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(*R*)-4-MENTHEN-3-ONE *anti*-OXIME AND ITS TRANSFORMATION UNDER BECKMAN REARRANGEMENT CONDITIONS

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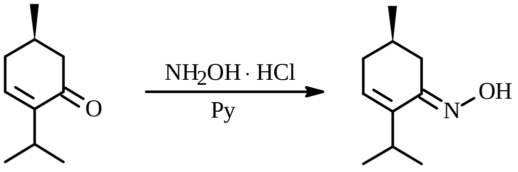
(R)-4-Menthenone anti-oxime was synthesized for the first time. Its transformations under Beckman rearrangement conditions were studied.

Key words: *anti*-oxime, Beckman rearrangement, (*R*)-4-menthenone, (*S*)-3,7-dimethyl-6-oxooctanoic acid methyl ester, Semmler—Wolf reaction.

The synthesis of a totally optically pure chiral unit that was based on ozonolytic decyclization of (*R*)-4-menthenone (**1**) was reported previously [1, 2]. In order to expand the use of **1**, we prepared its oxime **2** (Scheme 1), which was synthesized previously [3] by the reaction of racemic menthene and nitrosyl chloride with subsequent dehydrochlorination. It was proposed to have the *syn*-configuration. However, the stereochemistry of the ketoxime could not be unambiguously determined using the traditional Beckman rearrangement. The *syn*-structure of the oxime was confirmed only later [4].



Scheme 1.

A comparison of the mp (57-58°C) and UV spectrum (EtOH, λ_{max} 232 nm, log ε 3.55) of **2** synthesized by us with data for the compound prepared earlier (mp 66-67°C, λ_{max} 242 nm, log ε 4.1 [4]) showed that they differ substantially.

Based on these differences and the fact that *syn*-oximes usually have higher melting points [5], we assigned the *anti*-configuration of the hydroxyl and double bond to our **2**. Furthermore, it is known that *anti*-oximes, with rare exceptions, either decompose to tars or do not react under Beckman-rearrangement conditions [6]. Oxime **2** would be converted to tetrahydroazepinone **3** through a successful reaction. However, it did not rearrange upon treatment with thionyl chloride and decomposed upon treatment with P_2O_5 and conc. H_2SO_4. Use of the Beckman mixture (Ac_2O—AcOH—HCl) at various temperatures (20 and 100°C) produced the O-acyl derivative **4** and the product of its further aromatization, acetamide **5**. This can be explained by the initial formation of **4**, which then was transformed further (according to Semmler—Wolf) into amine **6** with subsequent acylation to **5** (Scheme 2).

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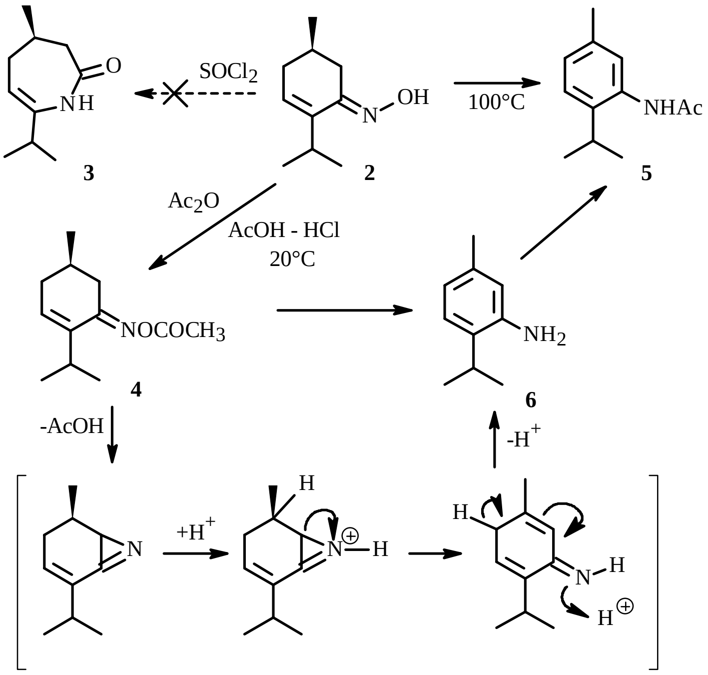
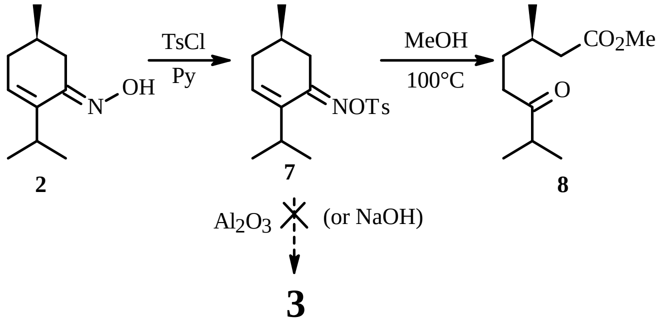


