Chemistry of Natural Compounds, Vol. 36, No. 2, 2000

SYNTHESIS AND CRYSTAL STRUCTURE OF A PYRAZOLE DERIVATIVE OF ARTEMISIA KETONE

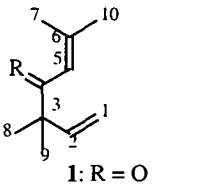
G. A. Atazhanova,[1] A. T. Kulyyasov,[1] A. D. Dembitskii,[1] V. A. Raldugin,[2] M. M. Shakirov,[2] I. Yu. Bagryanskaya,[2] Yu. V. Gatilov,[2] S. M. Adekenov,[1] and G. A. Tolstikov [2]

UDC 547.913+547.737

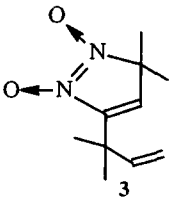
The oxime of artemisia ketone is smoothly converted to the pyrazole derivative by sodium nitrite and acetic acid in $CHCl_3$. The structure of the pyrazole was found by x-ray structural analysis. The PMR and ^{13}C NMR spectra were interpreted using two-dimensional ^{1}H—^{13}C NMR (COSY, COLOC).

Key words: *Artemisia glabella*, artemisia ketone, 5-(1′,1′-dimethylallyl)-3,3-dimethyl-3H-pyrazole-N,N′-dioxide, synthesis.

Artemisia ketone (**1**) was first isolated by Japanese researchers from the essential oil of annual wormwood *Artemisia annua* L. and is accompanied by the optically active acetate of the corresponding secondary alcohol [1]. Later **1** was found among the essential-oil components of *Santolina chamaecyparis* L. [2] and *Artemisia glabella* Kar. et Kir. [3]. Its structure was established as 3,3,6-trimethylhepta-1,5-dien-4-one using chemical data [1], which were confirmed by PMR spectral data [2].



1: R = O
2: R = N–OH



3

The development of the technology for processing the above-ground part of *Artemisia glabella* Kar. et Kir. [4] to produce the pharmacologically valuable guaianolide arglabin and the essential oil, which has a wide spectrum of biological activity, prompted us to study the chemical transformations of one of the components of this oil, ketone **1**, which is rarely encountered in plants [5]. This study is a continuation of some of us on the preparation of heterocyclic derivatives based on oximes of monoterpene α,β-unsaturated ketones [6].

Artemisia ketone forms one product according to TLC if boiled in pyridine with hydroxylamine hydrochloride. The product, the oxime of the starting ketone, is isolated as low-melting crystals. This is consistent with the PMR, ^{13}C NMR (Table 1), mass (*m/z* for ions with the highest mass correspond to the empirical formula $C_{10}H_{17}NO$), and IR spectra.

We then converted oxime **2** into the heterocyclic derivative, in analogy with the conversion of the oxime of mesityloxide (4-methylpent-3-en-2-one) into 3,5,5-trimethyl-3H-pyrazole-N,N′-dioxide [7].

According to TLC, a single product is formed upon slow addition of glacial acetic acid to a stirred suspension of sodium nitrite in a $CHCl_3$ solution of oxime **2**. The elemental composition of the product, according to high-resolution mass spectroscopy, corresponds to the empirical formula $C_{10}H_{16}N_2O_2$. The molecular structure of this product is **3**, which was established using ^{13}C NMR spectra [Table 1, interpreted using two-dimensional ^{13}C—^{1}H NMR spectra (COSY, COLOC)],

1) Institute of Phytochemistry, Ministry of Education and Science, Republic of Kazakhstan, 470032, Karaganda, ul. Gazalieva, 4, fax 7(3212) 43 37 73, e-mail: arglabin@phyto.karaganda.su; 2) Novosibirsk Institute of Organic Chemistry, Siberian Division, Russian Academy of Sciences, 630090, Novosibirsk, prosp. Akad. Lavrent'eva, 9, fax (3832) 34 47 52, e-mail: raldugin@nioch.nsc.ru. Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 121-123, March-April, 2000. Original article submitted May 8, 2000.

 0009-3130/00/3602-0152$25.00

TABLE 1. ^{13}C NMR Spectra of **1-3** (δ, ppm, $CDCl_3$, 0 = TMS)

C atom	1	2	3
1	113.58	111.98	113.94
2	143.12	144.48	141.59
3	29.59	43.10	37.69
4	202.83	161.57	149.33
5	120.41	114.06	121.45
6	155.76	141.92	71.41
7	20.76	21.29	23.49
8	23.52	24.78	24.53
9	23.52	24.78	24.53
10	27.80	25.18	23.49

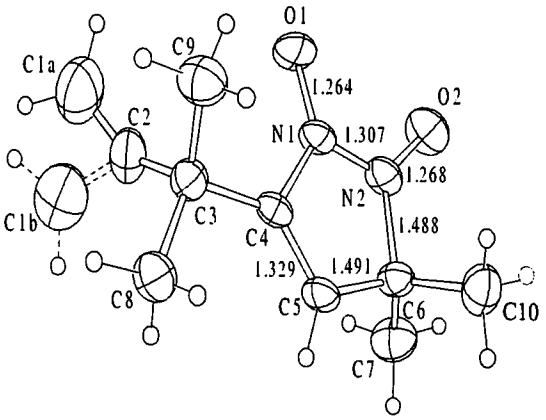


Fig. 1. Crystal structure and certain bond lengths in **3**.
Uncertainties are 0.004-0.006 Å.

