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SYNTHESIS OF DERIVATIVES OF THE MONOTERPENOID PULEGONE

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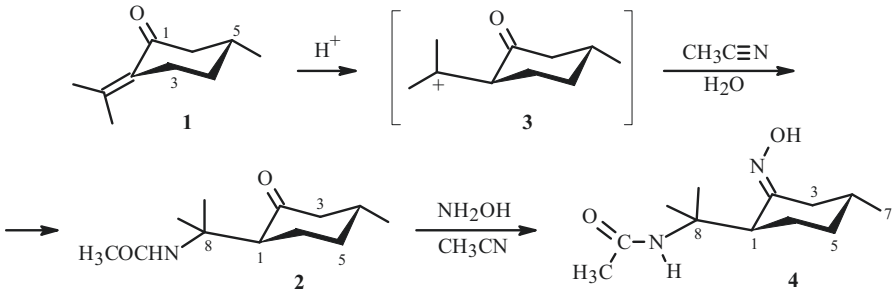
N-*containing derivatives that were promising as biologically active compounds were synthesized via a series of transformations of the monoterpenoid pulegone isolated from* Ziziphora clinopodioides *essential oil.*

Keywords: pulegone, ketoamide, oxime, *N*-containing derivatives.

Pulegone (**1**) is a monocyclic unsaturated ketone of the *p*-menthane series and the principal component of *Ziziphora clinopodioides* Lam. [1] and *Mentha longifolia* L. [2] essential oils.



Herein we present results for the synthesis of *N*-containing derivatives of **1** via a Ritter reaction with acetonitrile (MeCN) in the presence a catalytic amount of conc. H_2SO_4. Neutralization of the reaction mixture produced the ketoamide *N*-[2-(4-methyl-2-oxocyclohexyl)propan-2-yl]acetamide (**2**) in 56% yield and ~95% purity.

Obviously, the process occurred through formation of a tertiary carbonium ion (**3**) with subsequent addition to it of MeCN and formation of the amide. The reaction was strictly stereoselective and formed the pure ketoamide with both the methyl and isopropylamide in equatorial positions. The properties of synthesized **2** agreed with the literature for **2** prepared via intermolecular Ritter-type C–H amination of menthone [3].

Resonances in the PMR spectrum of **2** could not be fully assigned because of the mutual overlap of many of them. Nevertheless, the following conclusions could be drawn based on the spectrum.

The C-4 methyl appeared as a doublet at 0.94 ppm. The resonance for the proton geminal to this methyl was a complicated multiplet that appeared at even stronger field (δ 0.83 ppm), which indicated that it was axially oriented. Therefore, the ring did not invert during the reaction.

The C-8 methyls gave singlets, which indicated unambiguously that MeCN added to this C atom (and not C-1 as an alternative). The resonances of these methyls were distinctly nonequivalent (δ 1.17 and 1.33 ppm). This was consistent with hindered rotation around the C-1–C-8 bond that was obviously a consequence of the formation of a strong H-bond between the ketone and the acetamide (NH) H atom. The chemical shift of the acetamide methyl was 1.75 ppm.

Conversely, the ^{13}C NMR spectrum of **2** was easily interpreted. Resonances were assigned by comparing them with those in spectra of previously synthesized analogs. Their multiplicities were determined using DEPT data. Thus, the spectrum showed two weak-field singlets characteristic of carbonyl C atoms at 210.2 and 168.3 ppm (the ketone and amide, respectively). Doublets with chemical shifts 53.4 and 35.2 ppm were assigned to C-1 and C-4, respectively; triplets at δ 51.1, 33.5, and

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27.4 ppm, to C-3, C-5, and C-6. The spectrum also had four quartets for methyls (δ 21.8, 23.2, 23.3, and 24.5 ppm). The lack of a quartet near 16 ppm also indicated that the C-4 methyl was equatorial. A singlet associated with the acetamide C-8 appeared at 53.3 ppm.