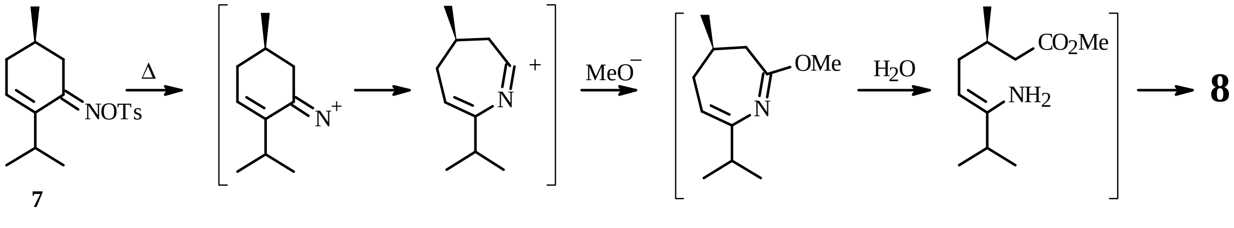
Scheme 2.

The majority of oxime arylsulfonates are exceedingly reactive compounds that undergo the Beckman rearrangement during synthesis [7]. However, reaction of **2** with *p*-toluenesulfonyl chloride produced O-tosyl derivative **7**, which was unreactive toward several traditional reagents, for example, aluminum oxide [8] and NaOH (in THF—H_2O) [9]. Also, heating (100°C) in MeOH formed a complicated mixture from which we isolated using column chromatography (*S*)-3,7-dimethyl-6-oxooctanoic acid methyl ester (**8**) in 70% yield (Scheme 3). Compound **8** was identical to that prepared previously by us from menthone through an intermediate Baeyer—Villager reaction [10].



Scheme 3.

The proposed reaction mechanism is consistent with already known transformations of oxime tosylates [7] (Scheme 4).



Scheme 4.

Thus, we prepared for the first time the *anti*-oxime of optically pure menthenone. For this, the Beckman rearrangement could be used successfully only for the corresponding tosylate. The reaction occurs with deazotization, giving ketoester **8**.

EXPERIMENTAL

IR spectra were recorded on a Specord M-82 instrument as thin layers. NMR spectra (δ, ppm, J/Hz) were obtained on a Bruker AM-300 spectrometer (working frequency 300.13 MHz for PMR and 75.47 MHz for ^{13}C) in $CDCl_3$ relative to TMS. Signals in PMR spectra were assigned and spin—spin coupling constants (SSCC) were determined using double resonance and two-dimensional correlation spectroscopy (COSY-H-H). Mass spectra were measured in an MX-1320 instrument at ionizing potential 70 eV. UV spectra were recorded on a Specord M400 instrument. Chromatographic analysis was performed on a Chrom-5 instrument [column length, 2.4 m; stationary phase, PEG-6000 (5%) on Inerton AW-DMCS (0.125-0.160 mm); working temperature 50-200°C] with He carrier gas. Optical rotations were measured on a Perkin—Elmer-241-MC polarimeter. Solvents were dried as usual. Column chromatography was performed over SiO_2 (L, 60-200 μm, Lancaster, England). TLC monitoring was carried out over SiO_2 (Silufol, Czech Rep.). Petroleum ether (PE) (bp 40-70°C) was used for chromatography.

Elemental analyses of all compounds agreed with those calculated.

(*R*)-5-Methyl-2-(1-methylethyl)-2-cyclohexen-1-one Oxime (2). A solution of **1** (2.00 g, 13.2 mmol) in Py (22 mL) was stirred (20°C) and treated with $NH_2OH\cdot HCl$ (4.40 g, 55.7 mmol). After 1 h the reaction mixture was diluted with ethylacetate (50 mL), washed with H_2O (2 × 50 mL), dried over Na_2SO_4, and evaporated. The solid was recrystallized from aqueous EtOH (50%) to afford **2** (1.66 g, 77%) as white crystals, $C_{10}H_{17}NO$, mp 57-58°C, $[\alpha]_D^{19}$ -47.9° (*c* 9.99, $CHCl_3$), R_f 0.6 (PE:MeO-*t*-Bu, 2:1).

UV spectrum (EtOH, λ_{max}, nm): 232 (log ε 3.55) [4].

