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NEW ASPECTS IN THE HYDROGENOLYTIC OPENING OF 2-ISOXAZOLINES

SERGIO AURICCHIO* and ALDO RICCA

Dipartimento di Chimica, Politecnico di Milano,
Piazza Leonardo da Vinci 32, 20133 Milano, Italy

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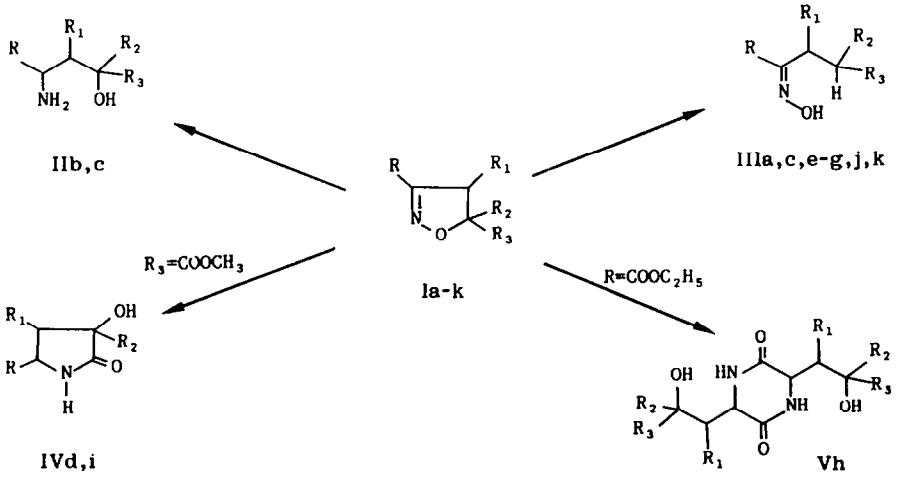
Abstract - It has been observed that the hydrogenolytic opening of 2-isoxazolines depends on the substituents present in positions 3 and 5. The hydrogenolysis on 10% Pd/C of 2-isoxazolines, substituted in position 3 with carbonyl or carboxyl groups and in position 5 with an aromatic group, gives oximes, in contrast to other isoxazoline derivatives. From the 5-aryl-2-isoxazolines it is possible to obtain aminoalcohols in ethanol and oximes in acetic acid.

The 1,3-dipolar addition of a nitrile oxide to a double bond is a well known reaction[1]. The resulting cyclic compounds, 2-isoxazolines I, have the structure of a cyclic oxime ether. The isoxazoline system is a very versatile heterocycle, in fact an appropriate manipulation provides access to several compounds. A general scheme to obtain open structures has been reported by Kozikowski and Stein[2].

In general, to convert an isoxazoline into an open compound there are two possibilities: cleavage of either N-O or O-C bond by reductive and oxidative treatments.

We wish to report the results obtained in the catalytic reduction of selected 2-isoxazolines.



It is generally accepted that catalytic hydrogenation of I invariably leads to cleavage of the N-O bond with formation of II; our results, reported in **Table I**, show that a few exceptions are possible.

TABLE I

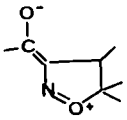
	R	R_1	R_2	R_3	EtOH as solvent	AcOH as solvent
Ia	CH_3	H	H	C_6H_5	-	IIIa
Ib	C_6H_5	H	H	n-C_3H_7	IIb	IIb
Ic	C_6H_5	H	H	C_6H_5	IIc	IIIc
Id	C_6H_5	H	H	$COOCH_3$	IVd	
Ie	CH_3CO	H	H	C_6H_5	IIIe	
If	COOH	H	H	C_6H_5	IIIf	
Ig	COOEt	H	H	C_6H_5	IIIg	
Ih	COOEt	H	H	n-C_6H_{13}	Vh	
Ii	COOEt	H	H	$COOCH_3$	IVi	
Ij	COOEt	$-(CH_2)_4-$		C_6H_5	IIIj	
Ik	COOEt	$-CH_2-C_6H_4-$		H	IIIk	

It is interesting to note that only when in I, R is a carboxyl or carbonyl group and R_2 or R_3 are aromatic groups, the catalytic hydrogenation results in the cleavage of the C-O bond with the formation of the oximes **III**. When R is an aromatic or alkyl group and R_2 or R_3 are not aromatic substituents, the opening of the heterocycle occurs normally, with the N-O bond involved.

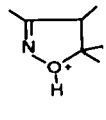
The catalitic hydrogenolysis of the C-O bond is a new aspect of the reactivity of 2-isoxazolines. In fact, when Drefahl and Hoerhold[3] report the synthesis of α-amino-γ-hydroxyacids by catalitic hydrogenation of 3-carboxyethylisoxazolines, in the case of **Ig** they meet with difficulties and by-pass the problem using Sodium amalgam and acetic acid as reducing agent.