The oxime of the ketoamide was synthesized using hydroxylamine in MeCN according to the method developed by us. NMR data established that the previously undescribed pure *N*-{2-[(1*S*,4*R*)-2-hydroxyimino-4-methylcyclohexyl]propan-2-yl}acetamide (**4**) formed in 41% yield and ~95% purity.

The PMR spectrum of **4** was just as difficult to interpret as the aforementioned one for the ketone analog. A weak-field doublet at 3.19 ppm that was characteristic of a pseudo-equatorial proton positioned near the oxime hydroxyl was identified. The appearance of this resonance argued in favor of the formation of the oxime *E*-isomer. The nonequivalence of the C-8 methyls (δ 1.27 and 1.45 ppm) indicating, as mentioned above, the formation of an intramolecular H-bond between the NH and oxime N atom provided indirect confirmation of this stereochemistry for the oxime. Such chelation would be problematical for the *Z*-isomer of the oxime.

The ^{13}C NMR spectrum had weak-field singlets with chemical shifts 168.9 and 157.8 ppm that were characteristic of an amide carbonyl and a C atom bonded to the oxime. Furthermore, the spectrum showed one singlet, two doublets, three triplets, and four quartets, the chemical shifts of most of which were similar to those of the ketone analog. The exception was a triplet for C-3, which appeared at much stronger field (34.5 ppm) than that of the ketone analog (51.1 ppm). This indicated that this atom was shielded by the oxime hydroxyl and confirmed its *E*-configuration.

EXPERIMENTAL

IR spectra were recorded from thin layers or KBr pellets on a Nicolet Protege-460 Fourier spectrophotometer. PMR and ^{13}C NMR spectra were recorded on a Bruker-Biospin Avance-500 spectrometer (operating frequency 500.13 and 125.77 MHz for ^{1}H and ^{13}C, respectively).

Elemental analyses of **2** and **4** agreed with those calculated.

Pulegone (2-isopropylidene-5-methylcyclohexanone) was isolated from essential oil of *Z. clinopodioides*, the aerial part of which was collected in Kordai District (in the vicinity of Gvardeiskii village), Jambyl Province, Republic of Kazakhstan, in June 2010 during flowering and fruiting. The yield of essential oil was 0.3%. A total of 21 constituents or 58.35% of all observed were identified. The principal constituents of *Z. clinopodioides* essential oil were pulegone (36.1%), 8-hydroxy-4(5)-*p*-menthen-3-one (10.27%), and isomenthone (6.02%).

Essential oil (40 g) was vacuum distilled. The fraction with bp 89–94°C/15 mm Hg was collected (14.4 g) and additionally purified by column chromatography using SiO_2 (compound–adsorbent ratio 1:15) and elution by petroleum ether to afford pulegone (10.1 g).

Pulegone (1), bp 89–94°C/10 mm Hg, $[\alpha]_D^{20}$ +22° (*c* 0.50, $CHCl_3$), n_D^{22} 1.4790, d_4^{20} 0.9357. IR spectrum (CCl_4, ν, cm^{-1}): 3466, 2958, 2927, 2873, 2851, 1738(C=O), 1711, 1679 (C=C), 1620, 1552, 1456, 1437, 1419, 1373,1335, 1287, 1264, 1240, 1209, 1128, 1092, 1074, 1025, 986, 806. ^{1}H NMR spectrum (500 MHz, $CDCl_3$, δ, ppm): 1.01 (3H, s, CH_3-7), 1.76 (3H, s, CH_3-9), 1.93 (3H, s, CH_3-10). ^{13}C NMR spectrum (125.76 MHz, $CDCl_3$, δ, ppm): 31.7 (d, C-5), 51.0 (t, C-6), 200.8 (s, C-1), 130.0 (s, C-2), 28.8 (t, C-3), 33.2 (t, C-4), 22.0 (q, C-7), 23.0 (q, C-9), 139.3 (s, C-8), 22.1 (q, C-10). Mass spectrum (EI, 70 eV), *m/z*, (I_{rel}, %): 152 (M^+, 44), 137 (20), 109 (40), 95 (30), 82 (40), 81 (100), 69 (26), 68 (23), 67 (72), 55 (20), 53 (25), 43 (18), 41 (60), 39 (44).