IR spectrum (KBr, ν, cm^{-1}): 964 (N–O), 1636 (C≡N), 3268 (O–H).

PMR (δ, ppm, J/Hz): 1.01 (d, 3H, J = 5.5, CH_3C-5), 1.07 [d, 6H, J = 6.9, $(CH_3)_2C$], 1.70-1.90 (m, 2H, H_a-4, H-5), 1.92 (d, 1H, J = 13.3, H_a-6), 2.23 (dd, 1H, ^2J = 13.8; ^3J = 9.0, H_e-4), 2.80 (sept., 1H, J = 6.9, HCC-2), 3.12 (d, 1H, ^2J = 13.3, H_e-6), 6.01 (d, 1H, J = 4.5, H-3), 9.30 (br.s, 1H, O–H).

^{13}C NMR (δ, ppm): 21.27 ($\underline{C}H_3C$-5), 21.29 and 22.39 [$(\underline{C}H_3)_2C$], 27.03 (C-8), 27.78 (C-5), 30.81 (C-4), 33.42 (C-6), 129.19 (C-3), 140.14 (C-2), 155.51 (C-1).

(*R*)-5-Methyl-2-(1-methylethyl)-2-cyclohexen-1-one Tosylate Oxime (7). A mixture of **2** (0.35 g, 2.1 mmol) and dry Py (10 mL) at 0°C was treated with *p*-TsCl (0.44 g, 2.3 mmol), stirred and heated to room temperature, and left for 18 h. The Py was evaporated in vacuum. The solid was dissolved in H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The extract was washed successively with H_2O and saturated NaCl and $NaHCO_3$ solutions, dried over $MgSO_4$, and evaporated to afford crude product (0.56 g), recrystallization of which from aqueous EtOH (50%) isolated **7** (0.51 g, 76%) as white crystals, mp 95.5-96.5°C, R_f 0.63 (PE:MeO-*t*-Bu, 2:1), $[\alpha]_D^{18}$ -20.4° (*c* 1.57, $CHCl_3$).

IR spectrum (KBr, ν, cm^{-1}): 952 (N–O); 1192, 1366 (S=O); 1492, 1594 (C=C); 1636 (C–N).

PMR (δ, ppm, J/Hz): 0.96 (d, 3H, ^3J = 5.5, H_3CC-5), 0.99 [d, 6H, ^3J = 5.9, $(CH_3)_2C$], 1.70-1.83 (m, 2H, H_a-4, H-5), 1.94 (d, 1H, ^2J = 12.9, H_a-6), 2.25 (dd, 1H, ^2J = 15.3, ^3J = 7.2, H_e-4), 2.44 (s, 3H, H_3C-Ar), 2.76 (g, 1H, ^3J = 5.9, HCC-2), 6.19 (dd, 1H, J = 6.2, J = 2.3, H-3), 7.33 and 7.89 (both d, 4H, ^3J = 8.3, H-Ar).

Beckman Rearrangement Methods. Preparation of 4, 5, and 8.

A. Dry HCl was bubbled through a solution of **2** (0.64 g, 3.8 mmol) in a mixture of glacial AcOH (3.7 mL) and Ac_2O (1.85 mL) at 20°C for 1 h. The reaction mixture was left for 43 h, treated with H_2O (10 mL), extracted with CH_2Cl_2 (3 × 20 mL), dried over $MgSO_4$, and evaporated. The solid (0.70 g) was chromatographed over SiO_2 (eluent PE:MeO-*t*-Bu, 10:1) to afford **4** (0.45 g, 64%).

B. Dry HCl was bubbled until saturated (45 min) through a solution of **2** (1.00 g, 5.99 mmol) in a mixture of glacial AcOH (9.52 mL, 9.99 g, 1.667 mmol) and Ac_2O (1.85 mL, 19.6 mmol) in a glass ampul. The ampul was sealed and heated for 3 h on a boiling-water bath. The reaction mixture was left for 48 h at room temperature, diluted with H_2O (5 mL), and extracted with Et_2O (3 × 30 mL). The extract was washed with saturated $NaHCO_3$ solution (until the pH was 7), dried over $MgSO_4$, and evaporated. The solid (0.94 g) was chromatographed over SiO_2 (eluent PE:MeO-*t*-Bu, 10:1) to afford **5** (0.25 g, 27%).

C. A solution of **7** (2.53 g, 7.88 mmol) in absolute MeOH (50 mL) was heated in an ampul for 4.5 h on a boiling-water bath, evaporated in vacuum, treated with aqueous NaOH solution (10%, until the pH was ~10), extracted with CH_2Cl_2, dried over Na_2SO_4, and evaporated. The solid (1.58 g) was chromatographed (eluent PE:CH_2Cl_2, 5:1) to afford **8** (1.10 g, 70%) [10].

