

M. Ginanneschi, M. Chelli and G. Rapi*

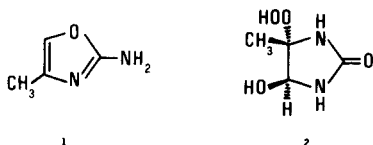
Cattedra di Chimica e Propedeutica Biochimica, Facoltà di Medicina e Chirurgia, e
Centro di Studio del C.N.R. sulla Chimica e la Struttura dei Composti Eterociclici e loro Applicazioni,
c/o Dipartimento di Chimica Organica dell'Università,
via G. Capponi 9, 50121 Firenze, Italy
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The reaction of some 2-aminooxazoles and imidazolidin-2-ones with hydrogen peroxide afforded stable *trans*- β -hydroxyhydroperoxy- or dihydroperoxyimidazolidin-2-ones according to the reaction conditions. In the case of 3a-hydroxy-7a-hydroperoxyoctahydro-2*H*-benzimidazolidin-2-one, the *trans* isomer is forbidden and *cis* adduct was isolated. A radical pathway to these hydroperoxides is proposed. From 2-amino-4-methyloxazole and hydrogen peroxide 2-amino-2-hydroxy-4-methyloxazolidin-4-yl peroxyacetate was also isolated.

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The pharmacological and biological researches carried out on a series of 17 β -(2-aminooxazol-4-yl) steroids (17 β -AOS) synthesized by us [2] showed that these substances possess effective antiinflammatory activity [3]. Since 17 β -AOS do not inhibit the PGs synthesis *in vitro* we suggested that these substances may act as radical scavengers or as antioxidant by means of their heterocyclic moiety [3]. In order to substantiate this hypothesis we carried out preliminary research on the behavior of 2-amino-4-methyloxazole (1) with hydrogen peroxide: we could isolate, as the major product, *r*-4-hydroperoxy-*t*-5-hydroxy-4-methylimidazolidin-2-one (2).

Figure 1

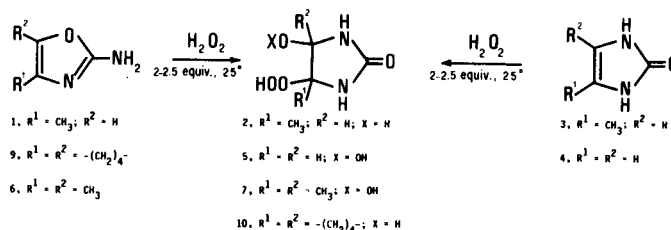


The *trans* structure of this stable hydroperoxide has been ascertained by X-ray diffraction [4]. The only rearrangement of the type 2-aminooxazole to 2-imidazolinone, in the presence of hydrogen peroxide, reported in the literature, concerns the transformation of 7-aminooxazolyl-[5,6-*d*]pyrimidine into 6,8-dihydroxypurine in acetic acid medium [5].

The peculiar behavior of 1 with hydrogen peroxide, gave credence to the above mentioned hypothesis about the action mechanism of 17 β -AOS, and prompted us to accomplish a more detailed study on this subject which we report in this paper.

We found that β -hydroxyhydroperoxide 2 could also be obtained, in high yield, directly from 4-methylimidazolin-2-one (3) while from the unsubstituted imidazolin-2-one (4) and hydrogen peroxide, under more effective oxidizing conditions, we obtained *trans*-4,5-dihydroperoxyimidazolidin-2-one (5) (Scheme 1).

Scheme 1



These results seem to indicate that the rearrangement of 2-aminooxazole to the imidazolinone nucleus precedes the formation of the hydroperoxidic groups. *Trans* configuration of compound 5 was well established by 1H -nmr, in dimethylsulfoxide- d_6 (DMSO- d_6) (Table). In fact, the *in situ* reduction of 5 by DMSO [6] produces, at first, the related β -hydroxyhydroperoxide and, later on, the dihydroxy derivative. The former compound shows a singlet at δ 4.84 (5-H) and a doublet at *ca.* 4.88 (4-H, coupled with 4-OH) which, shaking with deuterium oxide, became sharp singlets at δ 4.86 and 4.89, respectively; the lack of the expected coupling found in the analogous *cis*-4,5-disubstituted imidazolidinones [7a,b] supports the *trans* structure.

