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STUDIES ON ISOMERIC PYRIDYLISOXAZOLES

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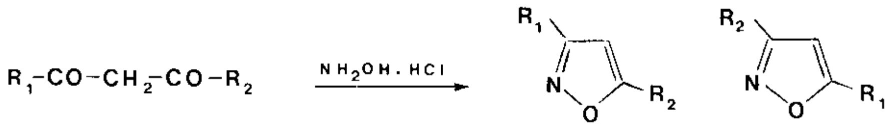
Abstract– Data concerning the reaction between hydroxylamine hydrochloride and 1-(2-pyridyl)-3-phenyl- (I a) and 1-(2-thienyl)-3-phenyl-1,3-propanedione (I 1) disagree with those previously reported in literature.
The same reaction was also studied employing a series of 1,3-diketones-1-(pyridyl)-substituted I b-i. The direction of enolization of 1,3-diketones accounted for the isomeric isoxazoles formation.

It was reported[1] that 1,3-diketones I a and I 1 react with hydroxylamine hydrochloride to give as the sole products 5-phenyl-3-(2-pyridyl)- (II a) and 3-phenyl-5-(2-thienyl)-isoxazole (III 1) respectively[2]. Instead a careful examination of these reactions showed that a mixture of two isomers was always formed. These results together with the pharmaceutical interest of isoxazole-pyridinium salts[3,4] stimulated to extend the same reaction to 1,3-diketones I b-i[5].
At the same time the combined substituent effects on the formation of isomeric isoxazoles II and III can be studied. The hitherto unknown diketones[6] were prepared by standard procedures.
The isoxazolepyridinium salts resulting from the cyclization reaction of I a-i were converted to free bases with sodium carbonate.



I a-1 II a-1 III a-1

I, II, III a : R_1 = 2-pyridyl, R_2 = phenyl
b : R_1 = 3-pyridyl, R_2 = phenyl
c : R_1 = 4-pyridyl, R_2 = phenyl
d : R_1 = 2-pyridyl, R_2 = 2-thienyl
e : R_1 = 3-pyridyl, R_2 = 2-thienyl
f : R_1 = 4-pyridyl, R_2 = 2-thienyl
g : R_1 = 2-pyridyl, R_2 = methyl
h : R_1 = 3-pyridyl, R_2 = methyl
i : R_1 = 4-pyridyl, R_2 = methyl
l : R_1 = 2-thienyl, R_2 = phenyl

A mixture of two isomers was also obtained from diketones I b and I c. The relative amounts of the isomer couples II -III a,b,c,l were determined by nmr analyses of the mixtures.

Such a determination was possible since, especially in deuterochloroform, two well-separated singlets appear, due to the isoxazole ring proton of II and III. The same isomer ratios were found comparing the uv spectra of isoxazoles separated from the mixture by tlc with those of related compounds obtained by unequivocal synthesis[7] (Table 1 and 2).

Table 1 : Relative percentages of II-III a,b,c,l.

Starting product	Mp°C	Isoxazoles obtained %		Rf[a]		Eluent (v/v)
I	II+III	II	III	II	III	
a	87-88	75	25	0.92	0.86	benzene-ethanol (100:1)
b	144-145	40	60	0.59	0.65	chloroform-benzene (10:1)
c	167-168	68	32	0.51	0.56	chloroform-benzene (10:1)
l	99-100	20	80	0.38	0.45	benzene-eptane (3:1)

a)- Silica gel plates Merck F_{254}.

Table 2 : Analytical and spectral data of authentic isoxazoles II-III a,b,c,l.

