2,3-DIHYDRO-BENZO-γ-PYRONE OXIMES. PART VII*

A SIMPLE METHOD OF DIFFERENTIATION OF ISOMERIC DERIVATIVES OF Δ^2-ISOXAZOLINE AND FLAVANONE OXIMES. A CORRECTION OF SOME STRUCTURES

Zbigniew Witczak

Department of Organic Chemistry, Institute of Fundamental Chemical Sciences, Faculty of Pharmacy, School of Medicine

90-145 Łódź, Narutowicza 120a, Poland

Abstract - The simple method of differentiation of isomeric derivatives i.e. (E)-2,3-dihydro-2-(4-ethoxyphenyl)-4H-benzopyran-4-one oxime (2) and corresponding Δ^2-isoxazoline (3) on the basis of their UV and ^{1}H NMR data, allows us to establish that the 2,3-dihydro-4H-benzopyran-4-one derivatives (4a-4d) in the reaction with hydroxylamine give oximes (5a-5d) instead of isomeric Δ^2-isoxazolines as previously described [12]. The isomeric Δ^2-isoxazoline derivatives (6b-6d) were obtained by trifluoroacetic acid-catalyzed rearrangement of obtained oximes (5b-5d).

As a part of continuing work on the synthesis of flavonoid heterocycles[1-3] and in conjunction with our interest in their biological properties[4] we initiated an extended study of the reaction of hydroxylamine with 4-substituted 2'-hydroxychalcones.[5]

In our previous communication[6-7] we have shown that this reaction affords the products of 1,2-addition and simultaneous 1,4 and 1,2-addition as well as cyclization into flavanone system and next oximation. In the case of 2'-hydroxy-4-ethoxychalcone[8] (1) in a slightly acid medium ($NH_2OH \cdot HCl$ in ethanol) and at substrate ratio 1:1 two compounds are formed; compound (2) m.p. 182-184°C as a major product and compound (3) m.p. 82-84°C as a co-product. On the basis of spectroscopic analyses (UV, IR, ^{1}H NMR) compound (2) was identified as 4'-ethoxyflavanone oxime [1] whereas compound (3) as 3-(2-hydroxyphenyl)-5-(4-ethoxyphenyl)-Δ^2-isoxazoline.[9] Oxime (2) undergoes TFA catalyzed rearrangement to isomeric Δ^2-isoxazoline (3).[9]

The initial differentiation of isomeric oxime (2) and Δ^2-isoxazoline (3) may be based on the test with the alcoholic solution of ferric chloride (positive for Δ^2-isoxazolines).

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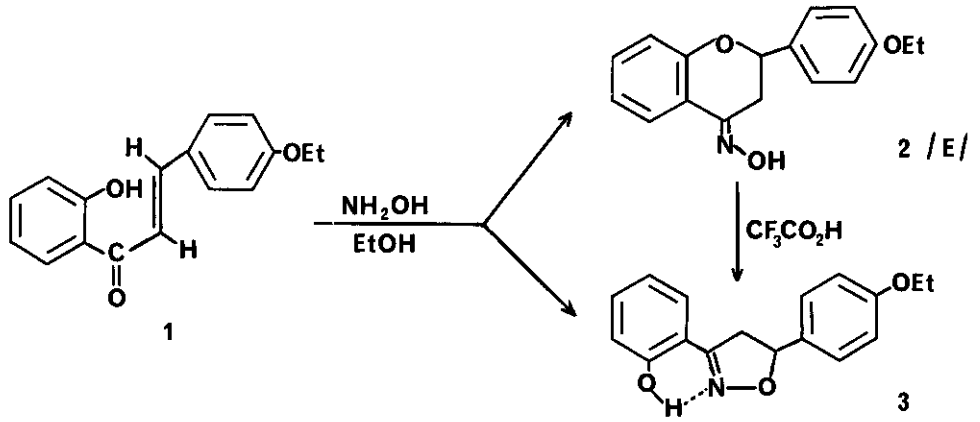


SCHEME 1

The ^{1}H NMR spestra of both isomeric compounds (2) and (3) (typical ABX system) are very similar to Δ^2-isoxazolines[10] as well as flavanones oximes[1,11]. The coupling constants (particularly diagnostic J_{AX}) were different and (2) has the appropriate values J_{AB}= 17 Hz, J_{BX}= 13 Hz and J_{AX}= 3.2 Hz[1] ,whereas (3) has the values J_{AB}= 17 Hz, J_{BX}= 13 Hz and J_{AX}= 8 Hz[9] , which correspond closely to values reported for Δ^2-isoxazolines respectively [10]. The comparison of the value of J_{AX} for (2) and (3) permits their easy differentiation. The second method of simple differentiation between Δ^2-isoxazolines and flavanones oximes is comparison of their UV spectra. The UV spectra of (2)[1] and (3)[9] are shown in Fig.1 and the UV spectrum of (3) is quite distinct with its characteristic second peak.

