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SYNTHESIS AND CRYSTAL STRUCTURE OF PYRAZOLINE DERIVATIVE OF PULEGONE

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Abstract- An interesting pyrazoline derivative, 3,3-dimethyl-*3H*-pyrazo[4,5-2'(*S*)-methyl] cyclohexane-1,2-dioxide (**3**), has been obtained by the transformation of monoterpene ketone, pulegone (**1**) using hydroxylamine hydrochloride and sodium nitrite through a stable intermediate (**2**).

INTRODUCTION

Pulegone (**1**), a monoterpene ketone, is the main component of essential oil of the *Ziziphora* species, and its content in the essential oil varies from 20 to 87%.[1-6] This monoterpene and its isomers had been utilized as chiral building blocks for the total synthesis of natural compounds.[7-11] (*R*)-(+)-Pulegone (**1**) had been used for the synthesis of pheromones.[12,13] Synthetically useful sulfones have also been obtained from this monoterpene.[14] The four possible *cis*- and *trans*-isomers of the odiferous thioketone have been synthesized from each of (+)-pulegone and its three other enantiomers.[15] On the basis of (+)-pulegone several thio alcohols were synthesized which had been utilized for the optical resolution.[16] In order to investigate the biological activities of pulegone derivatives we synthesized a new pyrazoline derivative of this monoterpene.

RESULTS AND DISCUSSION

Pulegone (**1**) was transformed to 3,3-dimethyl-*3H*-pyrazo[4,5-2'(*S*)-methyl]cyclohexane-1,2-dioxide (**3**) using a two-step synthetic strategy (Scheme **1**). In the first step, pulegone (**1**) was treated with hydroxylamine hydrochloride to yield a stable intermediate, an oxime (**2**). In the second step, treatment of intermediate (**2**) with sodium nitrite resulted in the formation of **3**.

The HREI MS of compound (**3**) showed the M^+ at *m/z* 196.1212, corresponding to the molecular formula $C_{10}H_{16}N_2O_2$ (calcd 196.1211) indicating the presence of four degrees of unsaturation in the molecule. Its MS spectrum displayed the base peak at *m/z* 43 (100%). The UV spectrum of **3** in ethanol exhibited absorptions at 219 and 315 nm. The IR spectrum of **3** showed strong absorptions at 1452 and 1372 cm^{-1} which were due to *N*-oxide stretching vibrations. The ^1H-NMR ($CDCl_3$, 500 MHz) spectrum of **3** displayed five multiplets at δ 1.41, 1.91, 2.27, 2.64 and 2.02 which were assigned to H-2′, H_2-1′, H_2-4′, Hα-3′ and Hβ-3′, respectively. The C-3 geminal methyls resonated as a 6H singlet at δ 1.47, whereas the CH_3-2′ resonated as a doublet at δ 1.09 (*d*, $J_{7',2'}$ = 6.5 Hz).

The structure of compound (**3**) was unambiguously determined by single crystal X-Ray diffraction studies. A suitable crystal with dimensions 0.25 x 0.33 x 0.30 mm^3 was selected for diffraction studies. Monochromated CuKα radiations (1.54178 Å) were used and 1490 reflections were collected. The structure was solved by direct methods to a final discrepency index of 5.2%. The computer-generated perspective view of **3** is presented in Figure **1**. The bond lengths in the molecule were close to the mean statistical values.[17] The conformation of the six-membered ring was found to be half-chair. The methyl group attached to atom C-2′ was in an equatorial orientation. The five-membered ring was found to be planar with accuracy ±0.02 Å. The CH_3-5′, CH_3-6′, O1 and O2 were out of plane by -1.18, 1.36, 0.06 and –0.04 Å, respectively. The bond lengths between N1-O1, N2-O2 and N1-N2 were found to be 1.264, 1.257 and 1.328 Å, respectively.

