Synthesis, Structure, and Potential Biological Implications of *r*-4-Hydroperoxy-*t*-5-hydroxy-4-methylimidazolidin-2-one

Gianfranco Rapi,*[a] Mario Chelli,[a] Mauro Ginanneschi,[a] Donato Donati,[b] and Antonio Selva[c]

[a] *Cattedra di Chimica e Propedeutica Biochimica, Facoltà di Medicina e Chirurgia, and Centro C.N.R. per lo Studio della Chimica e la Struttura dei Composti Eterociclici e loro Applicazioni, c/o Istituto Interfacoltà di Chimica Organica, via G. Capponi 9, I-50121 Firenze, Italy*

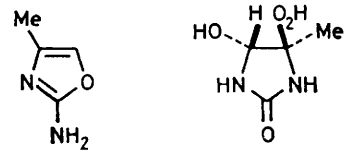
[b] *Istituto di Chimica Organica dell'Università, Siena, Italy*

[c] *Istituto di Chimica del Politecnico, Centro C.N.R. per lo Studio delle Sostanze Organiche Naturali, Milano, Italy*

The reaction of 2-amino-4-methyloxazole, a topical anti-inflammatory agent, with hydrogen peroxide gave the title compound which was characterised by ^{1}H n.m.r., i.r., and mass spectroscopy, and *X*-ray crystallography.

We describe here a facile stereoselective synthesis, from 2-amino-4-methyloxazole (**1**), of a quite stable β-hydroxy-hydroperoxide, identified as racemic *r*-4-hydroperoxy-*t*-5-hydroxy-4-methylimidazolidin-2-one (**2**). β-Hydroperoxides have been prepared previously with difficulty by *X*-ray irradiation[1] and by other, more complicated methods.[2] With regard to the isomerisation of the oxazole nucleus, analogous rearrangements of amino-oxazoles and imino-oxazolines to the more stable imidazolin-2-ones have been reported.[3]

Special interest in this reaction arises from its possible biological implications. Many 2-amino-oxazoles derivatives are anti-inflammatory agents;[4] we have already reported the synthesis and structure of several 17β-(2-amino-oxazol-4-yl)-steroids (A.O.S.),[3b,5,6] together with an account of their pharmacological properties.[7] The A.O.S. are much more potent as topical anti-inflammatory agents than (**1**), they lack corticoid activity, and do not inhibit *in vitro* prostaglandin (PG) synthesis. These results led to suggestions that substances distinct from PGE and PGF, namely the hydroperoxides which are involved in the biosynthesis of PGs, thromboxanes, and other natural lipids, might be mediators or agents of the inflammatory process.[8] Our work implies that the steroidal moiety of the A.O.S. acts essentially as a carrier for the amino-oxazole residue. The heterocyclic part can then interact, intracellularly, with natural hydroperoxides (or related oxidising species) involved in the inflammatory process, to form the corresponding, stable, hydroperoxides.



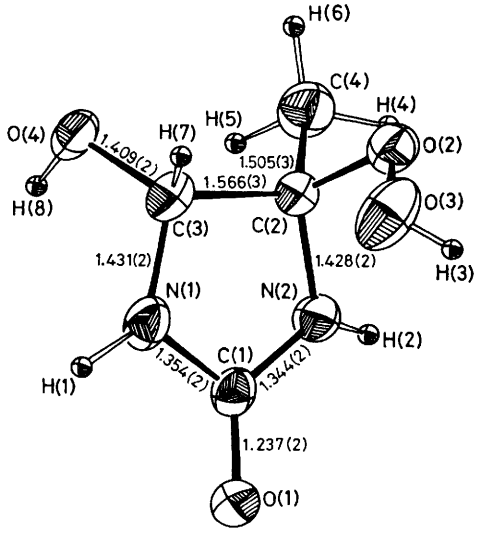


Figure 1. ORTEP view of the structure of (**2**) with bond lengths in Å. Selected bond angles: N(1)–C(1)–N(2) 108.7(1), C(1)–N(2)–C(2) 113.0(1), N(2)–C(2)–C(3) 102.3(1), C(2)–C(3)–N(1) 102.8(1), N(2)–C(2)–O(2) 111.4(1), N(2)–C(2)–C(4) 114.6(2), N(1)–C(3)–O(4) 112.5(2)°.