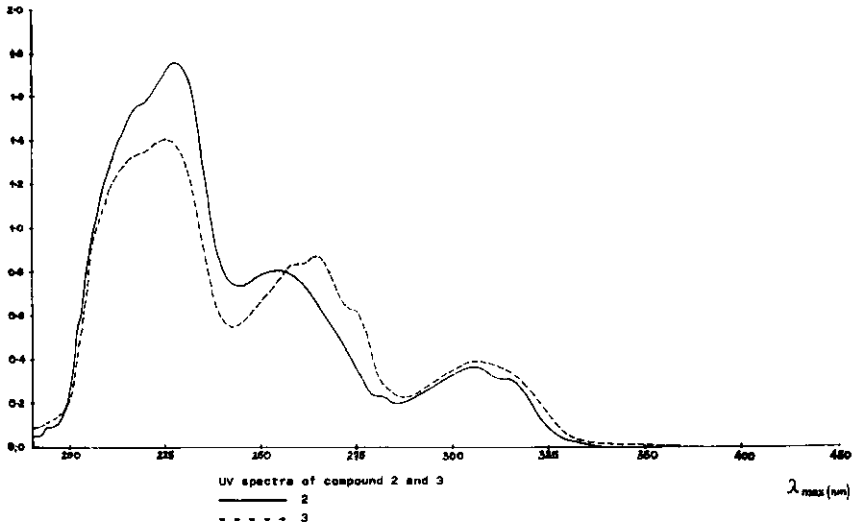
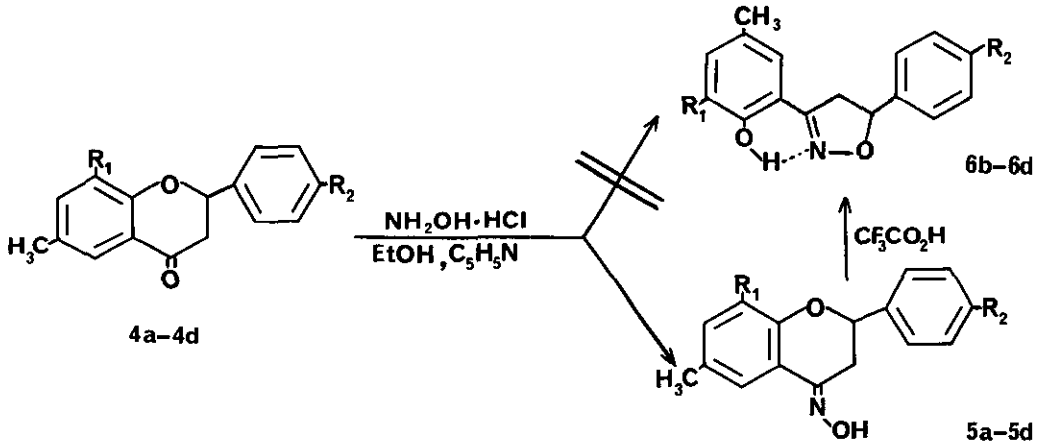