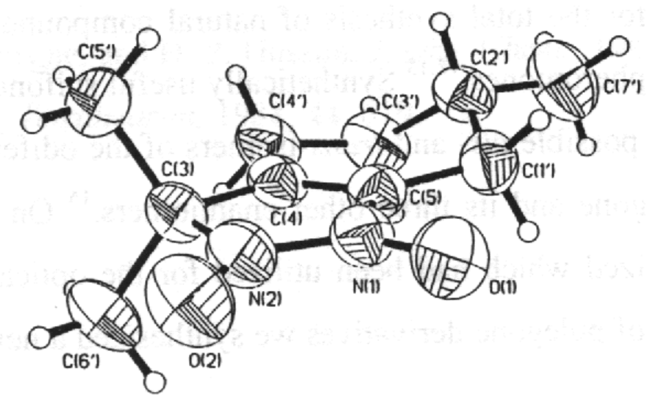
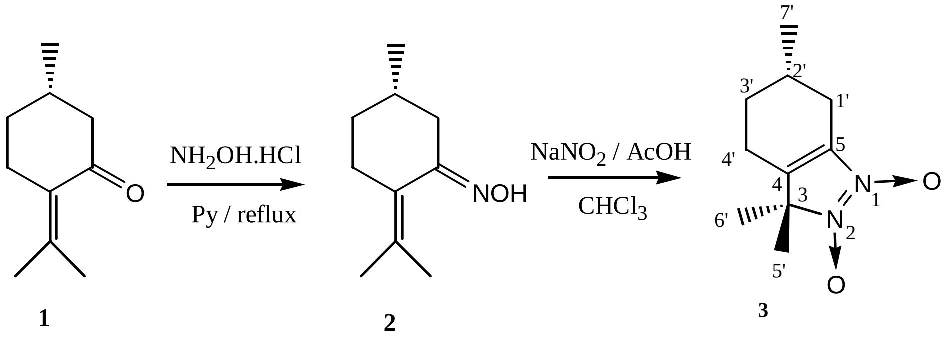


Figure1:A computer generated ORTEP drawing of **3**.



Scheme 1: Conversion of pulegone (**1**) to 3,3-dimethyl-*3H*-pyrazo[4,5,2'(*S*)-methyl]-cyclohexane-1,2-dioxide (**3**) *via* oxime (**2**).

EXPERIMENTAL

General Experimental Procedures: Melting points were determined by using Boetius melting point apparatus. The IR spectra were recorded on Vector 22 spectrophotometer. The UV spectrum was measured on a Specord UV-VIS spectrophotometer. The EI and HREI MS were recorded on Finnigan MAT 8200 mass spectrometer. The ^{1}H-NMR spectra were recorded on Bruker DRX-500 using standard Bruker programs data system at 500 MHz. X-Ray diffraction measurements were carried out on a Nicolet P4 diffractometer and the structure was solved by SHELXTL program. The full crystallographic data have been deposited at the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, U. K.

Materials: Hydroxylamine hydrochloride, pyridine, sodium nitrite and other chemicals were purchased from “Moskhimreactiv” (USSR).

Pulegone (**1**): This was isolated from the essential oil of *Ziziphora clinopodioides* which was collected from Dogalan village of Semipalatinsk region of Kazakhstan during August, 1999 according to the procedure described in the literature.[6] The yield of essential oil from aerial parts of the plant was found to be 0.42 % and the content of pulegone (**1**) in the essential oil was found to be 52% according to the GLC analysis. $[\alpha]_D^{27}$ +28° (c; 0.2, EtOH).

Oxime of pulegone (**2**): 0.5 g (7.0 mmol) of $NH_2OH.HCl$ was added to a solution of 1.0 g (6.49 mmol) of pulegone (**1**) in 5 mL of pyridine. The reaction mixture was refluxed for 1 h. After complete conversion of the starting ketone, which was monitored by periodic TLC examination, the reaction mixture was cooled to rt and was added to a stirred mixture of 20 mL of Et_2O and 20 mL of H_2O. The organic layer was washed with 5% HCl, dried over Na_2SO_4 and finally evaporated under vacuum. The residue was subjected to chromatographic separation on silica gel column using petroleum ether:EtOAc (95:5) which afforded 0.79 g (72%) of the an oxime (**2**) as a yellow oil.

3,3-Dimethyl-*3H*-pyrazo[4,5-2’(*S*)-methyl]cyclohexane-1,2-dioxide (**3**): Powdered $NaNO_2$ (0.402 g, 6 mmol) was added to a solution of 0.5 g (2.96 mmol) of oxime (**2**) in 10 mL of $CHCl_3$. Then under stirring of the reaction mixture, 2 mL of AcOH was added in small portions during 1 h at rt. After completion of the reaction, which was monitored by TLC examination, mixture was washed with 5% aqueous solution of $NaHCO_3$ and dried over Na_2SO_4. The solvent was removed under vacuum and the residue was chromatographed on silica gel column using petroleum ether-EtOAc (8:2) as the solvent system, which afforded 0.383 g (66%) of colorless crystalline compound (**3**), mp 118-120 °C (EtOAc was used for recrystallization). The procedure is modified in comparison with the literature.[18]

