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FORMATION OF THE DINITRO-3H-PYRAZOLE DERIVATIVE OF CYCLOARTEMISIAKETONE OXIME

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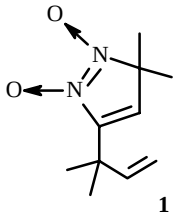
(3aR,6aR*)-3,3,5,5-Tetramethyl-3a,6a-dinitro-3a,6a-dihydro-3H-cyclopentano[c]pyrazol-2-oxide was formed by reaction of cycloartemisiaketone oxime [4,4-dimethyl-2-(1-methylethylidene)cyclopentanone oxime] with AcOH and $NaNO_2$ in $CHCl_3$ solution. The structure was solved by x-ray structure analysis.*

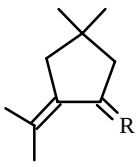
Key words: artemisiaketone, cycloartemisiaketone, dinitro-3H-pyrazole derivative N-oxide, X-ray structure analysis.

The monoterpenoid artemisiaketone is the principal component of the essential oil of *Artemisia annua* L. (annual wormwood), *Tanacetum vulgare* L. (common tansy), and other Asteraceae species [1]. Artemisiaketone is an acyclic monoterpene and has an irregular fusion of isoprene units. This molecule has two double bonds, monosubstituted and trisubstituted, with the latter conjugated to the ketone. The presence of such reaction centers was proved by various chemical transformations and total syntheses of artemisiaketone [2-4].

In order to synthesize new N-containing derivatives based on available monoterpenoids, we continued the study of chemical transformations of 3,3,6-trimethylhepta-1,5-dien-4-one, a component of certain essential oils [1] that we used in a two-step synthesis of 3H-pyrazole derivative **1** [4]. We attempted to prepare by the same method an analogous compound from cycloartemisiaketone **2**, a known derivative of acidic cyclization of artemisiaketone [5, 6], in order to study its biological activity.



1



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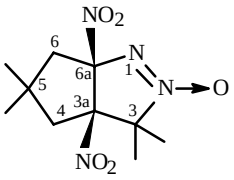

4

2: R = O; **3:** R = NOH

The product of the first synthetic step was oxime **3**, which was smoothly formed under conditions analogous to those in the literature [4]. Treatment of **3** with AcOH in $CHCl_3$ in the presence of $NaNO_2$ gave a mixture of products, only one of which was easily isolated using adsorption chromatography and crystallization. According to high-resolution mass spectrometry, the fragment peak from the isolated product with the highest *m*/*z* value corresponded to the empirical formula $C_{10}H_{16}N_3O_3$. The presence of the third N atom made it impossible to propose a structure so an x-ray structure analysis was performed. As it turned out, the structure of the isolated product has formula **4** (Fig. 1).

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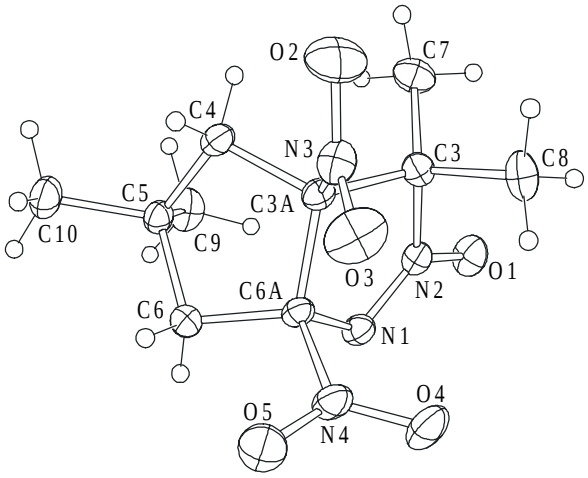

Fig. 1. Crystal structure of the dinitropyrazole derivative of artemisiaketone **4** from XSA.

We did not find any report of the formation of such dinitro compounds under analogous conditions. We managed to isolate only the N-oxide and not the N,N′-dioxide like in known transformations of 3H-pyrazole derivatives of oximes of two other monoterpene ketones, artemisiaketone [4] and pulegone [7].