Fig. 1

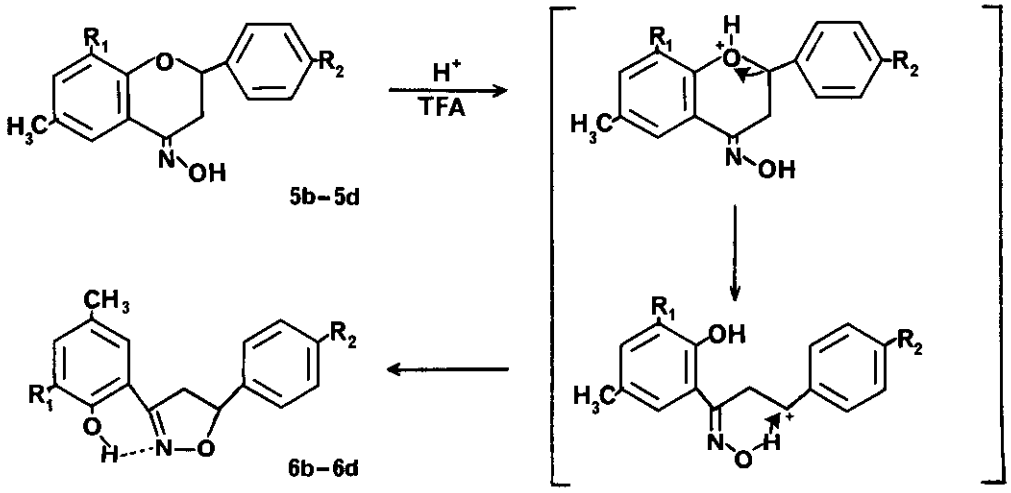
The above obtained results prompted us to study the literature data concerned with the synthesis of Δ^2-isoxazolines and isomeric flavanones oximes from 2'-hydroxychalcones. In 1970 Borkhade and Marathey [12] reported the formation of Δ^2-isoxazolines (without any confirmation of structures) on condensing of mixture of flavanones and corresponding 2'-hydroxychalcones with hydroxylamine. The fact that compound of the type of Δ^2-isoxazolines have the melting point that is almost always low [13] encouraged us to conduct a systematic reexamination of the structures of reported products [12]. Taking into consideration that reported compounds [12] may posses the structures of isomeric flavanones oximes, for the sake of comparison we have attempted to synthesize these oximes from the corresponding flavanones (4a-4d). Generally, physico-chemical data (m.p.) of obtained compounds (5a-5d) and their acetyl derivatives ($5a_1$-$5d_1$) are in agreement with the Δ^2-isoxazolines structures and their acetyl derivatives quoted by Borkhade and Marathey [12]. UV and ^{1}H NMR data comparison with the model oxime (2) demonstrates the similarity of all compounds (5a-5d) obtained. Each compound exhibits three bands within the ranges of 218-221,253-264, and 312-316 nm in UV. This UV evidence fully suports the structures of obtained compounds [12] as oximes of flavanones. The oximes (5a-5d) exist in the (E) form as proved on the basis of their ^{1}H NMR (Table 2) by analogy with our earlier reports [1,9] of characteristic downfield shift of $-H_B$ proton in similar oximes possesing (E) configurations.



SCHEME 2

According to our recent investigations [9] we have also attempted to synthesize compounds of a Δ^2-isoxazoline structure by TFA catalyzed rearrangement of appropriate oximes of flavanones. Thus when (E) oximes (5b-5d) were treated with boiling trifluoroacetic acid (for 1.5-3 h) the corresponding Δ^2-isoxazoline derivatives (6b-6d) were obtained. The oxime (5a) similar to the oximes with 4'-Cl, 4'-Br, 4'-I, 4'-CH_3 and 4'-NO_2 substituents [9] was not rearranged under

above-mentioned reaction conditions. These observations suggested that the γ-pyrone ring opening process may be due to a -M effect of the phenyl group as a substituent. The oximes ($5a_1$-$5d_1$) were not rearranged under above-mentioned reaction conditions.



SCHEME 3

The first step of the course of this rearrangement will be the initial protonation at oxygen atom and after that the opening of the γ-pyrone ring. The intermediate oxime thus would further cyclise under above-mentioned reaction conditions with the formation of the five membered ring of Δ^2-isoxazoline. This course of the above reaction not only additionally confirms the structures of parent compounds as oximes, but also shows that authors [12] obtained oximes instead of these isomeric Δ^2-isoxazolines. In the light of these results, the present work describes the first synthesis of Δ^2-isoxazoline derivatives (6b-6d). The tentative assignments of the UV and ^{1}H NMR spectra of (6b-6d) are given in Table 1 and 2. The comparison of the UV data of (6b-6d) with the model Δ^2-isoxazoline (3) in contrast to model oxime (2) demonstrates the similarity of obtained compounds (6b-6d) and determines the simple method of differentiation of Δ^2-isoxazolines from isomeric flavanone oximes hitherto not observed in the literature. Moreover in the ^{1}H NMR spectra of compounds (6b-6d) and earlier series of Δ^2-isoxazolines[9], the signal characteristic of chelated phenolic group -OH appeared at 9.6-9.8 ppm, while for oximes (5a-5d) at 10.36-10.44 ppm. The above results easy permit to distinquish Δ^2-isoxazoline from the isomeric flavanone oximes.

EXPERIMENTAL SECTION

The purity of the products was determined by TLC Kieselgel $60F_{254}$ benzene-ethyl acetate 38:12 (v:v). Melting points (uncorected) were determined on a Boetius apparatus (Carl Zeiss Jena). UV spectra were recorded on a UNICAM SP-800 spectrometer in an ethanol solution.

Table 1.

