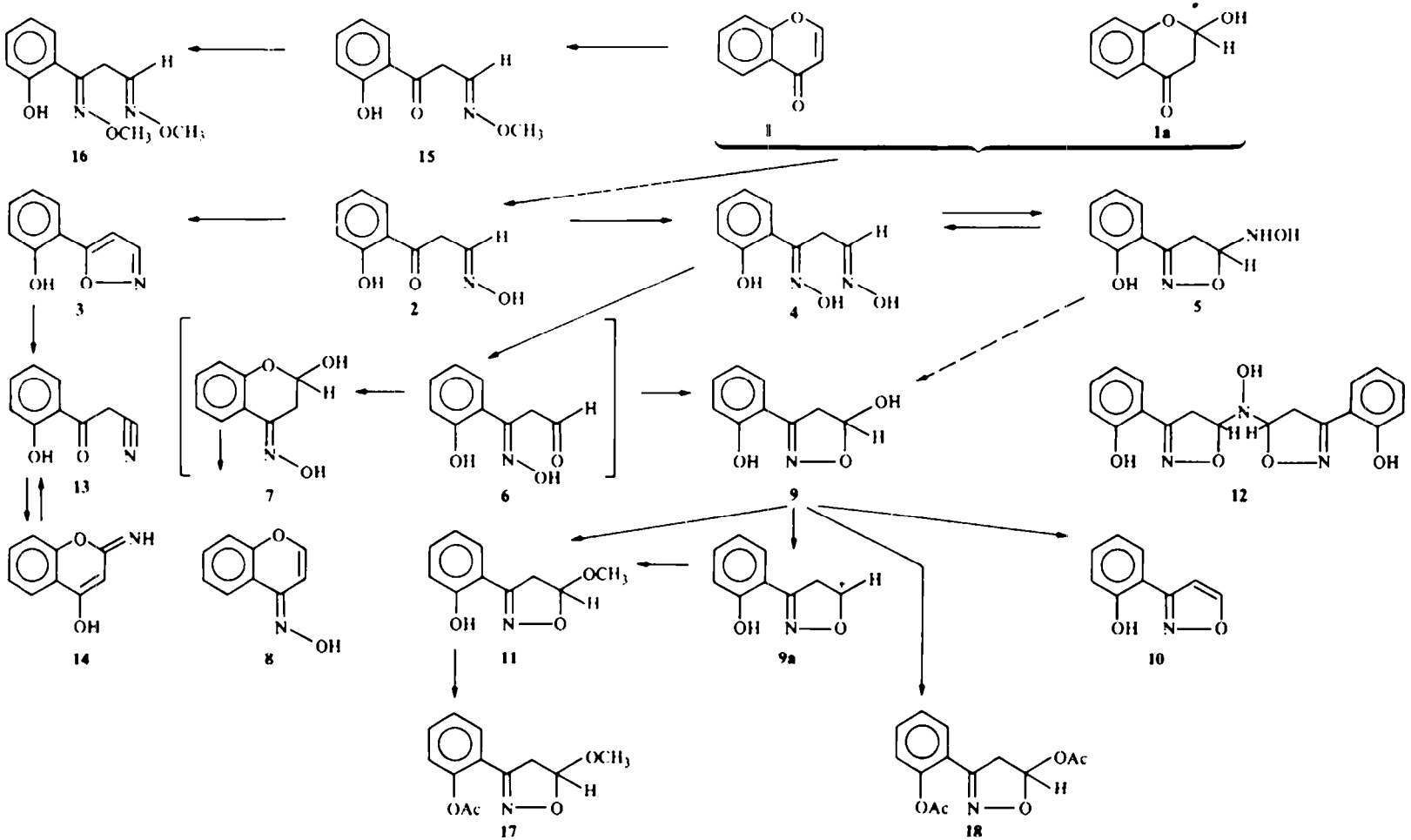
The existence of the cation **9a** supported by the transformation **9**→**11**, which takes place in anhydrous methanol/HCl. Cation **9a** and **5** give **12** as a result of attack on the cation by the nucleophilic nitrogen of **5**.

12 is stable in cold, acidic solution. In alkaline solution pH 12 however, **12** decomposes to an equimolar mixture of **4** and **9** at 20°. Hydroxylamine transforms **12** to **4** in aqueous alkaline ethanol pH 12[3].

Hence, it is probable that in aqueous solution a complex equilibrium exists:

$$(\mathbf{4}\rightleftharpoons\mathbf{5}) + \mathbf{9} \rightleftharpoons \mathbf{12} + NH_2OH$$

†Presented in part at the International Bioflavonoid Symposium, Munich, 1981.