EXPERIMENTAL

Melting points were determined on a Boetius apparatus. IR spectra were obtained on a Vector 22 instrument; UV spectra, on a Specord UV-VIZ; NMR spectra, on a DRX-500 (Bruker) spectrometer (working frequency 500.13 MHz for ^{1}H; 125.76 MHz, ^{13}C, δ-scale). High-resolution mass spectra (EI, 70 eV) were recorded on a Finnigan MAT 8200 instrument. Column chromatography was performed on SiO_2 (Armsorbsil 200/400, Aldrich) with a compound:sorbent ratio ~1:20. We used Silufol plates for TLC with development by spraying with vanillin in H_2SO_4 (1% solution) and aqueous $KMnO_4$ solution.

Owing to the low content of **1** in essential oil of *A. annua*, we prepared it by vacuum distillation of the lipophilic fractions of the extract of annual wormwood which, in turn, were a side product from column chromatographic isolation of the sesquiterpene lactone artemisinin. Raw *A. annua* was collected at the beginning of August 2000 in Almaty district. According to GC-MS, the artemisiaketone content was 5.1%, which is sufficient for its isolation. Lipophilic fractions containing artemisiaketone were combined, separated by fractional distillation, and purified as necessary by column chromatography.

Starting artemisiaketone was also isolated from essential oil of *T. vulgare* [1]. Ketone **2** was obtained from artemisiaketone by the literature method [5].

4,4-Dimethyl-2-(1-methylethylidene)cyclopentanone (2). Yellow oil, UV spectrum (EtOH, λ_{max}, nm): 252 (logε 4.30) (lit. [5] λ_{max} 251.5, log ε 4.30).

IR spectrum (CCl_4, ν, cm^{-1}): 2957, 2928, 2866, 1817, 1771, 1711 (C=O), 1636 (C=C), 1462, 1410, 1369, 1311, 1266, 1223, 1194, 1163, 1069, 1032, 968, 893, 804.

PMR spectrum (δ, ppm, J/Hz, CCl_4+$CDCl_3$, 1:1): 2.19 (2H, t, $^4J_{3,5}$ = 2.0, 2H-5), 2.37 (2H, narrow m, 2H-3), 2.13 (3H, br.s, 3H-8), 1.79 (3H, br.s, 3H-7), 1.07 (6H, s, 2Me-4).

4,4-Dimethyl-2-(1-methylethylidene)cyclopentanone Oxime (3). A solution of **2** (0.96 g, 6.3 mmol) in pyridine (5 mL) was treated with ground hydroxylamine hydrochloride (0.53 g, 7.6 mmol). The resulting mixture was refluxed for 30 min, cooled, treated with EtOAc (20 mL), washed with HCl (50 mL, 3%) and water (20 mL), and dried over Na_2SO_4. After solvent was removed, the solid was recrystallized from petroleum ether to afford **3** (0.97 g, 92%) as colorless needles, mp 105-106°C. UV spectrum (EtOH, λ_{max}, nm): 250 (log ε 4.00).

IR spectrum (CCl_4, ν, cm^{-1}): 3291, 3114, 2954, 1665, 1617, 1462, 1443, 1273, 1234, 1215, 1046, 926, 910, 727, 624. Mass spectrum (*m*/*z*, I_{rel}, %): 167 (49) $[M]^+$, 152 (100) $[M - CH_3]^+$, 100 (52), 94 (51), 85 (43), 77 (13), 67 (38), 57 (21), 43 (36), 41 (43). Found, *m*/*z*: 167.13197; calc. for $C_{10}H_{17}NO$, 167.1310.

PMR spectrum (δ, ppm, $CDCl_3$): 8.78 (1H, br.s, NO<u>H</u>), 2.42 (2H, br.s, 2H-5), 2.22 (2H, m, 2H-3), 2.01 (3H, br.s, 3H-8), 1.76 (3H, br.s, 3H-7), 1.02 (6H, s, 2Me-4).