PMR, and ^{14}N NMR spectra. The last exhibits two broad singlets of approximately equal integrated intensity centered at 304 and 317 ppm (two N atoms).

The structure of **3** was finally proved by x-ray structure analysis and is shown in Fig. 1. The bond lengths are close to the statistically averaged values [8]. The pyrazoline ring is planar within ±0.01 Å. The closest analog to **3** in the Cambridge Structure Database [9] is 3,5,5-trimethyl-3H-pyrazole-N,N′-dioxide [10]. In general, the geometries of these two compounds are identical. Infinite dimeric chains along the b axis are formed in the crystal of **3** through short O...H van der Waals contacts: O(1)...H(5)–C(5) 2.25 Å and O(2)...H(10A)–C(10) 2.52 Å.

EXPERIMENTAL

General Observations. IR spectra were recorded on a Vector 22 instrument; UV spectra, on a Specord UV-VIS; NMR spectra, on a Bruker DRX-500 spectrometer (working frequency 500.13 MHz for ^1H, 125.76 MHz for ^{13}C, and 36.13 MHz for ^{14}N; $CDCl_3$ solvent; δ scale). High-resolution mass spectra were recorded on a Finnigan MAT 8200 instrument.

The starting ketone **1** was isolated by fractional distillation of the essential oil of *Artemisia glabella* [5].

3,3,6-Trimethylhepta-1,5-dien-4-one Oxime (2). A solution of **1** (1.01 g, 6.6 mmole) in pyridine (5 ml) was treated with hydroxylamine hydrochloride (0.5 g, 7.0 mmole). The mixture was refluxed for 2 h, cooled, treated with diethylether (20 ml) and water (20 ml), and stirred. The ether layer was separated and washed with water (15 ml), HCl (5%, 20 ml), water, and sodium bicarbonate solution (5%). The ether was removed to give a yellow oil that was chromatographed on silica gel (20 g) and eluted by hexane with an increasing amount of ethylacetate (from 0 to 20%). Yield 0.76 g of oxime **2** (72%), mp 36-38°C. UV spectrum (C_2H_5OH, λ_{max}, nm): 215 and 239 (log ε 3.49 and 3.44). IR spectrum (KBr, ν, cm^{-1}): 1668, 3292, and 3594 (oxime).

TABLE 2. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Parameters ($Å^2 \times 10^3$) of Nonhydrogen Atoms in **3**

Atom	*x*	*y*	*z*	U_{eq}
C1A	2850(3)	4750(4)	5591(9)	128(7)
C1B	1480(4)	2090(4)	5527(11)	170(9)
C2	1970(9)	3586(10)	6088(3)	79(1)
C3	182(6)	3740(6)	6641(2)	54(1)
C4	1136(5)	3453(5)	7424(2)	46(1)
C5	218(6)	1814(6)	7917(2)	51(1)
C6	1907(6)	2438(6)	8642(2)	54(1)
C7	2924(9)	553(9)	8807(3)	84(1)
C8	-2413(7)	1657(8)	6435(2)	75(1)
C9	-24(8)	6182(8)	6641(3)	76(1)
C10	760(8)	3055(9)	9319(2)	75(1)
N1	3555(4)	5255(5)	7780(2)	51(1)
N2	3997(5)	4710(5)	8462(2)	58(1)
O1	5058(5)	7106(5)	7498(2)	74(1)
O2	5988(5)	6001(6)	8896(2)	87(1)

Mass spectrum, *m/z* (%): 167 [M^+] (24), 152 (80), 150 (25), 109 (21), 108 (20), 98 (24), 85 (17), 82 (49), 81 (21), 70 (26), 69 (100), 67 (24), 55 (62), 43 (55), 41 (94).

PMR spectrum (δ, ppm, $CDCl_3$, TMS): 1.17 (6H, s, CH_3-8, CH_3-9), 1.57 (3H, br. s, CH_3-7), 1.83 (3H, br. s, CH_3-10), 4.75-5.20 (2H, m, 2H-1), 5.40 (1H, br. s, H-5), 5.87 (1H, dd, J = 11.0, 17.5, H-2). For the ^{13}C NMR spectrum, see Table 1.