To explain the mechanistical aspect of this new behavior one has to consider the influence of both substituents present in 3 and 5 positions. The results reported in **Table I** show that the oximes **III** are obtained only when groups like -COOEt or $-COCH_3$ are present in position 3; mechanistically, these groups can affect the resistance to attack of the N-O bond. In fact, it is reasonable to think that the presence of the carbonyl group allows the existence of limiting forms, as **VI**, making the normally weak N-O bond more resistant to attack by hydrogen. When only this effect is present in the considered heterocyclic system, the relative weakness of N-O and C-O bonds is again in favour of the former.

If an aromatic substituent is also present in position 5, another effect can be considered; in fact, now the C-O bond corresponds to O-benzyl oxime. It is known that in the benzyl oximes, by attack of hydrogen in the presence of the catalyst, the C-O bond is easily broken[4].



VI



VII

Evidently, only one of these effects is not sufficient to divert the course of the reaction; in fact, the isoxazolines **Ic,h,i** open normally, the N-O bond being cleaved.

If all the above considerations hold, the attack by hydrogen can be affected varying the medium of the reaction. Carrying out the hydrogenation of **Ia-d,h,i** in acetic acid as solvent, the protonation of the isoxazoline should take place to yield **VII**, with the N-O being stronger

than the same bond in the non-protonated compound. In fact, in these conditions the isoxazoline **Ia** gives **IIIa**; likewise **Ic** changes its behavior giving only **IIIc** in a quantitative yield. As was to be expected, all other isoxazolines **Ib,d,h,i**, not substituted in position 5 with an aromatic group, give the same products as are formed in ethanolic solution.

In conclusion, catalytic hydrogenation of 2-isoxazolines with an aromatic substituent in position 5 follows different pathways depending on the substituent in position 3: if a group able to stabilize the N-O bond is present in position 3, only the C-O bond cleavage occurs with consequential formation of oximes III.

When the substituents, whether in 3 or in 5 positions , are -COOEt the normally expected compound II cyclises; so, from **Ii** and **Ih** respectively, the cyclic compounds **IVi** and **Vh** are directly obtained.

Moreover, the formation of the oximes **III** can be influenced also by the choice of the reaction medium; operating in the presence of a protonating system it is possible to divert the course of the hydrogenolysis of those 5-aromatic-substituted isoxazolines unable to form oximes under the usual conditions.

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 177 instrument. ^{1}NMR spectra were determined with TMS as internal standard on Varian A 90. Mass spectra were recorded with VG MM ZAB-2F. All solvents and reagents were purified and dried by standard tecniques. Chromatographic separations were performed using Merck Kieselgel 60 F-254 (preparative t.l.c.), Merck Kieselgel 60 (column chromatography at atmospheric pressure or slightly above). M.p.s are uncorrected.

2-Isoxazolines (Ia-k) - The 2-isoxazolines Ia-g,i were obtained as described in literature[5]. The 2-isoxazolines Ih,j,k were obtained from addition of carbethoxy fulmide with substituted alkenes: the stechiometric amount of NEt_3 was slowly added under stirring to ethylchlorohydroxyimino acetate dissolved in an excess of the appropriate alkene. The mixture was shaken with water and extracted with diethylether and the extracts separated and dried. After removing the solvent, the crude product was purified by chromatography over silica gel. The yields were > than 80 %.

3-Carbethoxy-5-hexyl-2-isoxazoline (Ih) - Oil; IR (film) 1740, 1720 and 1585 cm^{-1}; NMR ($CDCl_3$) 4.80 (m, 1H), 4.32 (q, 2H), 3.20 (dd, J = 18 and 10.5 Hz, 1H), 2.80 (dd, J = 18 and 8.5 Hz, 1H), 1.1-1.8 (m, 10 H), 0.90 (t, J = 7.1 Hz, 3H);MS m/z 227 (M^+, 15), 210 (19), 198 (18), 182 (44), 154 (67), 142 (100).

3-Carbethoxy-7a-phenyl-3a,4,5,6,7,7a-hexahydro-indoxazene (Ij) - M.p. 67 ° (hexane); IR (nujol) 1740, 1554 cm^{-1}; NMR ($CDCl_3$) 7.20-7.60 (m, 5H), 4.32 (q, J = 7.1 Hz, 2H), 3.50 (m, 1H), 1.4-2.4 (m, 8H), 1.3 (t, J = 7.1 Hz, 3H). MS m/z 273 (M+, 6), 256 (15), 228 (31), 200 (29), 105 (100).