Compound	Mp°C Solvent	Formula	Analysis[a] C	H	N	Uv[b] λ max nm (Logε)	^{1}H-Nmr[c] isoxazole
II a	94-95 subl.	$C_{14}H_{10}N_2O$	75.75 (75.65	4.63 4.53	12.38 12.56)	238(4.24),272(4.40)	7.19
III a[d]	79-80 subl.		75.50	4.57	12.42	238(4.29),250sh(4.25), 280(4.26)	7.25
II b	143-144 ligroin		75.61	4.58	12.76	240(4.28),273(4.35)	6.88
III b[d]	145-146 ligroin		75.62	4.49	12.65	244(4.31),261(4.31)	6.95
II c	162-163 subl.		75.35	4.63	12.71	240(4.32),266(4.28)	6.96
III c[d]	171-172 subl.		75.39	4.45	12.74	245sh(4.25),263(4.35)	7.08
II l	109-110 EtOH/H_2O	$C_{13}H_9NOS$	68.52 (68.70	4.01 3.99	6.05 6.16)	272(4.45)	7.76
III l	95-96 heptane		68.65	3.88	6.12	246(4.18),292(4.28)	7.70

a)- Values in parentheses refer to calculated percentages; *b)*- Solvent: methanol;
c)- Solvent: 99.9% chloroform-d_1, the chemical shifts are reported in ppm(δ) from TMS;
d)- Ref.8 : values reported for III a mp 85-86°C, λ max 284; III b mp 167-168°C, λ max 261; III c mp 165-166°C, λ max 255 (solvent: ethanol).

Unlikely single isomers II d-f and III g-i resulted from I d-f and I g-i respectively.
In fact, the tlc analyses showed only one component and nmr spectra exhibited a sole singlet for the isoxazole ring proton, whose integral corresponds to one hydrogen.
The comparison (Rf values, nmr and uv spectra) of II d-f and III g-i with the corresponding authentic isoxazoles provided evidence for the structures (Table 3).

Table 3 : Analytical and spectral data of authentic isoxazoles II d-f, III f, and II - III g-i.

Compound	Mp°C	Formula	Analysis a)			Uv b)	^{1}H-Nmr c)	
	Solvent		C	H	N	λ max nm (Logε)	isoxazole	CH_3
II d	114-115 ethanol	$C_{12}H_8N_2OS$	62.87 (63.14	3.68 3.53	12.15 12.27)	234(4.11),237sh(4.11), 247(4.08),270sh(4.15), 285(4.28),291(4.29)	7.43	-
II e	129-130 EtOH/H_2O		62.95	3.45	12.30	237(4.12),265sh(4.09), 291(4.27)	7.52	-
II f	143-144 propanol		63.05	3.59	12.04	234(4.21),237sh(4.20), 246sh(4.14),267sh(4.14), 285(4.23),295(4.23)	7.55	-
III f	147-148 propanol		63.11	3.61	12.58	268(4.52)	7.85	-
II g	41-42 subl.	$C_9H_8N_2O$	67.38 (67.48	4.97 5.03	17.47 17.49)	232(4.03),266(3.80), 270(3.79),277sh(3.64)	6.83	2.52
III g	57-58 heptane		67.66	5.10	17.39	251(4.17),282(4.13), 290sh(4.02)	6.98	2.31
II h	71-72 subl.		67.79	5.05	17.63	232(4.10),266(3.58)	6.88	2.52
III h	54-55 subl.		67.30	4.92	17.29	257(4.17),277sh(4.00)	7.03	2.31
II i	84-85 subl.		67.61	4.98	17.32	232(4.12),265sh(3.52), 275sh(3.37)	6.98	2.55
III i	67-68 subl.		67.27	5.09	17.60	262(4.24) d)	7.16	2.34

a)- Values in parentheses refer to calculated percentages; *b)*- Solvent: methanol;
c)- Solvent: 99.9% DMSO-d_6, the chemical shifts are reported in ppm (δ) from TMS;
d)- Ref.9: Logε value reported: 4.36.

The experimental results above reported agree with observations based on the structures of compounds I. It is known[10] that 1,3-diketones exhibit in solution a cis-enolic structure stabilized by a strong intramolecular hydrogen bond. The direction of enolization is towards the more extended conjugative system that determines a further stabilization of the enol by resonance effect[11]. Assuming therefore that the enolic modification of 1,3-diketones reacts with hydroxylamine hydrochloride by addition to the carbonyl group, this can be taken as evidence for the formation of isomeric isoxazoles[12]. The uv analysis (Table 4) gave useful indications on the structure of diketones I a-l. With regard to I d-f the longest wavelength bands at 350-355 nm agree with a planar 3-(2-thienyl)acryloyl chromophoric system, stabilized by the formation of the chelated ring, rather than with the less conjugate 3-(pyridyl)acryloyl system. Then the enolization is towards the thienyl group; accordingly, the 5-thienyl derivatives II d-f were obtained.