Scheme 1.

Table 1. ^{1}H-NMR data of compounds **2**, **4**, **5**, **15** and **16** (Chemical shifts are given in δ ppm: $\delta_{TMS} = 0$ ppm, coupling constants in Hz)

Compound Solvent	C_2–CH_2/C_4–CH_2 in chain/in ring $^3J_{H,H}$		C_3–CH/C_5–CH in chain/in ring $^3J_{H,H}$	C_1–NOR	C_3–NOR/C_5–NHOR in chain/in ring	C_2–OH	*anti*/*syn* ratio	*chain*/*ring* ratio
					R=H			
2 *anti*	4.00 *d**	6.0 Hz	7.45 *t*	–	11.6 *bs** –	10.82 *s**		
DMSO-d_6					R=H		2:3	–
2 *syn*	4.10 *d**	6.0 Hz	6.90 *t*	–	11.6 *bs**	11.19 *s**		
					$R=CH_3$			
15 *anti*	3.80 *d*	6.0 Hz	7.52 *t*	–	3.93 *s*			
Acetone-d_6					$R=CH_3$	10.0 *bs**	2:3	–
15 *syn*	3.92 *d*	5.0 Hz	6.75 *t*	–	4.08 *s**			
				R=H	R=H			
4 *anti*	3.66 *d*	5.0 Hz	7.50 *t*	11.30 *s**	10.69 *s**	11.80 *s**		
DMSO-d_6				R=H	R=H		1:2	50:1
4 *syn*	3.76 *d*	5.0 Hz	6.62 *t*	11.23 *s**	11.20 *s**	11.82 *s**		
				R=H	*R=H*			
4 *anti*	4.30 *d*	5.0 Hz	8.20 *t*	12.0 *bs**	11.3 *bs**	13.3 *bs**		
Piridine-d_5				R=H	R=H		1:2	50:1
4 *syn*	4.63 *d*	5.0 Hz	7.08 *t*	12.7 *bs**	11.4 *bs**	13.2 *bs**		
5 *ring*	$\delta_A = 3.45$ *dq*	$\delta_B = 3.58$ *dq*	$\delta_X = 5.64$ *m* $J_{AX} = 10.1$ Hz	–	– $\delta_{NH} = 7.3$ *bs**	9.87 *s**		
Acetone-d_6	$J_{AB} = 18$ Hz		$J_{BX} = 3.9$ Hz	R=H	R=H $\delta_{OH} = 6.2$ *bs**			
4 *chain anti*	3.80 *d*	5.3 Hz	7.48 *t*	10.93 *s**	9.82 *s** –	11.17 *s**	5:7	4:3
4 *chain syn*	3.95 *d*	5.8 Hz	6.64 *t*	11.04 *s**	10.50 *s** –	11.20 *s**		
5 *ring*	$\delta_A = 3.50$ *dq*	$\delta_B = 3.70$ *dq*	$\delta_X = 5.56$ *m*	are changed		are changed		
4 *anty* Methanol-d_4	3.75 *d*	6.0 Hz	7.40 *t*	are changed		are changed	1:2	5:1
4 *syn*	4.00 *d*	5.0 Hz	6.65 *t*	are changed		are changed		
16 *anti*				$R=CH_3$	$R=CH_3$			
	3.80 *d*		7.23 *t*	4.10 *s*	3.90 *s*	10.0 *s**		
DMSO-d_6				$R=CH_3$	$R=CH_3$		2:3	–
16 *syn*	3.92 *d*		6.70 *t*	4.08 *s*	3.80 *s*	9.9 *s*		
1a Acetone-d_6	H – 3 = 2.70 *q** and 3.08 *q** $^2J_{A,B} = 16.0$		*H* – 2 = 5.85 *m* $^3J_{AX} = 4.1$ $^3J_{BX} = 2.9$		*C_2–OH* = 6.52 *bs**			

s: singulet, *bs*: broad singulet, *t*: triplet, *q*: quartet, *m*: multiplet, *: after addition D_2O the signal disappears.

