

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

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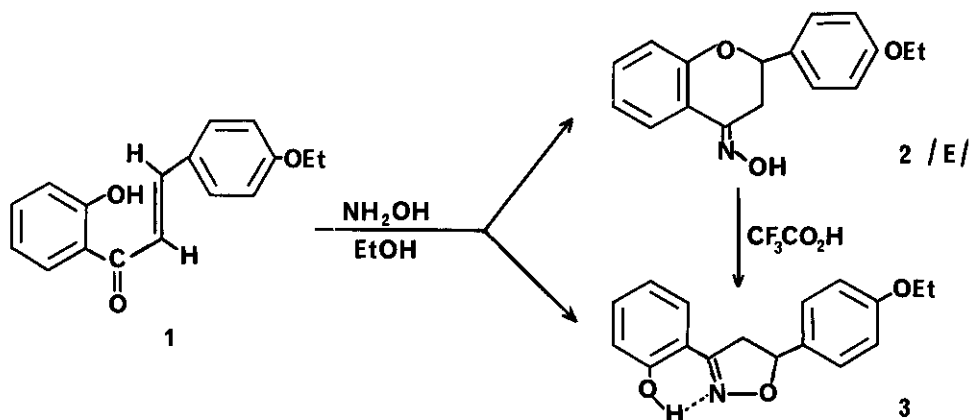
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Abstract - The simple method of differentiation of isomeric derivatives i.e. (E)-2,3-dihydro-2-(4-ethoxyphenyl)-4H-benzopyran-4-one oxime (2) and corresponding Δ^2 -isoxazoline (3) on the basis of their UV and ^1H NMR data, allows us to establish that 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 described¹². 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 heterocycles¹⁻³ and in conjunction with our interest in their biological properties⁴ we initiated an extended study of the reaction of hydroxylamine with 4-substituted 2'-hydroxychalcones.⁵ In our previous communication⁶⁻⁷ 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-ethoxychalcone⁸ (1) in a slightly acid medium ($\text{NH}_2\text{OH}\cdot\text{HCl}$ 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, ^1H NMR) compound (2) was identified as 4'-ethoxyflavanone oxime¹ 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).

* Previous Parts entitled "CHALCONE OXIMES", Part VI. Heterocycles, 14, 1319 (1980).



SCHEME 1

The ^1H NMR spectra of both isomeric compounds (2) and (3) (typical ABX system) are very similar to Δ^2 -isoxazolines¹⁰ as well as flavanones oximes^{1,11}. The coupling constants (particularly diagnostic J_{AX}) were different and (2) has the appropriate values $J_{\text{AB}} = 17$ Hz, $J_{\text{BX}} = 13$ Hz and $J_{\text{AX}} = 3.2$ Hz¹, whereas (3) has the values $J_{\text{AB}} = 17$ Hz, $J_{\text{BX}} = 13$ Hz and $J_{\text{AX}} = 8$ Hz⁹, which correspond closely to values reported for Δ^2 -isoxazolines respectively¹⁰. 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.

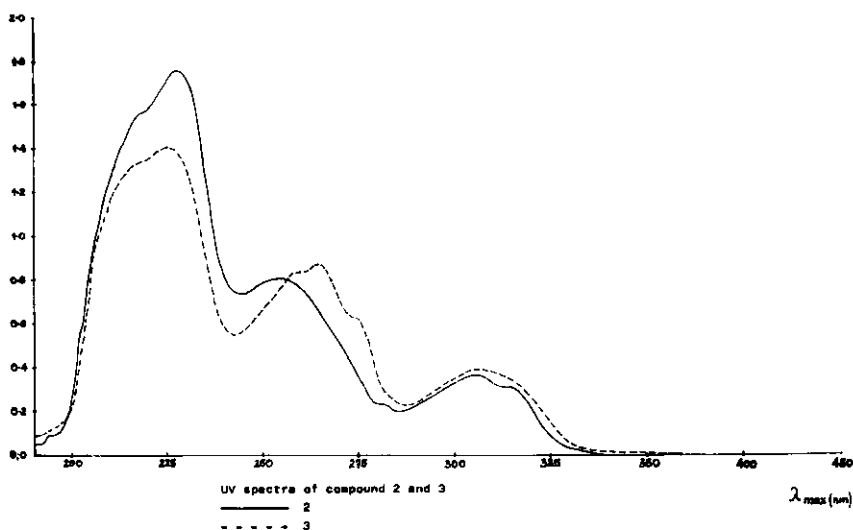
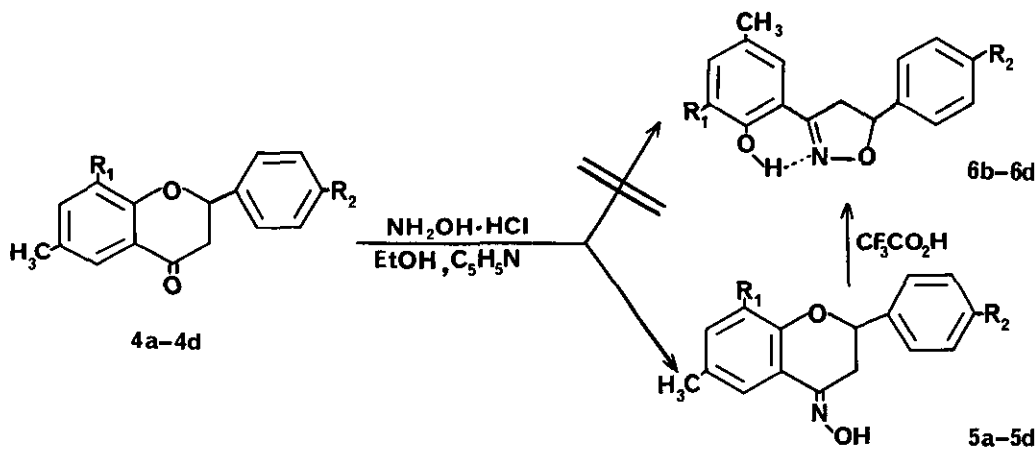