Properties and IR, UV, data of compounds (5a-5d) and (6b-6d)

Compound	R_1	R_2	Yield (%)	M.p. (°C)	R_f	Formula	IR bands ν_{max}^{KBr} (cm^{-1})	UV λ_{max}^{EtOH} (nm) (log ε)
5a	-H	-H	88	187-188[a]	0.78	$C_{16}H_{15}NO_2$	3230 (OH),2900 ($-CH_2-$), 1600 (C=N),1220 (-C-O-C), 1135,1070 (=N-O)	218, 255, 312, 318 (4.28),(4.00),(3.66),(3.61)
5b	-Br	-H	92	196-197	0.77	$C_{16}H_{14}BrNO_2$	3240 (OH),2900 ($-CH_2-$) 1600 (C=N),1250 (-C-O-C), 1090 (=N-O)	221, 264, 316, 326 (4.39),(3.95),(3.69),(3.62)
5c	-H	$-OCH_3$	85	210-212[b]	0.75	$C_{17}H_{17}NO_3$	3240 (OH),2920 ($-CH_2-$), 1605 (C=N),1235 (-C-O-C) 1140,1120 (=N-O)	227, 256, 313, 323 (4.38),(3.99),(3.63),(3.56)
5d	-Br	$-OCH_3$	90	187-189	0.79	$C_{17}H_{16}BrNO_3$	3240 (OH),2910,2810, ($-CH_2-$),1600 (C=N),1235, (-C-O-C),1135,1070 (=N-O)	221, 253, 313, 323 (4.50),(3.82),(3.65),(3.57)
6b	-Br	-H	80	98-100	0.81	$C_{16}H_{14}BrNO_2$	3230 (OH),2900 ($-CH_2-$), 1600 (C=N),1155,1065,(=N-O)	221, 260, 265, 320 (4.42),(3.95),(3.98),(3.66)
6c	-H	$-OCH_3$	72	80-82	0.83	$C_{17}H_{17}NO_3$	3125 (OH),2920 ($-CH_2-$), 1600 (C=N),1185,1070,(=N-O)	223, 266, 265, 320 (4.30),(4.06),(3.92),(3.68)
6d	-Br	$-OCH_3$	93	71-73	0.84	$C_{17}H_{16}BrNO_3$	3160 (OH), 2940 ($-CH_2-$) 1615,(C=N), 1175,1035,(=N-O)	223, 266, 276, 318 (4.41),(4.15),(4.02),(3.77)

a) Reported m.p. 122° C [15] b) Reported m.p. 203-204°C [16]

Table 2

^{1}H NMR data of compounds (5a-5d) and (6b-6d) and properties of their acetyl derivatives

Compounds	^{1}H NMR δ in ppm	Acetyl derivatives		
		Compound	m.p. °C	IR ν_{max}^{KBr} (cm^{-1})
5a**	2.33(s,3H,-CH_3),2.73(dd,1H,-H_A),3.4(dd,1H,-H_B),J_{AB}=17Hz,5.0(q,1H,-H_X), J_{BX}=12Hz, J_{AX}=3Hz, 7.5-7.63(dd,1H,-C_5), 6.73-7.63(m,8H,aromatic), 10.36(s,1H,-OH)	$5a_1$	184-185	1755 (-$COCH_3$) 1615 (-C=N-)
5b*	2.33(s,3H,-CH_3),2.72(dd,1H,-H_A),3.46(dd,1H,-H_B),J_{AB}=17Hz,5.1(q,1H,H_X), J_{BX}=13Hz, J_{AX}=3.2Hz,7.46-7.53(dd,1H,-C_5),7.20-7.53(m,7H,aromatic), 10.44(s,1H,-OH)	$5b_1$	158-160	1750 (-$COCH_3$) 1615 (-C=N-)
5c**	2.33(s,3H,-CH_3),2.7(dd,1H,-H_A),3.4(dd,1H,-H_B),J_{AB}=17Hz,5.03(q,1H-H_X), J_{BX}=12.8Hz, J_{AX}=3Hz,3.8(s,3H,-OCH_3),7.63-7.7(dd,1H,-C_5),6.9-7.7(m,7H, aromatic),10.36(s,1H,-OH)	$5c_1$	187-189	1755 (-$COCH_3$) 1610 (-C=N-)
5d**	2.3(s,3H,-CH_3),2.7(dd,1H,-H_A),3.26(dd,1H,-H_B),J_{AB}=17Hz,4.9(q,1H,-H_X), J_{BX}=12Hz, J_{AX}=3Hz,3.83(s,3H,-OCH_3),7.46-7.6(dd,1H,-C_5),6.7-7.6(m,7H, aromatic),10.26(s,1H,-OH)	$5d_1$	184-186	1755 (-$COCH_3$) 1610 (-C=N-)
6b**	2.33(s,3H,-CH_3),3.16(dd,1H,-H_A),3.46(dd,1H,-H_B),J_{AB}=17Hz,5.3(t,1H,-H_X), J_{BX}=12Hz, J_{AX}=8.2Hz,7.2-7.56(m,7H,aromatic),9.8(s,1H,-OH)	$6b_1$	152-154	1750 (-$COCH_3$) 1605 (-C=N-)
6c*	2.3(s,3H,-CH_3),3.16(dd,1H,-H_A),3.63(dd,1H,-H_B),J_{AB}=17Hz,5.36(t,1H,-H_X), J_{BX}=12Hz, J_{AX}=9Hz,3.8(s,3H,-OCH_3),6.7-7.26(m,7H,aromatic),9.66(s,1H,-OH)	$6c_1$	83-85	1755 (-$COCH_3$) 1610 (-C=N-)
6d*	2.3(s,3H,-CH_3),3.2(dd,1H,-H_A),3.66(dd,1H,-H_B),J_{AB}=17Hz,5.36(t,1H,-H_X), J_{BX}=12Hz, J_{AX}=9Hz,3.8(s,3H,-OCH_3),6.73-7.3(m,6H,aromatic),9.66(s,1H,-OH)	$6d_1$	79-80	1750 (-$COCH_3$) 1610 (-C=N-)