(*R*)-6-[(Acetyloxy)imino]-4-methyl-1-isopropylcyclohex-1-ene (4). R_f 0.56 (PE:MeO-*t*-Bu, 2:1), $[\alpha]_D^{24}$ -52.8° (*c* 3.08, $CHCl_3$), $C_{12}H_{19}NO_2$.

IR spectrum (KBr, ν, cm^{-1}): 1640 (C=C), 1685 (C=N), 1775 (C=O).

PMR (δ, ppm, J/Hz): 0.93 (d, 3H, ^3J = 5.4, CH_3C-5), 1.03 [d, 6H, J = 6.9, $(CH_3)_2C$], 1.70-1.85 (m, 2H, H_a-4, H-5), 1.90 (d, 1H, ^2J = 11.8, H_a-6), 2.23 (dd, 1H, ^2J = 12.8, ^3J = 6.3, H_e-4), 2.18 (s, 3H, CH_3CO), 3.03 (d, 1H, ^2J = 11.8, H_e-6), 6.18 (d, 1H, J = 4.3, H-3).

^{13}C NMR (δ, ppm): 19.81 ($\underline{C}H_3CO$), 20.94 and 21.81 [$(\underline{C}H_3)_2C$], 22.18 ($\underline{C}H_3C$-5), 26.97 ($H\underline{C}C$-2), 27.67 (C-5), 32.24 (C-4), 33.24 (C-6), 133.15 (C-3), 139.97 (C-2), 161.31 (C-1), 169.60 (C=O).

Mass spectrum (EI, 70 eV, *m/z*, I_{rel}, %): 209 (0.8) $[M]^+$, 167 (3) $[M - CH_2CO]^+$, 150 (32) $[M - CH_3COO]^+$, 148 (19), 134 (54), 107 (54), 94 (21), 93 (23), 91 (14), 81 (17), 79 (21), 77 (18), 67 (31), 65 (11), 55 (20), 53 (20), 43 (100) $[CH_3CO]^+$, 42 (22), 41 (69), 39 (35), 27 (33).

5-Methyl-2-isopropylacetanilide (5). R_f 0.36 (CH_2Cl_2).

IR spectrum (KBr, ν, cm^{-1}): 1490, 1600 (C=C); 1555, 3310 (N–H); 1685 (C=O).

PMR (δ, ppm, J/Hz): 1.20 [d, 6H, J = 6.72, $(CH_3)_2C$], 2.17 (s, 3H, CH_3CO), 2.30 (s, 3H, CH_3C-5), 2.96-3.08 (m, 1H, HC), 6.93-7.21 (m, H-Ar).

^{13}C NMR (δ, ppm): 19.55 ($\underline{C}H_3CO$), 20.83 ($\underline{C}H_3C$-5), 23.15 and 23.91 [$(\underline{C}H_3)_2C$], 27.58 (HC), 125.41 (C-3), 126.11 (C-6), 127.18 (C-4), 133.61 (C-1), 135.85 (C-5), 138.41 (C-2), 169.05 (C=O).

(*S*)-3,7-Dimethyl-6-oxooctanoic acid methyl ester (8). R_f 0.5 (PE:MeO-*t*-Bu, 2:1), $[\alpha]_D^{18}$ +9.5° (*c* 0.16, $CHCl_3$) [10]. The IR spectrum is practically identical to that described previously [10].

PMR (δ, ppm, J/Hz): 0.95 (d, 3H, ^3J = 6.6, CH_3C-3), 1.09 [d, 6H, ^3J = 6.9, $(CH_3)_2C$], 1.40-1.54 (m, 1H, H-4), 1.56-1.68 (m, H, H′-4), 1.87-2.00 (m, 1H, H-3), 2.13 (dd, 1H, ^2J = 14.8, ^3J = 8.1, H′-2), 2.31 (dd, 1H, ^2J = 14.8, ^3J = 5.9, H-2), 2.43-2.50 (m, 2H, H-5), 2.61 (g, 1H, H-7), 3.68 (s, 3H, CH_3O).

^{13}C NMR (δ, ppm): 18.26 [$(\underline{C}H_3)_2C$-6], 19.51 ($\underline{C}H_3C$-3), 30.01 (C-3), 30.29 (C-4), 37.81 (C-5), 40.84 (C-7), 41.39 (C-2), 51.45 (CH_3O), 173.36 (C-1), 214.49 (C-6).

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