^{13}C NMR spectrum: singlets at 34.55 (C-4), 128.95 (C-6), 133.71 (C-2), 163.22 (C-1); triplet at 46.19 (C-3 and C-5); quartets at 22.74, 23.85, and 28.75 (2C).

(3aR*,6aR*)-3,3,5,5-Tetramethyl-3a,6a-dinitro-3a,6a-dihydro-3H-cyclopentano[*c*]-pyrazol-2-oxide (4). A stirred solution of oxime **3** (0.97 g, 5.8 mmol) in $CHCl_3$ (10 mL) was treated with powdered $NaNO_2$ (1.9 g, 29 mmol) at room temperature, stirred further, and treated with AcOH (3 mL) in small portions over 1 h. The reaction mixture was diluted with EtOAc (25 mL), washed with saturated $NaHCO_3$ solution (25 mL) and water (10 mL), and dried over Na_2SO_4. Solvent was removed in vacuum. The solid (1 g) was chromatographed over SiO_2 with elution by petroleum ether and its mixture with EtOAc (EtOAc content from 0 to 50%). The fraction that was eluted by the mixture with 50% EtOAc was evaporated to afford cubic colorless crystals, mp 120-121°C, yield 0.54 g (34%). IR spectrum (CCl_4, ν, cm^{-1}): 2961, 2875, 1625, 1557 (NO_2), 1375, 1347, 1319, 1282, 1242, 1215, 1167, 1006, 952, 856, 797, 738, 707, 682. Mass spectrum (*m*/*z*, I_{rel}, %): 226 (13) $[M - NO_2]^+$, 180 (49) $[M - 2NO_2]^+$, 150 (100) $[M - 2NO_2 - NO]^+$, 134 (6), 108 (23), 94 (29), 82 (15), 67 (29), 55 (19), 45 (23), 41 (31), 31 (46). Found, *m*/*z*: 226.11342 $[M - NO_2]^+$; calc. for $C_{10}H_{16}N_3O_3$, 226.11916.

PMR spectrum (δ, ppm, J/Hz, $CDCl_3$): 2.82 (H, d, J_{AB} = 15.0, H-6B), 2.73 (H, dd, J_{AB} = 15.0, $J_{4B,6A}$ = 2.0, H-6A), 2.70 (H, dd, J_{AB} = 19.0, $J_{4B,6A}$ = 2.0, H-4B), 2.35 (1H, d, J_{AB} = 19.0, H-4A), 1.84 and 1.75 (both s, 3H each, 2Me-3), 1.20 and 0.89 (both s, 3H each, 2Me-5).

^{13}C NMR spectrum (ppm): singlets at 34.85, 45.04, 120.72, and 158.81; triplets at 41.74 (C-4) and 49.07 (C-6); quartets at 23.78 and 24.29 (2<u>C</u>H_3-C-3), 28.35 and 30.68 (2<u>C</u>H_3-C-5).

X-ray structure analysis was performed on a Syntex $P2_1$ diffractometer (Cu Kα-radiation with graphite monochromator). Intensities of reflections were measured by 2θ/θ-scanning. Absorption was calculated empirically using φ-scans. The structure was solved by direct methods using the SHELXS-97 program. Structure factors were refined over all F^2 by full-matrix anisotropic (isotropic for H atoms) least-squares methods using the SHELXL-97 program.

Crystals of **4** are monoclinic: *a* = 15.198(2), *b* = 8.2980(8), *c* = 20.247(3) Å, β = 94.383(17)°, V = 2545.9(6) $Å^3$, space group *C*2/*c*, *Z* = 8, $C_{10}H_{16}N_4O_5$, M = 272.27, d = 1.421 $g \cdot cm^{-3}$, λ = 1.54178 Å, μ = 0.981 mm^{-1}, transmission 0.625-1.000, 2408 independent reflections with 2θ < 140°, wR_2 = 0.1243, S = 1.062, 237 parameters (R = 0.0445 for 2064 $F_0 > 4\sigma$).

Coordinates and equivalent thermal factors for nonhydrogen atoms of **4** were deposited in the Cambridge Structural Database.

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