3-Carbethoxy-3a,8a-dihydro-4H-indeno[2,1-d] (Ik) - Viscous oil; IR (nujol) 1720, 1590 cm^{-1}; NMR ($CDCl_3$) 7.20-7.60 (m, 4H), 6.24 (d, J = 9 Hz), 4.32 (q, J = 7.1 Hz, 2H), 4.26 (ddd, J = 9.0, 6.6 and 4.8, 1H Hz), 3.40(dd, J = 18 and 6.6 Hz, 1H), 3.32(dd, J = 18 and 4.8 Hz, 1H), 1.34(t, J = 7.1 Hz, 3H). MS m/z 231 (M^+, 18), 186 (3), 158 (18), 142 (100).

Hydrogenolysis of 2-isoxazolines Ia-k in Ethanol

The hydrogenolysis was carried out with 10% Pd/C at room temperature and under normal pressure. The reaction was followed by TLC. Then the catalyst was removed by filtration, the solvent was evaporated. The crude materials were purified by cristallization or chromatography over silica gel. In all cases the yields were pratically quantitative.

Hydrogenation of

Ia : Hydrogen was not absorbed and starting material was recovered inalterated.

Ib : **1-Amino-1-phenyl-hexan-3-ol (IIb)** - M.p. 76°C (cyclohexane); IR (nujol) 3340, 3280, 1600 cm^{-1}; NMR ($CDCl_3$) 7.0-7.4 (m, 5H), 3.5-4.4 (m, 2H), 2.6 (s broad, 3H), 1.5-2.2 (m, 2H), 1.2-1.6 (m, 4H), 0.9 (m, 3H); MS m/z 193 (M^+, 0.8), 174 (0.8), 150 (16), 133 (3), 106 (100); (Found: C, 74.66; H, 10.04; N, 7.04. $C_{12}H_{19}NO$ requires C, 74.57; H, 9.91; N, 7.25%).

Ic : **3-Amino-1,3-diphenyl-propan-1-ol (IIc)** - Analytical data are identical to the ones reported in lit.[6].

Id : **3-Hydroxy-5-phenyl-2-pyrrolidinone (IVd)** - Mixture 1:1 of cis and trans isomers that recristallizes without change from ethanol, m.p. 150°C; IR (KBr) 3350, 3220, 1710 cm^{-1}; the IR

data are correspondent to reported ones for the cis isomer[7]; NMR ($CDCl_3$) 7.2-7.5 (m, 10H), 4.82 (dd, J = 3.5 and 7.5 Hz, 1H), 4.56 (dd, J = 9 and 6 Hz, 1H), 4.48 (t, J = 9 Hz, 1H), 4.44 (t, J = 9 Hz, 1H), 3.88 (ddd, J = 13.5, 9.0 and 7.5 Hz, 1H), 2.2-2.7 (m, 2H), 1.98 (dt, J = 4.5 and 3.0 Hz, 1H); MS, m/z 177 (M^+, 100), 134 (59), 105 (56), 91 (97).

Ie : **3-Hydroxyimino-4-oxo-1-phenyl-pentane (IIIe)** - M.p. 98 °C (ethanol); IR(nujol) 3250, 3200, 1730 cm^{-1}; NMR($CDCl_3$) 8.8 (s broad, 1H), 7.1-7.4 (m,5H), 2.6-3.0 (m, 4H), 2.32 (s, 3H); MS m/z 191 (M^+,7), 174(33), 148 (23), 131 (33), 105 (100); (Found: C, 69.23; H, 7.14; N, 7.01.$C_{11}H_{13}NO_2$ requires C,69.09; H,6.85;N, 7.33 %).

If : **2-Hydroxyimino-4-phenyl-butanoic acid (IIIf)** - M.p. 150 °C (benzene/hexane); IR (nujol) 3230, 1690 cm^{-1}; NMR ($CDCl_3$ 7.2-7.4 (m, 5H), 2.7- 3.1 (m, 4H); MS m/z 193 (M^+, 3), 176 (37), 148 (5), 131 (100), 104 (32). (Found: C, 62.22; H, 5.71; N, 7.17. $C_{10}H_{11}NO_3$ requires C, 62.16; H, 5.74; N, 7.25 %).

Ig : **Ethyl 2-hydroxyimino-4-phenyl-butanoate (IIIg)** - M.p. 86°C (benzene/hexane); IR (nujol) 3240, 1750 cm^{-1}; NMR ($CDCl_3$) 7.1-7.5 (m, 5H), 4.22 (q, J = 7.1 Hz, 2H), 2.7-3.1 (m, 4H), 1.3 (t, J = 7.1, 3H); MS m/z 221 (M^+, 1.5), 204 (100), 176 (23), 159 (10), 148 (7), 131 (38). (Found: C, 65.18; H, 6.90; N, 6.28. $C_{12}H_{15}NO_3$ requires C, 65.14; H, 6.83; N, 6.33 %).