5-(1′,1′-Dimethylallyl)-3,3-dimethyl-3H-pyrazole-N,N′-dioxide (3). A solution of **2** (0.56 g, 3.35 mmole) in $CHCl_3$ (10 ml) was treated with finely ground $NaNO_2$ (0.46 g, 6.67 mmole). Glacial acetic acid (2 ml) was added dropwise with constant stirring on a magnetic stirrer over a period of 1 h at 20°C. The reaction mixture was treated with aqueous $NaHCO_3$ (5%, 2×20 ml). The resulting solution was dried over anhydrous Na_2SO_4. The solvent was removed to produce white crystals of **3**, mp 113-115°C (methanol). Yield 0.43 g (66%). UV spectrum (C_2H_5OH, λ_{max}, nm): 216 and 313 (log ε 4.05 and 3.67). IR spectrum (KBr, ν, cm^{-1}): 3080, 1647, 992 (–CH=CH_2), 1475, 1448, 1425 (=N–O), 1377, 1365, 1298, 1251, 1227, 916, 875, 856, 783, 717, 587.

Mass spectrum, *m/z* (%): 196 [M^+] (10), 136 (6), 98 (48), 69 (100), 55 (17).

Elemental analysis. Found (*m/z*): 196.12121. Calc. for $C_{10}H_{16}N_2O_2$ 196.12117.

PMR spectrum (δ, ppm, $CDCl_3$, TMS): 1.44 (6H, s, CH_3-8, CH_3-9), 1.47 (6H, s, CH_3-7, CH_3-10), 5.06-5.12 (2H, m, 2H-1), 5.08 (1H, dd, H-2, J = 10.5 and 18.0 Hz), 6.22 (1H, br. s, H-5). For the ^{13}C NMR spectrum, see Table 1.

X-ray structure analysis of 3 was performed on a Bruker P4 diffractometer (Mo Kα-radiation with a graphite monochromator, 2Θ/Θ scanning for 2Θ < 50°). A colorless crystal of **3** with dimensions 1.20×0.50×0.13 mm was selected. The crystal was triclinic, a = 5.914(6), b = 6.048(4), c = 17.741(11) Å, α = 93.19(4), β = 94.59(6), γ = 114.64(7)°, V = 572.1(8) $Å^3$, space group $P\bar{1}$, Z = 2, $C_{10}H_{16}N_2O_2$, d_{calc} = 1.139 g/cm^3, μ = 0.080 mm^{-1}. Intensities of 1857 independent reflections were measured.

The structure was solved using direct methods and the program SHELXS-86. The positions of H atoms were calculated geometrically. The structure was refined by full-matrix anisotropic least-squares methods using the program SHELXL-97. Coordinates of H atoms were not refined. Their positions were calculated in each refinement cycle using the coordinates of the corresponding C atom. The vinyl group was disordered over two positions that were designated C(1A) and C(1B) [with corresponding weights 0.48:0.52(2), respectively]. The structure was finally refined over all F^2 with wR_2 = 0.2512 and S = 1.059 for 138 parameters (R = 0.0783 for 1184 F > 4 σ). The rather high R-factor is explained by the poor quality of the crystal. The peak width was 2.5° (a crystal of better quality could not be obtained). The coordinates and equivalent thermal parameters of nonhydrogen atoms are listed in Table 2.

ACKNOWLEDGMENT

The authors thank the Ministry of Education and Science of the Republic of Kazakhstan for support through the Basic Research Program (No. F0092) for the present work and the Russian Basic Research Foundation (project 96-07-89187) for assistance in obtaining a license for the Cambridge Structure Database.

REFERENCES

1. K. Takemoto and T. Nakajima, *Yakugaku Zasshi*, **77**, 1307 (1957); *Chem. Abstr.*, **52**, 4478 (1958).
2. L. H. Zalkow, D. R. Brannon, and J. W. Uecke, *J. Org. Chem.*, **29**, 2786 (1964).
3. G. A. Atazhanova, A. D. Dembitskii, N. I. Zhizhin, and S. M. Adekenov, *Khim. Prir. Soedin.*, 193 (1999).
4. G. A. Atazhanova, Author's Abstract of a Candidate Dissertation in Chemical Sciences, Karaganda (1999).
5. M. I. Goryaev, T. E. Serkebaeva, G. I. Krotova, and A. D. Dembitskii, *Rast. Resur.*, **3**, 63 (1967).
6. Yu. V. Gatilov, L. V. Basalaeva, N. K. Kozlov, M. M. Shakirov, and V. A. Raldugin, *Khim. Prir. Soedin.*, 704 (1995).
7. J. P. Freeman, *J. Org. Chem.*, **27**, 1309 (1962).
8. F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen, and R. Taylor, *J. Chem. Soc., Perkin Trans. II*, No. 12, 1 (1987).
9. F. H. Allen and O. Kennard, *Chem. Des. Automat. News*, **8**, 131 (1993).
10. P. Joergensen, R. Koksbang, and P. Lindhardt, *Acta Crystallogr. Sect. C: Cryst. Struct. Commun.*, **42**, 1273 (1986); *Chem. Abstr.*, **105**, 144004 (1986).