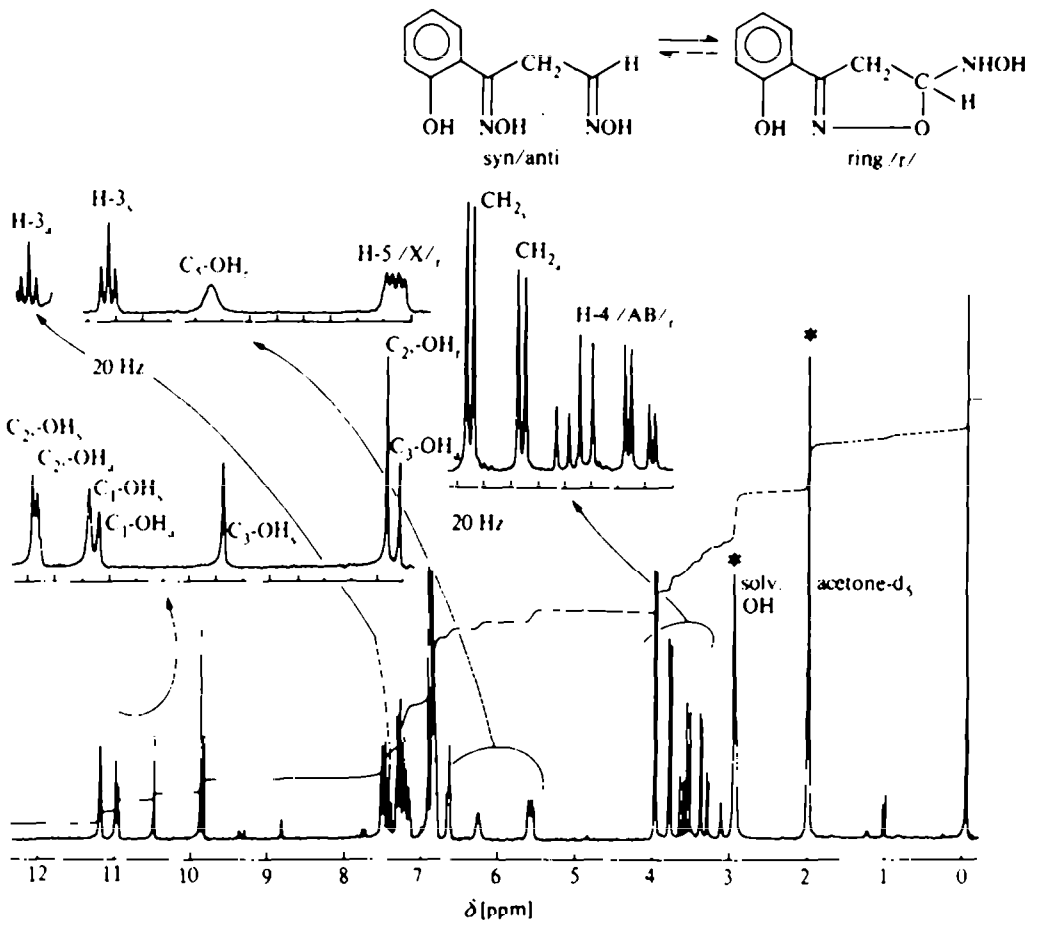


Fig. 1 ^{1}H-NMR spectra of 4⇌5 in acetone-d_6.

At room temperature **12** crystallizes from the reaction mixture so the equilibrium moves to the right. In hot solution **4** is hydrolysed to **2** and **6**; these are then cyclized to give **3**, **9** and possibly **7**. **9** and **7** dehydrated to **10** and **8**. **12** gives the same hydrolysis products in cold or hot aqueous ethanol of acetone as **4**, but at a lower rate, especially in cold solution, because of solubility difficulties of **12**. The stable end-products in cold solution are **8**, **9** and **10**, but **3** and **10** in hot solution.

The above experiments suggest that the result of the "oxo" reaction of chromones is determined by the reactivity of **2**, and also by the reactivity of **4**. The reaction conditions further influence the rate and direction of the decomposition of the dioxime.

EXPERIMENTAL

M.p.s are uncorrected. ^{1}H-NMR spectra were recorded on a Bruker WP 200 SY instrument. Merck Kieselgel DC-Alurolle was used for tlc. Solvent systems A: dichloroethane: 2-butanone = 95:5; B: diisopropyl ether; C: benzene–ethanol = 9:1.

1-(2'-Hydroxyphenyl)-propane-1,3-dione-1,3-dioxome (**4**)

(a) *From* **1**. 0.438 g (3.0 mmole) **1** was dissolved in 6 cm^3 ethanol and to this a soln of 0.84 g (12.0 mmole) hydroxylamine HCl was added. The pH was maintained at pH 12 with 2N NaOH. After 24 h the solution was acidified with HCl and part of the ethanol was removed in vacuo. The white precipitate was washed with water and crystallized from ethyl acetate–hexane/(0.5 g, 85.3%, m.p. 136–138° and then at 184–7° (double melting point)).