***N*-[2-(4-Methyl-2-oxocyclohexyl)propan-2-yl]acetamide (2).** Pulegone (**1**, 2 g, 0.013 mol) was dissolved in MeCN (10 mL) at 0°C, treated dropwise with conc. H_2SO_4 (2 mL), stirred at room temperature for 18 h, and neutralized with cooling by aqueous NH_4OH. The product was extracted with Et_2O. The extract was dried over $MgSO_4$ and evaporated. The resulting crystals were dried in air. Yield 1.55 g (56%), mp 97–99°C. $C_{12}H_{21}NO_2$. IR spectrum (KBr, ν, cm^{-1}): 3293 (NH), 3088, 2949, 2926, 2868, 1710 (C=O), 1643 (C=O, amide 1), 1560 (NH, amide 2), 1455, 1440, 1368, 1300, 1205, 1121, 1053, 610. ^{1}H NMR spectrum (500 MHz, $CDCl_3$, δ, ppm): 7.33 (1H, s, NH), 2.06 (2H, m), 1.94 (3H, m), 1.75 (3H, s, $NHCOCH_3$), 1.71 (2H, m), 1.33 (3H, s, CH_3-9), 1.17 (3H, s, CH_3-10), 0.94 (3H, d, J = 7, CH_3-4), 0.83 (1H, m). ^{13}C NMR spectrum (125.76 MHz, $CDCl_3$, δ, ppm): 210.2 (s, C-2), 168.3 (s, NHCO), 53.4 (d, C-1), 53.3 (s, C-8), 51.1 (t, C-3), 35.2 (d, C-4), 33.5 (t, C-5), 27.4 (t, C-6), 23.3 (q, CH_3), 24.5 (q, CH_3), 23.2 (q, CH_3), 21.8 (q, CH_3).

***N*-{2-[(1*S*,4*R*)-2-Hydroxyimino-4-methylcyclohexyl]propan-2-yl}acetamide (4).** Ketoamide **2** (0.53 g, 0.0026 mol) was dissolved in MeCN (30 mL) with added distilled H_2O (7 mL), treated dropwise with a solution of NaOAc

(0.5 g, 0.005 mol) in distilled H_2O (10 mL) and hydroxylamine hydrochloride (0.4 g, 0.005 mol) in distilled H_2O (10 mL), stirred at 50°C for 18 h, and poured onto ice (80 mL). The product was extracted with Et_2O. The extract was dried over $MgSO_4$ and evaporated to afford a sticky solid. Yield 0.23 g (41%). $C_{12}H_{22}N_2O_2$. IR spectrum (KBr, ν, cm^{-1}): 3314 (NOH), 3088, 2950, 2925, 2868, 1656 (C=O, amide 1), 1548 (NH, amide 2), 1453, 1372, 1302, 1196, 1157, 1027, 932. ^1H NMR spectrum (500 MHz, $CDCl_3$, δ, ppm): 10.23 (1H, s, N-OH), 7.22 (1H, s, NH), 3.19 (1H, d, J = 16, H-3), 2.86 (1H, m), 1.86 (6H, m), 1.71 (3H, s, $COCH_3$), 1.45 (3H, s, CH_3-9), 1.27 (3H, s, CH_3-10), 0.92 (3H, d, J = 7, CH_3-4). ^{13}C NMR spectrum (125.76 MHz, $CDCl_3$, δ, ppm): 168.9 (s, NHCO), 157.8 (s, C-2), 51.1 (d, C-1), 48.4 (s, C-8), 34.5 (t, C-3), 33.55 (d, C-4), 28.52 (t, C-5), 25.49 (t, C-6), 24.52 (q, CH_3), 24.29 (q, CH_3), 24.22 (q, CH_3), 22.73 (q, CH_3).

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