*Solvent $CDCl_3$ **Solvent CD_3COCD_3

IR spectra were made by means of UNICAM SP-200G spectrometer. ^1H NMR were recorded on a VARIAN EM-360 (60 MHz) in $CDCl_3$ and CD_3COCD_3, using TMS as an internal standard. The flavanones used as starting materials were prepared by known procedures [12,14].

2,3-Dihydro-2-(4-ethoxyphenyl)-4H-benzopyran-4-one oxime (2) and 3-(2-hydroxyphenyl)-5-(4-ethoxyphenyl)-Δ^2-isoxazoline (3)

A solution of 2.68g (0.01 mole) of chalcone (1) in ethanol (75 ml) and 2.0g (0.028 mole) of hydroxylamine hydrochloride was heated under reflux for 8 h. The resulting solution was cooled. The precipitate (1.55g) was collected by filtration and purified by crystallization from ethanol followed by column chromatography on silica gel using benzene-ethyl acetate 38:12 v:v as eluant to yield (2) (1.35g 45%), R_f= 0.62. The above filtrate was left standing at room temperature for 4 h. The precipitate of (3) (0.77g) was filtered and purified by crystallization from ethanol followed by column chromatography on silica gel in ether-hexane 6:4 v:v to give (3) (0.5g 20%), R_f= 0.76, m.p.82-84°C.

2,3-Dihydro-2-(4-R_2-phenyl)-4H-6-methyl-8-R_1-benzopyran-4-one oximes (5a-5d)

A solution of 1.0g of appropriate flavanone in ethanol (40 ml) and anhydrous pyridine (2.5 ml) together with 1.0g (0.014 mole) of hydroxylamine hydrochloride was heated under reflux for 2 h. After cooling, the reaction mixture was poured into ice-water and the precipitate was collected by filtration, washed with cold water and crystallized from ethanol.

2,3-Dihydro-2-(4-R_2-phenyl)-4H-6-methyl-8-R_1-benzopyran-4-one oxime acetates ($5a_1$-$5d_1$)

A mixture of 0.5g of appropriate oxime (5a-5d) and acetic anhydride (10 ml) was left standing for 12 h at room temperature. The resulting solution was poured into ice-water. The products was collected and crystallized from ethanol. Yields 85-90%.

3-(2-Hydroxy-5-methyl-8-R_1-phenyl)-5-(4-R_2-phenyl)-Δ^2-isoxazolines (6b-6d)

A solution of 0.5g of appropriate oxime (5b-5d in trifluoroacetic acid (TFA) (5 ml) was heated under reflux for 1.5 to 3 h. After cooling, the reaction mixture was poured into ice-water. The resulting precipitate was collected by filtration, washed with dilute sodium hydroxide solution and water, and crystallized from ethanol.

3-(2-Acetoxy-5-methyl-8-R_1-phenyl)-5-(4-R_2-phenyl)-Δ^2-isoxazolines ($6b_1$-$6d_1$)

A mixture of 0.5g of Δ^2-isoxazolines, acetic anhydride (5 ml) and anhydrous sodium acetate was heated under reflux for 3 h. After cooling, the reaction mixture was poured into ice-water. The separated precipitate was purified by crystallization from ethanol. Yields 88-92%.

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