Compound (**2**) was prepared from (**1**) (ref. 5) with 35% H_2O_2 (2 mol. equiv.) in water or aqueous EtOH (room temp., for 12 h). CO_2 was evolved, and the product (**2**) precipitated on concentration of the solution *in vacuo*; it had m.p. 143.5 °C (decomp.) (from absolute EtOH, 26% overall yield). From the mother liquors we isolated *N*-acetylurea (7% yield) (m.p. 218 °C, from acetone; lit.[9] 218—219 °C from EtOH; ^{1}H n.m.r. and i.r. data in accordance).

Preliminary experiments showed that when the reaction is carried out in the presence of catalysts such as Fe^{2+} or Fe^{2+}–ethylenediaminetetra-acetic acid it is strongly exothermic and becomes explosive if not controlled, affording *N*-acetylurea and CO_2 but not the hydroperoxide.

The 90 MHz ^{1}H n.m.r. spectrum of (**2**) [$(CD_3)_2SO$] showed resonances at δ 1.29 (s, 3H, 4-Me), 4.86 (d, *J* 7.5 Hz, 1H, 5-H), 5.85 (d, *J* 7.5 Hz, 1H, 5-OH), 7.16 (s, 1H, NH), 7.25 (s, 1H, NH), and 11.2 (s, 1H, 4-OOH);[10] ν_{max} (KBr, cm^{-1}): 3330, 3260, 3140, 2830, and 1690 (CO) (1720 in Me_2SO solution); 1128 and 843 (OOH).[2b] The mass spectrum† did not show a detectable M^+ peak (*m/z* 148), but did show very weak peaks at *m/z* 147 and 149, together with other characteristic fragments. Of particular diagnostic value for the hydroperoxide function is the peak due to $[H_2O_2]^{+\cdot}$ at *m/z* 34 [5—10% relative to *m/z* 43 (100%)].

The crystal structure of (**2**) has been established by *X*-ray diffraction using direct methods and Fourier difference techniques of the SHELX 76 program system,[11] and was refined anisotropically for non-hydrogen atoms and isotropically for hydrogen atoms, to a final *R*-factor of 4.6%.‡

† Direct electron impact (P. Traldi, *Org. Mass Spectrom.*, 1982, **17**, 245); VG Micromass ZAB-2F instrument, 70 eV (200 μA), ion source heating switched off in order to maintain the temperature under 100 °C.

‡ *Crystal data:* $C_4H_8N_2O_4$, M = 148.12, monoclinic, space group $P2_1/n$, a = 9.128(4), b = 8.458(3), c = 8.142(4) Å, β = 95.17(3)°, U = 626.04 Å^3, Z = 4, D_c = 1.57 g cm^{-3}, $F(000)$ = 312.0, graphite monochromated Mo-K_α radiation, λ = 0.710 69. The 946 reflections [$I \geq 3\sigma(I)$] having $2\theta \leq 50°$ were measured with a fully automated Philips PW 1110-2 diffractometer. The observed decrease in intensity of three independent standard reflections (10%), was used to correct the remaining intensity data.

The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

Table 1. Interatomic distances (Å) and angles (°) for the hydrogen bonds.[a]

	O–O or O–N distance	O (or N)–H · · · O angle
O(3)–H(3) · · · O(1) (i)	2.685	178
O(4)–H(8) · · · O(1) (ii)	2.788	168
N(2)–H(2) · · · O(4) (iii)	2.904	173
N(1)–H(1) · · · O(2) (iv)	2.938	149

[a] (i)—(iv) denote the following symmetry operations: (i) $(1-x, -y, 1-z)$; (ii) $(1-x, -y, -z)$; (iii) $(\frac{1}{2}-x, \frac{1}{2}+y, \frac{1}{2}-z)$; (iv) $(\frac{1}{2}-x, y-\frac{1}{2}, \frac{1}{2}-z)$.

The hydroperoxy- and hydroxy-groups are in a *trans* configuration (Figure 1). The imidazolidinone ring is essentially planar, the maximum deviation from the least-squares plane through the ring atoms being 0.12 Å, for C(1).

The geometry of the hydroperoxy-group is given by: C(2)–O(2) 1.438(2), O(2)–O(3) 1.470(2), O(3)–H(3) 0.81(4) Å; ∠C(2)–O(2)–O(3) 108.2(1), O(2)–O(3)–H(3) 97(3)°; dihedral angle C(2)–O(2)–O(3)–H(3) 113°. These values agree with earlier results.[12]

Interatomic distances and angles for the intermolecular hydrogen bonds are shown in Table 1. The packing of the molecules and consequently the relatively high density of the crystal depend on these hydrogen bonds, the strongest of which involves the hydroperoxy hydrogen atom.

Received, 11th August 1982; Com. 957

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