(b) *From* **1a**. 0.82 g (5.0 mmole) **1a** was dissolved in 5.0 cm^3 ethanol and treated with 2.1 g (30.0 mmole) hydroxylamine HCl and 2.0 g (50.0 mmole) NaOH dissolved in 5.0 cm^3 water. The reaction mixture was shaken well, kept at 20–25° for 10 min and then acidified to pH 5 with glacial acetic acid. The precipitate crystallized upon stirring. The crystals were washed with water, and crystallized from ethyl acetate-hexane (0.92 g, 95%). m.p.: 133–135° and 184–186° (5°/min heating rate from 135°). R_{fA}: 0.18; R_{fB}: 0.49; R_{fC}: 0.26. Found: N, 14.00. $C_9H_{10}N_2O_3$ requires N, 14.43.

5-Hydroxy-3-(2'-hydroxyphenyl)-isoxazoline (**9**)

(a) *From* **4**. 1.0 g **4** was dissolved in a mixture of 40 cm^3 acetone, 50 cm^3 water and 10 cm^3 10% HCl. The reaction mixture was left to stand at 25° for 24 h. A crystalline mass separated. These crystals were filtered off. 0.2 g (27.4%) of **12** was obtained. From the filtrate 80–90% of the acetone was removed *in vacuo*, and the solution was extracted with hexane to remove **8** and **10**. The aqueous layer was then extracted with ether. Evaporation of the ethereal layer gave an oil (0.414 g). The oil crystallized upon treatment with hexane, giving 0.3 g (33%) **9** m.p. 87.0–87.5°.

(b) *From* **12**. 2.0 g **12** and 1.6 g NaOH were dissolved in 75 cm^3 water and the solution was left to stand for 25 h at room temp. The yellow solution was then acidified to pH 6 with acetic acid. The separated solid (1.02 g) contained **4**, **9** and a small amount of **10**. Only **4** and **9** were detected in the mother liquor. This was extracted with ether, and the ethereal was added to the crystalline mixture of **4**, **9** and **10** and separated by plc (Solvent system A). The R_f 0.25 band gave **4**, and the R_f 0.62 *band* **9** upon extraction with ether. Evaporation of the ethereal solution gave pure **4** and **9**. **4**: 0.76 g (21.9%), m.p. 135–136° and 185–186°. **9**: 0.70 g (34.6%), m.p. 86–87°. R_{fA}: 0.40, R_{fB}: 0.42, R_{fC}: 0.40. Found:

N, 7.98. $C_9H_9NO_3$ requires: N, 7.82. ^{1}H-NMR: (acetone-d_6) H_A-4: 3.74 *q*, H_B-4: 3.61 *q*, $^2J_{A,B}$ = 17.0, H_X - 5 = 6.12 *m*, J_{AX} = 6.7, J_{BX} = 1.8, C_3-OH: 6.3 *bs*, C_2, -OH: 9.95 *bs*.

3-(2'-Hydroxyphenyl)-5-methoxyisoxazoline (**11**)

0.225 g **9** was dissolved in 11 cm^3 1 N HCl in anhydrous methanol, and kept at room temp for 24 h. The solution was evaporated to half volume *in vacuo*. White crystals separated upon standing in the refrigerator. The crystals were filtered off and washed with hexane. 0.135 g (55.6%) **11** was obtained. m.p. 84–85°. R_{fA}: 0.77, R_{fB}: 0.64, R_{fC}: 0.78. (Found: N, 7.01. $C_{10}H_{11}NO_3$ requires: N, 7.25). ^{1}H-NMR: (acetone-d_6)H_A 4: 3.49 *q*, H_B - 4: 3.65 *q*, $^2J_{A,B}$ - 18.0 H_X - 5: 5.68 *m*, J_{AX} = 6.7, J_{BX} = 1.3, C_5-OCH_3:3.47 *s*, C_2, -OH: 9.68 *bs*.

5-Acetoxy-3-(2'-acetoxyphenyl)-isoxazoline (**18**)

0.150 g **9** was dissolved in 0.5 cm^3 anhydrous pyridine and treated with 0.4 cm^3 acetic anhydride. This solution was kept at room temp for 3 h and then poured into ice-water mixture. The separated oil solidified upon standing, and recrystallized from ethanol. 0.07 g(37.8%) **18** was obtained. m.p. 114–115°. Found: N, 5.04. $C_{13}H_{13}NO_5$ requires: N, 5.32. ^{1}H-NMR: (acetone-d_6) H_A - 4: 3.50 *q*, H_B-4: 3.64 *q*, $^2J_{A,B}$ - 18.0, H_X - 5: 6.80 *m*, J_{AX} = 6.5, J_{BX} = 1.4, C_5-OAc: 2.03 *s*, C_2-OAc: 2.27 *s*.