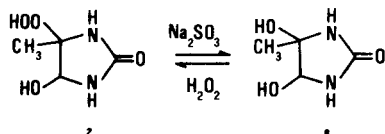
Whereas 2 crystallized by concentration of the reaction solution, from 4,5-dimethyl-2-aminooxazole (6) and hydrogen peroxide a product was obtained only after a complete evaporation of the solvent, namely under stronger oxidizing conditions) and it was shown to consist of 4,5-dihydroperoxy-4,5-dimethylimidazolidin-2-one (7). From tlc and proton decoupled ^{13}C -nmr spectrum, 7 appeared to be one of the two possible isomers and by analogy with 2 and 5 we assigned to it the *trans* structure. Therefore it seems probable that mono- or dihydroperoxides originate from a common 4,5-dihydroxyimidazolidinone intermediate, not isolated, accordingly with the oxidizing conditions. This is confirmed by the fact that the oxidation of 4,5-dihydroxy-4-methylimidazolidin-2-one (8), by hydrogen peroxide in the same procedure carried out for 1, afforded the expected β -hydroxyhydroperoxide 2 (Scheme 2).

Table
Key Spectral Data of Related Compounds

Compound	IR (potassium bromide cm ⁻¹) [a]					'H-NMR (DMSO-d ₆ , δ from tetramethylsilane) [b]							
	CO	OOH	4-CH ₃	5-CH ₃	4-H	5-H	4-OH [c]	5-OH [c]	1-H [c]	and	3-H [c]	4-OOH [c]	5-OOH [c]
2	1690 vs	842 m	1.29 (s, 3H)	—	—	4.86 [d] (d, 1H, J = 7.5 Hz)	—	5.85 (d, 1H, J = 7.5 Hz)	7.16 (s, 1H)	and	7.25 (s, 1H)	11.2 (s, 1H)	—
5 [e]	1700 vs	820 w	—	—	5.12 [f] (d, 2H, J _{NH} = 1 Hz)	—	—	—	—	7.7 (s, 2H)	—	11.26 (s, 2H)	—
7 [g]	1735 vs	848 m	1.33 (s, 6H)	—	—	—	—	—	—	7.21 (s, 2H)	—	11.18 (s, 2H)	—
8	1695 vs	—	1.24 (s, 3H)	—	—	4.6 [d] (d, 1H, J = 7.5 Hz)	5.47 (s, 1H)	5.69 (d, 1H, J = 7.5 Hz)	—	6.88 (s, 2H)	—	—	—
10 [h]	1730 vs	837 w	—	—	—	—	4.95 [i] (s, 1H)	—	6.88 (s, 1H)	and	6.96 (s, 1H)	—	11.19 [i] (s, 1H)

[a] vs = very strong; m = medium; w = weak. [b] s = singlet; d = doublet. [c] Exchanges with deuterium oxide. [d] Singlet with deuterium oxide. [e] In the DMSO-d₆ solution, after 15 hours at room temperature, ca. 50% (calculated on the basis of the integrated resonances) of the reduction product β -hydroxyhydroperoxide was formed: δ 4.84 (s, 1H, 5-H), ca. 4.88 (d, 1H, 4-H; partially overlapped by 5-H resonance; singlet with deuterium oxide and by irradiation at δ 6.07), 6.07 (d, 1H, J = 7.0 Hz, 4-OH), 7.3 and 7.5 (singlets, 2H, 1-H and 3-H), 11.15 (s, 1H, 5-OOH). After 42 hours **5** and β -hydroxy derivative were ca. 14% and 67%, respectively; 4,5-dihydroxy derivative (ca. 19%) was also formed: δ 4.63 (d, 2H, J = 6.4 Hz, 4-H and 5-H; s with deuterium oxide and by irradiation at δ 5.83), 5.83 (d, 2H, J = 6.4 Hz, 4-OH and 5-OH), 7.03 (s, 2H, 1-H and 3-H). [f] Singlet with deuterium oxide and by irradiation at δ 7.7. [g] The DMSO-d₆ solution, after 19 hours at room temperature, showed signals belonging to the β -hydroxy derivative (ca. 30%): δ 1.26 and 1.29 (singlets, 6H, 4- and 5-CH₃), 5.56 (s, 1H, 4-OH), 6.98 and 7.06 (singlets, 2H, 1-H and 3-H), 11.09 (s, 1H, 5-OOH). [h] In the ¹H-nmr spectrum CH₂ ring groups appeared as unresolved multiplets at δ 1.3-2. [i] In this compound locants for OH and OOH groups are 3a and 7a, respectively; after about 30 minutes at room temperature significant resonances related to dihydroxy derivative appeared at δ 5.08 (3a-OH and 7a-OH) and 6.68 (1-H and 3-H).

