Novel selective acid-catalysed rearrangement of the carane-type α-(*N*-acylamino)oximes: the X-ray structure of (1*S*,5*S*)-1-isopropyl-3,5-dimethyl-2-oxa-4-azabicyclo[3.3.1]non-3-en-6-one (*E*)-oxime

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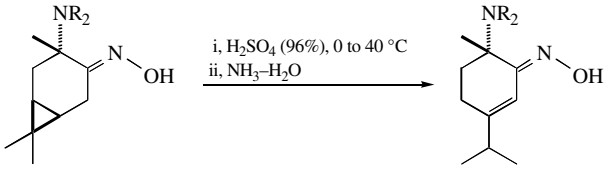
The acid-catalysed rearrangement of carane-type α-(*N*-acylamino)oximes results in the formation of new bridged heterocycles with the 3-substituted 1-isopropyl-6-hydroxyimino-3-methyl-2-oxa-4-azabicyclo[3.3.1]non-3-ene skeleton.

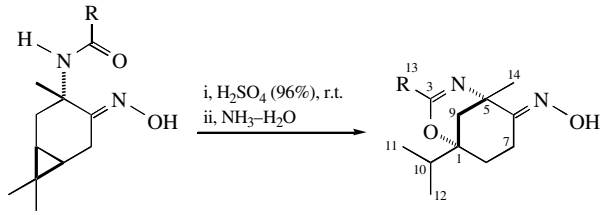
(+)-3-Carene and its oxygen-, nitrogen- and sulfur-containing derivatives represent one of the most important groups of monoterpenoids. Under acidic conditions, the derivatives of 3-carene are usually transformed to compounds of the *p*-menthane series and sometimes form the derivatives of *m*-menthane and eucarvone. Most of the reactions give complex mixtures of isomers and great amounts of tar-like products.[1] We describe here a new unusual stereoselective cyclization of 3-carene derivatives to bicyclic bridged heterocycles of the 2-oxa-4-azabicyclo-[3.3.1]non-3-ene series.



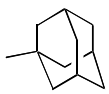
1 R = H, Alk — **2** 42%

Scheme 1

When dissolved in a concentrated sulfuric acid, α-amino oximes **1** derived from (+)-3-carene undergo isomerization to afford *p*-menthane derivatives **2** (Scheme 1).[2] We found that N-acyl derivatives **3** of the same structural type are transformed to *m*-menthane derivatives **4** in good yields under the action of sulfuric acid in chloroform (Scheme 2). The reaction proceeds



3a–d — **4a–d** 65–83%

a R = Me **b** R = Ph **c** R =  **d** R = 

Scheme 2

smoothly in the case of N-acetyl derivative **3a** to give compound **4a**,† as well as in the case of derivatives of benzoic (**3b** → **4b**),‡ 2-thiophencarboxylic (**3c** → **4c**)§ and 1-adamantane carboxylic (**3d** → **4d**)¶ acids. Analysis of high-field 2D ^{1}H–^{1}H and ^{13}C–^{1}H-correlation NMR spectra of new compounds **4a–d** showed similarity of the NMR parameters (proton and carbon chemical shifts and ^{1}H–^{1}H and ^{13}C–^{1}H spin–spin couplings) for the bicyclic system and thus proved compounds **4a–b** to belong to the same structural type. Configuration of the simplest N-acetyl derivative **4a** was solved by X-ray crystallography (Figure 1).††

The formation of compounds **4a–d** can be described by Scheme 3, which provides for addition of a proton and cyclopropane ring cleavage to form *m*-menthane-type cation **5** followed by participation of the carbonyl oxygen (structure **6**) and the formation of immonium cation **7** whose deprotonation results in the final product **4**.

