# SYNTHESIS AND CRYSTAL AND MOLECULAR STRUCTURE OF A PULEGONE ISOXAZOLE DERIVATIVE

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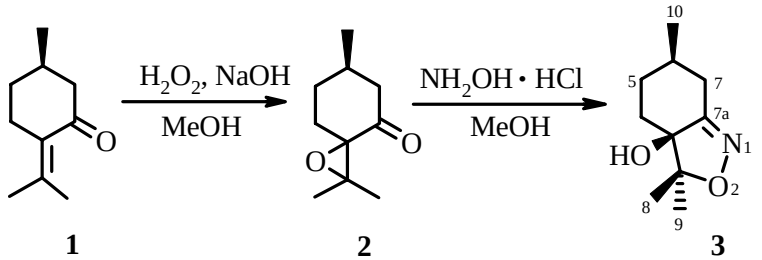
We continued work on chemical transformations of pulegone (**1**), which we have used previously in the two-step synthesis of its pyrazole derivative [1] that is analogous to the pyrazole derivative of artemisin ketone [2], in order to prepare biologically active compounds.

Compound **1** is a monocyclic unsaturated monoterpenoid of the paramenthane series and the principal component of essential oils of *Ziziphora clinopodioides* Lam. (47-60% pulegone content) [3] and *Mentha longifolia* L. (40-70% pulegone content) [4].

**$\Delta^{4(8)}$-*p*-Menthen-3-one (pulegone, 1)** was isolated by vacuum fractionation of *Z. clinopodioides* essential oil, bp 94-95.5°C/10 mm Hg, $[\alpha]_D^{26.3}$ +23.94° (*c* 0.026, $CHCl_3$).

**2,2,6-Trimethyl-1-oxaspiro[2,5]octan-4-one (pulegone epoxide, 2)** was prepared by the following method [5]: **1** (5 g) was dissolved in MeOH (40 mL), treated with $H_2O_2$ (5 mL), stirred, and treated in small portions over 1 h with NaOH solution (3.75 mL, 4%). The reaction mixture was extracted three times with ether. The combined extracts were dried over $MgSO_4$ and evaporated in vacuo to produce **2** (4 g, 80%) as colorless crystals, mp 43-45°C, $[\alpha]_D^{20}$ +10.28° (*c* 0.020, $CHCl_3$).




**1** **2** **3**

**3,3,6-Trimethyl-4,5,6,7-tetrahydrobenz[*c*]isoxazol-3a-ol.** Compound **2** (1 g) was dissolved in MeOH (5 mL) and treated with $NH_2OH \cdot HCl$ (5 g) and $CH_3COONa$ (10 g) dissolved in distilled water (15 mL). The resulting mixture was refluxed for 1 h. The product was precipitated by adding a large amount of cold water. The resulting crystals were separated by filtration and recrystallized from alcohol to give **3** (0.86 g, 86%) as colorless crystals, $C_{10}H_{17}NO_2$, mp 138-139.5° ($CHCl_3$), $[\alpha]_D^{15.6}$ +3.31° (*c* 0.016, $CHCl_3$).

PMR spectrum (δ, ppm, J/Hz): 1.78 (ddd, H-4a, J = 14.0, J = 3.0, J = 3.0), 1.66 (m, H-4b, overlaps with H-5a), 1.64 (m, H-5a, overlaps with H-4b), 1.49 (m, H-5b, overlaps with H-6), 1.54 (m, overlaps with H-5b), 2.61 (br.d, H-7a, J = 14.5), 2.02 (dd, H-7b, J = 14.5, J = 12.0), 1.35 (s, 3H), 1.14 (s, 3H), 1.04 (d, 3H, J = 6.0), 1.97 (br.s, OH).

$^{13}C$ NMR spectrum (δ, ppm): 85.81 (s, C-3), 83.47 (s, C-3a), 30.76 (t, C-4), 29.35 (t, C-5), 32.32 (d, C-6), 30.97 (t, C-7), 161.41 (s, C-7a), 23.52 (q, C-8), 19.68 (q, C-9), 21.72 (q, C-10).

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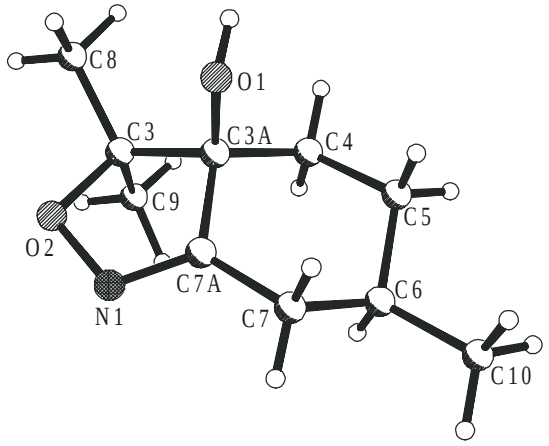


Fig. 1. Molecular structure of the pulegone isoxazole derivative from XSA.

The molecular structure of **3** was determined by an x-ray structure analysis (XSA) (Fig. 1). Cell constants and intensities of 1160 reflections from **3** were measured on a Syntex $P2_1$ diffractometer at 20°C (Cu Kα, graphite monochromator, θ/2θ-scanning, 2θ ≤ 140.26°). The crystals are orthorhombic, $a$ = 5.7560(12), $b$ = 10.811(2), $c$ = 16.584(3) Å, V = 1032.0(4) Å$^3$, $d_{calc}$ = 1.179 g/cm$^3$, $Z$ = 4 ($C_{10}H_{17}NO_2$), space group $P2_12_12_1$. The structure was solved by direct methods using the SHELXS-97 programs. Nonhydrogen atoms were refined by full-matrix anisotropic least-squares methods; H atoms found from a difference synthesis, isotropically using the SHELXL-97 programs. The final agreement factors were R = 0.0366 and wR = 0.0860 for 1013 independent reflections with $I \geq 2\sigma$.

Figure 1 shows that the six- and five-membered rings are fused in a pseudotrans manner (torsion angles C3C3aC7aN1 = -16.7°, C7C7aC3aC4 = 41.2°). The conformation of the five-membered ring is a 3α-envelope ($\Delta C_S^3$ = 1.4, C3a, C7a, N1, and O2 are coplanar within ±0.008 Å, C3 deviates from this plane by 0.41 Å to the α-side). The C3a hydroxyl has the β-orientation. The conformation of the six-membered ring is a distorted chair ($\Delta C_2^{65}$ = 3.3°). The C6 methyl has the β-orientation. Based on these data, the structure 3,3,6-trimethyl-4,5,6,7-tetrahydrobenz[*c*]isoxazol-3a-ol is proposed for **3**.

The XSA data were deposited as a CIF file in the Cambridge Crystallographic Database (CCDC 263000).

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