The spectra of I g-i exhibit absorption maxima at 307-312 nm attributable to the sole conjugative system that arises from the enolic modification towards the pyridyl group; the cyclization reaction afforded therefore only the 5-pyridyl derivatives III g-i. The absorption maxima at 338-342 nm of I a-c can be related both to cinnamoyl and 3-(pyridyl)acryloyl systems, so they were not indicative of the direction of enolization. On the other hand, since the stabilization by resonance effect of the two possible enols is closely similar, it is not surprising to have no single enolic modification and, consequently, to find an isomeric isoxazole mixture.

Table 4 : Uv spectral data of 1,3-diketones I a-l[a)].

I a[b)]	237(3.96),342(4.31)	I f	217(4.12),282(3.98),350(4.36)
I b[b)]	230(3.98),244(3.98),342(4.36)	I g[b)]	235(3.81),245sh(3.70),280sh(3.74),312(4.08)
I c	223sh(4.06),290sh(3.95),338(4.28)	I h[b)]	233(3.96),307(4.21)
I d	224(3.96),272(3.91),354(4.37)	I i	221(3.91),310(4.08)
I e	224(3.98),269(3.90),352(4.40)	I l	258(3.98),355(4.40)

a)- λ nm (Logε); solvent: methanol; *b)*-Ref.13: values reported for I a 245(3.92),341(4.35); I b 246(3.91),339(4.27); I g 225(3.77),313(4.13); I h 236(3.80),307(4.13).

The uv spectrum of I l, comparable with those of I d-f, should indicate an enolization towards the thienyl group, instead, in this case, the reaction of I l with hydroxylamine hydrochloride, as above reported, afforded both isomers II l and III l. However, as expected, 3-phenyl-5-(2-thienyl)isoxazole (III l) was, by far, the major constituent of the mixture.

REFERENCES AND NOTES

1 A.D.Mitchell and D.C.Nonhebel,*Tetrahedron*, 1976, **32**, 2437.

2 Although the compound II a should be correctly named, by IUPAC rules, 2-[3-(5-phenyl)isoxazolyl]pyridine, our compounds in this text are also treated as substituted isoxazoles since the interest is focused on the synthesis of this heterocyclic ring.

3 V.J.Bauer and S.R.Safir, *France Patent*, 1969, M.7030; *Chem.Abstr.*, 1971, **74**, 141749r.

4 C.M.Hofmann and S.R.Safir, *U.S. Patent*, 1976, 3,996,748; *Chem.Abstr.*, 1977, **86**, 29820d.

5 A solution of the appropriate diketone (0.01 mol) in methanol (60 ml) was added to an aqueous solution of hydroxylamine hydrochloride (1.4 g, 0.02 mol) and the mixture refluxed for 2 h.

6 I c: mp 83-84°C; I d: mp 84-85°C; I e: mp 133-134°C; I f: mp 145-146°C; I i: mp 66-67°C.

7 The isoxazoles II and III were synthesized from the appropriate hydroxamyl chloride with sodium acetylides or, as an alternative for II g-i, with acetylenic Grignard reagents.

8 H.J.Roth and M.Schwarz, *Arch.Pharm.*, 1961, **294**, 769.

9 V.J.Bauer, *J.Med.Chem.*, 1968, **11**, 984.

10 J.U.Lowe jr. and L.N.Ferguson, *J.Org.Chem.*, 1965, **30**, 3000.

11 L.N.Ferguson, "Electronic Structure of Organic Molecules", Prentice Hall Inc., New York, 1952, p.216.

12 R.P.Barnes and J.L.Snead, *J.Am.Chem.Soc.*, 1945, **67**, 138.

13 L.Sacconi and G.Giannoni, *J.Chem.Soc.*, 1954, 2751.

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