† Concentrated H_2SO_4 (2.5 ml, 96%, 50 mmol) was added dropwise to a stirred solution of N-acylated amine **4a** (438 mg, 1.92 mmol) in $CHCl_3$ (15 ml) at room temperature. The mixture was vigorously stirred for 3 h and then adjusted to pH 10–11 by the addition of concentrated aqueous ammonia (ice-cold bath). The organic phase was separated and the aqueous solution was extracted with *tert*-BuOMe (2×10 ml). The combined organic extract was dried over $MgSO_4$, filtered and concentrated at a reduced pressure to give a yellowish glass-like solid (400 mg), which was crystallised from acetonitrile to give pure (1*S*,5*S*)-1-isopropyl-3,5-dimethyl-2-oxa-4-azabicyclo[3.3.1]non-3-en-6-one (*E*)-oxime (**4a**, 312 mg, 71% yield) as white crystals with mp 216–220 °C (MeCN) and $[\alpha]_{578}^{20}$ +429 (*c* 0.83, $CHCl_3$). ^{1}H NMR (500 MHz, 10 mg cm^{-3} in $CDCl_3$) δ: 9.80 (s, 1H, N=OH), 3.27 (ddd, 7-H$_\beta$, *J* 15.5, 6.2, 0.8 Hz), 1.98 (s, 3H, 13-Me), 1.94 (ddd, 8-H$_\alpha$, *J* 13.4, 3.2, 0.8 Hz), 1.82 (ddd, 7-H$_\alpha$, *J* 15.5, 13.1, 6.6 Hz), 1.75 (qq, 10-H, *J* 6.8, 6.8 Hz), 1.74 (d, 9-H$_\beta$, *J* 13.2 Hz), 1.59 (ddd, 8-H$_\beta$, *J* 13.4, 13.1, 6.6 Hz), 1.51 (dd, H$_\alpha$, *J* 13.2, 3.2 Hz), 1.39 (s, 3H, 14-Me), 0.91 (d, 3H, 11-Me, *J* 6.8 Hz), 0.89 (d, 3H, 12-Me, *J* 6.8 Hz). ^{13}C NMR (125 MHz, 10 mg cm^{-3} in $CDCl_3$) δ: 160.64 (C-6), 160.04 (C-3), 79.56 (C-1), 54.31 (C-5), 37.59 (C-9), 36.38 (C-10), 33.18 (C-8), 24.91 (C-14), 21.32 (C-13), 17.02 (C-7), 16.61 (C-12), 16.42 (C-11). IR ($CHCl_3$, ν_{max}/cm^{-1}): 3590 (O–H), 1650 (C=N), 895 (N–O). MS, *m*/*z* (%): 224.15149 (15, M$^+$, calc. for $C_{12}H_{20}N_2O_2$: 224.16149), 165 (88), 159 (18), 148 (17), 123 (17), 107 (10), 82 (11), 60 (11), 55 (10), 43 (100), 42 (30), 41 (28), 28 (11).

‡ *(1S,5S)-1-Isopropyl-5-methyl-3-phenyl-2-oxa-4-azabicyclo[3.3.1]non-3-en-6-one* (E)*-oxime* **4b**: yield 83%, white crystals, mp 177–180 °C (MeCN), $[\alpha]_{578}^{20}$ +193 (*c* 0.38, $CHCl_3$).

§ *(1S,5S)-1-Isopropyl-5-methyl-3-(thiophen-2-yl)-2-oxa-4-azabicyclo-[3.3.1]non-3-en-6-one* (E)*-oxime* **4c**: yield 78%, white crystals, mp 164 °C (decomp., MeCN), $[\alpha]_{578}^{20}$ +92 (*c* 0.087, $CHCl_3$).

¶ *(1S,5S)-3-(Adamantan-1-yl)-1-isopropyl-5-methyl-2-oxa-4-azabicyclo-[3.3.1]non-3-en-6-one* (E)*-oxime* **4d**: yield 65%, white crystals, mp 230–233 °C (MeCN), $[\alpha]_{578}^{20}$ +136 (*c* 0.62, $CHCl_3$).

†† A Syntex P21 diffractometer with graphite-monochromated CuKα radiation was used to measure the unit cell parameters and to collect data (θ-2θ scans, θ < 140°).