IR ν_{max} (KBr): 1452, 1372, 906, 818, 687 cm^{-1}; UV λ_{max} (EtOH): 219 (log ε = 3.98) and 315 (log ε = 3.70) nm; $[\alpha]_D^{27}$ +13° (c; 0.01, EtOH); ^{1}H-NMR ($CDCl_3$, 500 MHz): 2.64 (1H, *m*, $H\alpha$-3′), 2.02 (1H, *m*, $H\beta$-3′), 1.47 (6H, *s*, 2 x CH_3-3), 1.41 (1H, *m*, H-2′), 1.91 (2H, *m*, H-1′), 1.09 (3H, *d*, *J* = 6.5 Hz, CH_3-2′); ^{15}N-NMR ($CDCl_3$, 36.13 MHz): δ 310.3 (N-1), 303.4 (N-2); HREI MS: *m/z* 196.1212, $C_{10}H_{16}N_2O_2$ (calcd 196.1211); EI MS: *m/z* 196 (18), 166 (4), 150 (2), 124 (10), 121 (3), 98 (40), 93 (11), 91 (15), 79 (7), 77 (17), 69 (57), 67 (11), 56 (10), 55 (31), 53 (13), 43 (100), 41 (71), 39 (16) and 29 (12).

X-Ray crystallography of 3,3-dimethyl-*3H*-pyrazo[4,5-2'(*S*)-methyl]cyclohexane-1,2-dioxide (**3**):
This compound was crystallized from ethyl acetate solution by slow solvent evaporation. A crystal with dimensions 0.25 x 0.33 x 0.30 mm^3 was selected for crystallographic measurements.

Molecular formula = $C_{10}H_{16}N_2O_2$, molecular mass = 196.25 a.m.u., crystal system = orthorhombic, space group = $P2_12_12_1$, unit cell dimensions: **a** = 5.953 (4) Å, **b** = 11.303 (7) Å, **c** = 15.857 Å, density = 1.222 mg/m^3, F (000) = 424, λ (CuKα) = 1.54178 Å. Unit cell dimensions were determined by least squares fit of 20 strong reflections measured at room temperature using CuKα radiation. X-Ray measurements were carried out on a Nicolet P4 diffractometer. The intensity data within 2θ range of 3.5-135° was collected at 293 (2) K. A total of 1490 reflections were recorded, of which 1335 reflections were observed on the basis of $I > 2\sigma(I)$. The structure was solved by direct method using SHELXTL program and refined by the full matrix least-squares calculations on F^2. All the hydrogen atoms were located from difference Fourier maps and included in the refinement at geometrically idealized positions with an over all isotropic thermal parameters. The final R and wR factors were 0.0526 and 0.1351, respectively. Crystal data for compound (**3**) is presented in Table **1**.

Table **1**. Crystal data and structure refinement for 3,3-dimethyl-3*H*-pyrazo[4,5-2'(*S*)-methyl]cyclohexane-1,2-dioxide (**3**).

Empirical formula	$C_{10}H_{16}N_2O_2$
Formula weight	196.25
Temperature	293 (2) K
Wavelength	1.54178 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 5.953(4) Å, alpha = 90°
	b = 11.303(7) Å, beta = 90°
	c = 15.857(11) Å, gamma = 90°
Volume, Z	1067.0 (12) Å^3, 4 molecules in unit cell
Density (calculated)	1.222 Mg/m^3
Absorption coefficient	0.699 mm^{-1}
F(000)	424
Crystal size	0.25 x 0.33 x 0.30 mm^3
θ Range for data collection	5 4.80 to 67.45°
Limiting indices	$-1 \leq I \leq 7-1 \leq k \leq 13, -1 \leq 1 \leq 19$
Reflections collected	1490
Independent reflections	1335 (R_{int} = 0.0721)
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1335 / 0 / 132
Goodness-of-fit on F^2	1.056
Final R indices [$I>2\sigma(I)$]	R1 = 0.0531, wR2 = 0.1393
R indices (all data)	R1 = 0.0556, wR2 = 0.1436
Absolute structure parameter	0.3 (5)
Extinction coefficient	0.012 (2)
Largest diff. peak and hole	0.192 and -0.200 eÅ^{-3}

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