Ih : **3,5-Di(2-hydroxy-oct-1-yl)-diketopiperazine (VI)** - M.p. 223 °C(dioxane); NMR (DMSO) 3.8-4.1 (m, 2H), 3.5-3.8 (m, 2H), 1.5-2.0 (m, 4H), 1.1-1.5 (m,20H), 0.85 (t, 6H); MS m/z 370 (M^+,31), 352 (8), 285 (30), 367 (31), 242 (86), 158 (100). (Found: C, 64.51; H, 10.48; N, 7.41. $C_{20}H_{38}N_2O_4$ requires C, 64.83; H, 10.34; N, 7.56%).

Ii : **5-Carbethoxy-3-hydroxy-2-pyrrolidinone (IVi)** - Mixture 1:1 cis and trans; IR (nujol) 3360, 3250, 1780, 1700 cm^{-1}; NMR ($CDCl_3$) 4.1-4.6 (m, 2H), 2.82(dt J = 13.5 and 7.5 Hz, 1H), 2.2-2.7 (m, 2H), 2.06 (dt J = 13.5 and 9), 2.28 (t, J = 7.1, 6H); MS m/z 173 (M^+, 11), 129 (100), 117 (18), 100 (91).

Ij : **Ethyl 2-hydroxyimino-2-(2-phenyl-cyclohexyl)acetate (IIIj)** - The cis and trans isomers were separated by TLC as viscous oils. Cis (IIIj): IR (film) 3280, 1720, 1680 cm^{-1}; NMR ($CDCl_3$) 7.1-7.3 (m, 5H), 3.84 (m, 2H) 3.30 (m, $w_{1/2}$ = 15 Hz, 1H), 2.94 (m, $w_{1/2}$= 22Hz, 1H), 1.2-2.3 (m, 8H), 1.1 (t, J = 7.1Hz, 3H). MS m/z 275 (M^+ 1), 258 (3), 168 (5), 159 (4), 143 (10), 120 (15), 105 (100). Trans (IIIj): IR(film) 3280, 1720, 1680 cm^{-1}; NMR ($CDCl_3$) 7.1-7.4 (m, 5H), 3.88 (q, J = 7.1 Hz, 2H), 3.72 (m, $w_{1/2}$=18 Hz, 1H), 3.30 (m, $w_{1/2}$=18 Hz, 1H), 1.3-2.4(m, 8H), 1.1(t, J = 7.1 Hz, 3H); MS m/z 275 (M^+, 5), 258 (38), 187 (13), 185 (14), 159 (36), 143 (31), 105 (100).

Ik : **Ethyl 2-hydroxyimino-2-(indan-2-yl)-acetate (IIIk)** - M.p. 130 °C (methanol); IR (nujol) 3210, 1720 cm^{-1}; NMR ($CDCl_3$) . 7.1-7.3(m, 4H), 4.2 (q, J = 7.1 Hz, 2H), 4.12 (quintet, J = 9 Hz, 1H), 3.20 (dq, J = 15 and 9 Hz, 4H), 1.2 (t, J = 7.1 Hz, 3H); MS m/z 233 (M^+, 2), 216 (95), 188 (12), 160 (5), 142 (60), 117 (100). (Found: C, 67.13; H, 6.56; N, 5.94. $C_{13}H_{15}NO_3$ requires C, 66.93; H, 6.48; N, 6.07 %).

Hydrogenolysis of 2-isoxazolines in acetic acid

The hydrogenolysis was carried out analogously as for ethanolic solutions. Acetic acid was used as solvent. The reactions are reported only were the products are different from those obtained in ethanolic solution.

Hydrogenation of

Ia : **3-Hydroxyimino-1-phenyl-butane (IIIa)** - M.p.80°C (hexane),lit.[8] 85°C; IR (nuiol) 3220, 1600 cm^{-1}; NMR ($CDCl_3$) 8.54 (s broad, 1H), 7.1-7.4 (m, 5H), 2.7-3.0 (m, 2H), 2.3-2.6 (m, 2H), 1.88 (s, 3H); MS m/z 163 (M^+, 33), 146 (16), 131 (17), 105 (31), 91 (100). (Found: C, 73.67; H, 8.13; N, 8.23. $C_{10}H_{13}NO$ requires C, 73.59; H, 8.03; N, 8.58 %).

Ic : **1-Hydroxyimino-1,3-diphenylpropane (IIIc)** - M.p. 88°C (lit.[9] 88 °C); NMR ($CDCl_3$) 7.3-8.1 (m, 5H), 7.1-7.3 (m, 5H), 2.9-3.1 (m, 2H), 3.12-3.40 (m, 2H).

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