Crystallographic data for compound **4a**: $C_{12}H_{20}N_2O_2$, M = 224.30, crystal class orthorhombic, space group $P2_12_12_1$, α = 7.050(1), b = = 10.671(2), c = 16.655(3) Å, V = 1253.0(4) Å^3, Z = 4, d_{calc} = 1.189 g cm^{-3}, μ = 0.653 mm^{-1}, λ = 1.54178 Å, crystal size 0.4×0.6×1.2 mm. Absorption corrections were applied by an empirical method based on psi-scans (transmission 0.806–1.000). The structure was solved by direct methods and refined by a full matrix least-squares anisotropic–isotropic (for H atoms) procedure using the SHELXL97 program. The hydrogen atom positions were located from a difference Fourier map. The final indexes are wR_2 = 0.1009, S = 1.079 for all 1378 F^2 and R_1 = 0.0352 for 1345 $F_0 > 4\sigma(F_0)$. The absolute structure parameter (Flack parameter) is equal to –0.2(4). Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2002. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/108.

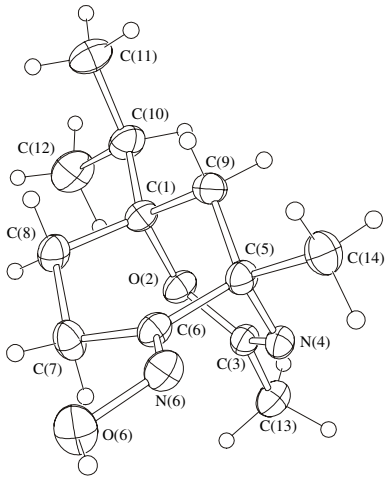


Figure 1 Molecular structure of crystalline compound **4a**. Selected bond lengths (Å): C(5)–N(4) 1.476(3), N(4)=C(3) 1.269(3), C(3)–O(2) 1.353(2), C(1)–O(2) 1.469(2), C(6)–N(6) 1.266(2), O(6)–N(6) 1.400(2). The sofa-like conformation of the dihydrooxazine ring is characterised with the planar within ±0.035(1) Å C(5)–N(4)=C(3)–O(2)–C(1) fragment and C(9) atom deviation from this plane by 0.696(4) Å. Infinite chains of molecules along *b* axis are formed in the crystal by the intermolecular H-bond O(6)–H···N(4) with the parameters H···N(4) 1.89(4) Å and O(6)–H···N(4) 171(3)°.

Compounds **4a–d** are white crystalline solids, which are insoluble in water and hydrocarbons, sparingly soluble in chloroform and methylene chloride, and readily soluble in methanol and dimethylsulfoxide. In spite of the presence of the imino ester group, compounds **4a–d** are stable in air and are not prone to hydrolysis.

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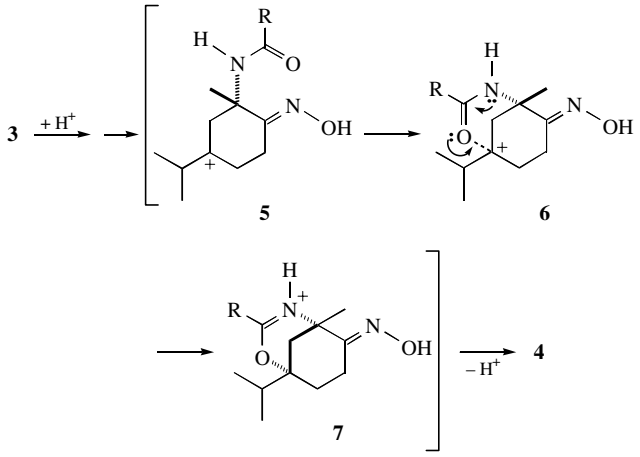

Scheme 3

References

1 (*a*) W. F. Erman, *Chemistry of the Monoterpenes. An Encyclopedic Handbook,* in *Studies in Organic Chemistry*, ed. P. G. Gassman, Marcel Dekker Inc., New York–Basel, 1985, vol. 11, part A, pp. 197–213; (*b*) W. F. Erman, *Chemistry of the Monoterpenes. An Encyclopedic Handbook,* in *Studies in Organic Chemistry*, ed. P. G. Gassman, Marcel Dekker Inc., New York–Basel, 1985, vol. 11, part B, pp. 861–928.

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