5-Methoxy-3-(2'-acetoxyphenyl)-isoxazoline (**17**)

Upon acetylation as in the previous experiment 0.10 g **11** gave 0.04 g (33.0%) **17**. m.p. 119–120°. Found: N, 6.01, $C_{12}H_{13}NO_4$ requires: N, 5.95). ^{1}H-NMR (acetone-d_6) H_A - 4: 3.29 *q*, H_B - 4: 3.43 *q*, $^2J_{A,B}$ - 18.0, H_X - 5: 5.59 *m*, J_{AX} = 6.6, J_{BX} = 1.5, C_5-OCH_3: 3.38 *s*, C_2-OAc: 2.28 *s*.

Methyl ethers of 1-(2'-hydroxyphenyl)-propanedione-1,3-monoxime (**15**) *and* (**16**)

0.492 g (3.0 mmole) **1a** was dissolved in 25 cm^3 ethanol and treated with 0.984 g (12.0 mmole) O-methylhydroxyl-amine · HCl dissolved in 25 cm^3 (pH 4) sodium acetate-acetic acid buffer. After 10 min standing half of the ethanol was removed *in vacuo* at room temp. The separated white crystals were filtered after standing for 0.5 h and washed with a small amount of water. 0.36 g (62.5%) **15** was obtained. m.p. 55.5–56°. Found: N, 7.34. $C_{10}H_{10}NO_3$ requires: N, 7.25. ^{1}H-NMR: Table 1. The mother liquor of the above reaction was acidified to pH 3 with dil HCl, and boiled for 3 h. The remaining ethanol was then removed *in vacuo* and the acidic aqueous solution was extracted with hexane. The hexane solution was dried over anhyd. $MgSO_4$, and evaporated to give a pale yellow oil. 0.2 g (29.4%) **16** was obtained in this way. The oil was homogenous by tlc. Found: N, 12.42. $C_{11}H_{14}N_2O_3$ requires: N, 12.6.

5,5-[3-(2'-Hydroxyphenyl)-isoxazolinyl]-hydroxylamine (**12**)

2.2 g **4** was dissolved in 220 cm^3 50% aqueous ethanol and treated dropwise with 2 cm^3 concentrated H_2SO_4. The soln was then left to stand at room temp. After 10–20 min white needles separated from the solution. After 24 h the crystals were filtered, washed with water and dried. 1.28 g (58%) **12** was obtained. m.p. 206–208°. R_{fA}: 0.48, R_{fC}: 0.56. Found; N, 11.93. $C_{18}H_{17}N_3O_5$ requires: N, 11.83. ^{1}H-NMR: (DMSO-d_6) H_A - 4: 3.71 *q*, H_B - 4: 3.79 *q*, $^2J_{A,B}$ = 18, H_X - 5: 5.93 *m*, J_{AX} - 8.3, J_{BX} = 5.2, N-OH: 7.9 *s*, C_2-OH: 9.85 *s*.

REFERENCES

[1]V. Szabó, J. Borda and E. Theisz, *Magy. Kém. Foly.* **84**, 134 (1978).
[2]W. Basinski and Z. Jerzmanowska, *Roczniki Chem.* **51**, 1971 (1977).
[3]W. Basinski and Z. Jerzmanowska, *Ibid.* **53**, 229 (1979).
[4]F. M. Dean and S. J. Murray, *J. Chem. Soc. Perkin I*. 1706 (1975).
[5]J. Borbély, V. Szabó and P. Sohár, *Tetrahedron* **37**, 2307 (1981).
[6]V. Szabó, J. Borda, and E. Theisz, *Acta Chim. Acad. Sci. Hung.* **103**, 271 (1980).
[7]V. Szabó and M. Zsuga, *Ibid.* **85**, 191 (1975).
[8]D. Gagnaire and P. Vottéro, *Bull. Soc. Chim. France*, 2779 (1963).
[9]K. Auwers and H. Wunderling, *Ber.* **67**, 1062 (1934).
[10]V. Szabó, J. Borda, and L. Losonczy, *Acta Chim. Acad. Sci. Hung.* **97**, 69 (1978).
[11]R. Beugelmans and C. Morin, *Tetrahedron Letters* 2145 (1976).
[12]R. Beugelmans and C. Morin, *J. Org. Chem.* **42**, 1356 (1977).