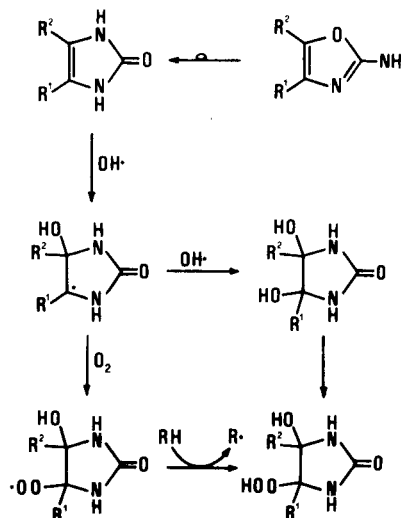
Scheme 2



Isolation of the *trans* isomers of compounds **2** and **5** could suggest this reaction to occur *via* a *trans* opening of an oxirane intermediate. However, 4,5-dihydroxyimidazolidinones are reported to undergo *cis-trans* isomerization [7a,8]. Performing the same reaction on 2-amino-4,5,6,7-tetrahydrobenzoxazole (**9**), which cannot furnish a *trans* adduct, we obtained smoothly *cis*-3a-hydroxy-7a-hydroperoxyoctahydro-2H-benzimidazolidin-2-one (**10**) (Scheme 1). A radical mechanism for the peroxidation is probably involved, as it was strongly suggested by the reaction of **1** with hydrogen peroxide in the presence of Fe²⁺ (Fenton's reagent) [3]. Literature data report the action of the OH[•] species on pyrimidine bases [9]. In this case hydroperoxides are formed, which are stable substances in aqueous solution. An analogous mechanism may be invoked for our compounds (Scheme 3).

A significant analogy exists in particular between our hydroperoxides and the thymine derivative, that is the most stable one [9]. Cytosine γ -radiolysis in oxygen saturated aqueous solution also afforded *cis*- and *trans*-1-car-

Scheme 3

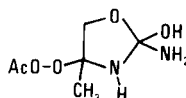


bamoyl-4,5-dihydroxyimidazolidin-2-one, susceptible to further oxidation even under mild conditions [7a].

Thoroughly examining the reaction of **1** with hydrogen peroxide we could also ascertain that, together with **2**, acetylurea and carbon dioxide [2], another product was formed, though in a very low yield (about 2%). The yield reached 6% when the reaction was quenched after only 6 hours (instead of 18 hours). This compound was tested for the presence of peroxide groups [10] giving a strongly positive

reaction, but no signals assignable to hydroperoxidic protons could be detected in the ^1H -nmr spectrum (DMSO-d_6). The strong absorption at 1730 cm^{-1} , in the ir spectrum, together with the singlet at $\delta\ 1.91$ (3H) in the pmr spectrum suggests the presence of a $-\text{COCH}_3$ group. The 4-CH_3 resonance is found at $\delta\ 1.31$ while a broad resonance between $\delta\ 6.3\text{--}7.5$ is originated from four exchangeable protons. The AB system at $\delta\ 3.88$ and $\delta\ 4.35$ can be attributed to the $\text{C}(5)\text{H}_2$ protons of an oxazolidine nucleus [11]. Very weak resonances are also present in the ^1H -nmr spectra belonging to the 4-CH_3 , 5-H and 2-NH_2 groups of the parent 2-amino-4-methyloxazole (**1**) [1]. These signals grow up with time and after 4 hours only compound **1** can be detected together with signals at $\delta\ 1.29$ (2H), $3\text{--}4$ (2H, exchange with deuterium oxide) and $9.9\text{--}10.5$ (1H, exchanges with deuterium oxide). The whole data strongly suggest for this compound the structure of 2-amino-2-hydroxy-4-methyl-oxazolidin-4-yl peroxyacetate (**11**).

Figure 2



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This compound is stable only in the solid state but decomposes in solution; in DMSO it loses water and peroxyacetic acid re-establishing the parent **1**. Efforts to determine molecular weight by mass spectroscopy failed; however, with direct electron impact (DEI) technique [12], the fragmentation pattern [m/e at 98 (**1**), 60 and 34] indirectly confirmed the structure. Finally analytical data are in perfect agreement for the proposed formula. The presence of small quantities of peroxyacetic acid during the reaction of **1** with hydrogen peroxide is due to the formation of acetic acid among the products of fragmentation of the heterocyclic nucleus. When this reaction was carried out in the presence of acetic acid, at 0° , it rapidly proceeded affording **11** in 20% yield; hydroperoxide **2** could not be isolated.

EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are uncorrected. The ir spectra were measured with a Perkin-Elmer model 281 instrument for potassium bromide discs. The nmr spectra were obtained with a Perkin-Elmer R-32 instrument operating at 90 MHz for ^1H and with a Varian FT-80A spectrometer operating at 20 MHz for ^{13}C -nmr spectra (TMS as internal standard). Mass spectra (DEI) were recorded on a VG Micromass ZAB-2F instrument operating at 70 eV or on a VG 7070-EQ, using fast atom bombardment (FAB) technique [13], with argon beam at 7 KeV (1 mA) (the samples were dissolved in thioglycerol). The reactions were checked on tlc silica gel F_{254} (Merck) using methylene dichloride-methanol (10:2) as solvent and spraying the chromatograms with a solution of dichloroquinonchloroimide in ethanol [1]; hydroperoxides were detected with potassium iodide/acetic acid reagent [10].

General Procedures.

Compounds **2**, **5**, **7**, and **10** have been prepared by mixing the solution of 2-aminoxazoles or imidazolones with 2.2.5 equivalents of 36% hydrogen peroxide at room temperature. Nitrogen was fluxed into the solutions of 2-aminoxazoles, the evolved carbon dioxide collected in aqueous barium hydroxide and determined as barium carbonate.

4-Methylimidazolin-2-one (**3**).

The product was prepared from aminoacetone hydrochloride and potassium cyanate according to the literature [14], mp $198\text{--}200^\circ$ dec (sealed tube), lit mp $185\text{--}188^\circ$ and $202\text{--}204^\circ$ (*in vacuo*) [14].

r-4-Hydroperoxy-*t*-5-hydroxy-4-methylimidazolidin-2-one (**2**) from **3**.

The parent compound (**1** g) was suspended in 6 ml of 95% ethanol-methanol (2:1) mixture. After 6 hours the reaction solution was concentrated under reduced pressure, acetone was added and the small amount of precipitate discarded. Concentration of the remaining solution and repeated addition of acetone afforded 0.7 g (80%) of crude **2**. Crystallization from 95% ethanol gave a product with mp and spectroscopic data in accordance with those of an authentic sample obtained from **1** [4].

Imidazolin-2-one (**4**).

The compound was prepared following the reported method [15], mp colors at 223° , red liquid at $237\text{--}240^\circ$ (lit colors at 225° , red liquid at $250\text{--}251^\circ$) [15].

Anal. Calcd. for $\text{C}_3\text{H}_4\text{N}_2\text{O}$: C, 42.85; H, 4.79; N, 32.32. Found: C, 43.07; H, 4.78; N, 33.38.

trans-4,5-Dihydroperoxyimidazolidin-2-one (**5**).

A solution of 0.103 g (1.2 mmol) of **4** in 6 ml of methanol was allowed to evaporate for two months. The oily residue was cooled at 0° ; the crystalline precipitate was washed with cold acetone and ether, affording 0.056 g (30%) of pure **5**, mp $129\text{--}130^\circ$ dec; ir: 3400 , 3340 , 3200 , 2820 , 1700 , 820 cm^{-1} .

Anal. Calcd. for $\text{C}_3\text{H}_6\text{N}_2\text{O}_5$: C, 24.0; H, 4.03; N, 18.66. Found: C, 24.25; H, 4.20; N, 18.93.

trans-4,5-Dihydroperoxy-4,5-dimethylimidazolidin-2-one (**7**).

2-Amino-4,5-dimethyloxazole (**6**) (1.49 g, 12.2 mmol), prepared following the reported procedure [1], in 6 ml of 95% ethanol, was allowed to react for 5 hours. The evolved carbon dioxide was 13% of the amino-oxazole (molar ratio). The reaction solution was concentrated under diminished pressure to a reduced volume and, by chilling at 0° , *N*-acetylurea precipitated (60 mg, 4.4%), identified by ir and ^1H -nmr spectra; the remaining solution was evaporated to dryness *in vacuo* and the residue was treated with acetone and the precipitate collected. This treatment was repeated four times. The product was recrystallized from anhydrous ethanol (0.51 g, 22% overall yield), mp $121.5\text{--}122^\circ$ dec; ir: 3435 , 3370 , 3320 , 3270 , 2820 , 1735 , 1656 , 848 cm^{-1} ; ^{13}C -nmr (deuterium oxide): $\delta\ 17.71$ (4- and 5- CH_3), 97.25 (C-4 and C-5), 163.81 (C-2); ms (FAB): 179 ($[\text{MH}]^+$), 163 ($[\text{MH}-16]^+$), 145 ($[\text{MH}-\text{H}_2\text{O}_2]^+$).