Fig. 1

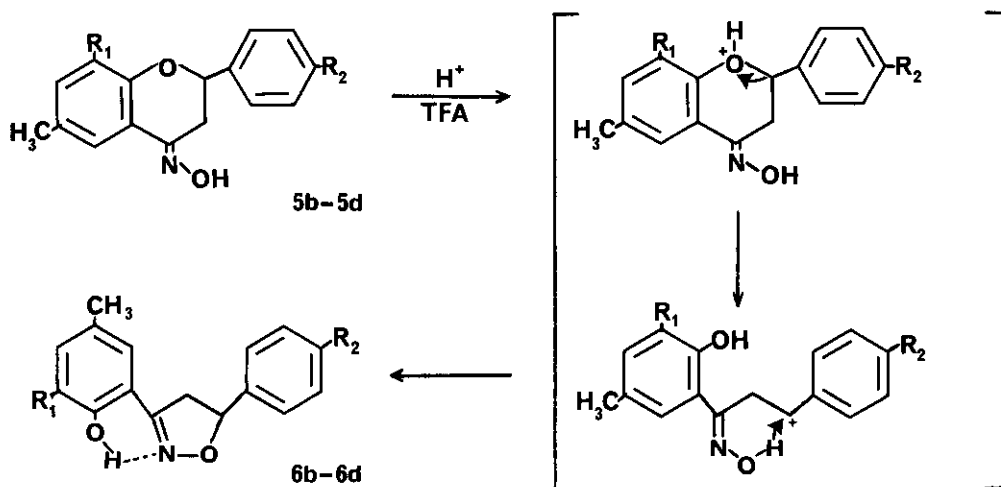
The above obtained results prompted us to study the literature data concerned with the synthesis of Δ^2 -isoxazolines and isomeric flavanones oximes from 2'-hydroxychalcones. In 1970 Borkhade and Marathe¹² reported the formation of Δ^2 -isoxazolines (without any confirmation of structures) on condensing 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 low¹³ encouraged us to conduct a systematic reexamination of the structures of reported products¹². Taking into consideration that reported compounds¹² may possess 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 (5a₁-5d₁) are in agreement with the Δ^2 -isoxazolines structures and their acetyl derivatives quoted by Borkhade and Marathe¹². UV and ¹H 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 supports the structures of obtained compounds¹² as oximes of flavanones. The oximes (5a-5d) exist in the (E) form as proved on the basis of their ¹H NMR (Table 2) by analogy with our earlier reports^{1,9} of characteristic downfield shift of -H_B proton in similar oximes possessing (E) configurations.



SCHEME 2

According to our recent investigations⁹ 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'-CH₃ and 4'-NO₂ substituents⁹ 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 (5a₁-5d₁) 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 authors¹² 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 ¹H 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 ¹H NMR spectra of compounds (6b-6d) and earlier series of Δ^2 -isoxazolines⁹, 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 distinguish Δ^2 -isoxazoline from the isomeric flavanone oximes.

EXPERIMENTAL SECTION

The purity of the products was determined by TIC Kieselgel 60F₂₅₄ benzene-ethyl acetate 38:12 (v:v). Melting points (uncorrected) 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 (KBr max 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° C¹⁵ b) Reported m.p. 203-204° C¹⁶

Table 2

¹H 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 $\frac{\text{KBr}}{\text{max}}$ (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 CDCl₃** Solvent CD₃COCD₃

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 2.66g (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-R₂-phenyl)-4H-6-methyl-8-R₁-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-R₂-phenyl)-4H-6-methyl-8-R₁-benzopyran-4-one oxime acetates (5a₁-5d₁)

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-R₁-phenyl)-5-(4-R₂-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-R₁-phenyl)-5-(4-R₂-phenyl)- Δ^2 -isoxazolines (6b₁-6d₁)

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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