Anal. Calcd. for $\text{C}_5\text{H}_{10}\text{N}_2\text{O}_5$: C, 33.7; H, 5.66; N, 15.72. Found: C, 34.09; H, 5.61; N, 15.65.

trans-4,5-Dihydroxy-4-methylimidazolidin-2-one (**8**).

Sodium sulphite (1 mmol) in water was added to an aqueous solution of **2** (1 mmol). After 30 minutes the solution was poured in ethanol, filtered and the solvent evaporated to dryness *in vacuo*. The residue was treated with acetone. The crude solid (22%) was crystallized from acetone-methanol saturated at $45\text{--}50^\circ$, mp $128\text{--}129^\circ$ dec; ir: $3700\text{--}3000$, 1695 cm^{-1} .

Anal. Calcd. for $\text{C}_4\text{H}_8\text{N}_2\text{O}_3$: C, 36.36; H, 6.10; N, 21.20. Found: C, 36.22; H, 6.12; N, 21.14.

Oxidation of **8** with Hydrogen Peroxide.

From the 4,5-dihydroxy derivative, carrying out the reaction as previously described for **1** [5] we obtained 64% of the β -hydroxyhydroperoxide **2**, identified on the basis of mp and spectroscopic data.

cis-3a-Hydroxy-7a-hydroperoxyoctahydro-2*H*-benzimidazolidin-2-one (**10**).

A solution of 0.6 g (4.34 mmoles) of **9** (prepared according to ref [16]) in 11 ml of methanol was allowed to react for 18 hours. The evolved carbon dioxide was 17% of the aminooxazole (molar ratio). The solution was then concentrated under diminished pressure and the collected precipitate was washed with 95% ethanol which was added to the mother solution. This procedure was repeated twice, affording 0.31 g (38% overall yield) of **10**, mp 125.5-126° dec (from 95% ethanol); ir: 3460, 3270, 3100, 2950, 2880, 2800, 1730, 837 cm⁻¹; ms (FAB): 189 ([MH]⁺), 173 ([MH-16]⁺), 155 ([MH-H₂O₂]⁺).

Anal. Calcd. for C₇H₁₂N₂O₄: C, 44.67; H, 6.43; N, 14.89. Found: C, 44.80; H, 6.30; N, 15.02.

2-Amino-2-hydroxy-4-methyloxazolidin-4-yl Peroxyacetate (**11**).

A mixture of 1.4 ml (15 mmoles) of 36% hydrogen peroxide and 0.42 g (7.35 mmoles) of glacial acetic acid, at 0°, was added dropwise to a solution of 1.4 g (14.3 mmoles) of **1** in 5 ml of water, under nitrogen fluxing and cooling by ice. After 40 minutes the precipitate was collected; recrystallization was performed by cooling at 0° a methanolic solution saturated at 30-40° (0.56 g, 20%), mp 118-118.5° dec; ir: 3500-2100, 1730 cm⁻¹; ms (DEI): 177 ([M-15]⁺, 1), 149 (10), 98 (100), 60 (70), 34 (1); ¹H-nmr (DMSO-d₆): δ 1.31 (s, 3H, 4-CH₃), 1.91 (s, 3H, COCH₃), 3.88 and 4.35 (AB system, 2H, 5-H₂, J = 9 Hz), 6.3-7.5 (4H, 2-OH, 2-NH₂ and 3-H; exchanges with deuterium oxide) [the relative intensities account of the small signals detectable at δ 1.86, 6.99 and 6.4; after 4 hours these resonances only are present together with signals at δ 1.90 (s, 3H, COCH₃), 3-4 (2H; exchanges with deuterium oxide), 9.9-10.5 (1H, carboxylic acid; exchanges with deuterium oxide)].

Anal. Calcd. for C₆H₁₂N₂O₅: C, 37.49; H, 6.29; N, 14.58. Found: C, 37.23; H, 6.01; N, 14.59.

Compound **11** was also isolated from the reaction of **1** with hydrogen peroxide [5], stopping it after 6 hours. By concentration of the reaction solution and addition of cold ethanol, crystalline **11** was obtained. The remaining solution was evaporated *in vacuo* to dryness and the residue treated twice with cold ethanol affording 5.8% of **11** (overall yield). Hydroperoxide **2** was also isolated in 25% yield.

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