Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2005, 15(1), 27–29
Mendeleev Communications

Transformation of isosteviol oxime to a lactone under Beckmann reaction conditions

Olesya I. Militsina, Galina I. Kovyljaeva, Galina A. Bakaleynik, Irina Yu. Strobykina, Vladimir E. Kataev,* Vladimir A. Alfonsov, Rashid Z. Musin, Dmitry V. Beskrovny and Igor A. Litvinov

A. E. Arbuzov Instituite of Organic and Physical Chemistry, Kazan Scientific Centre of the Russian Academy of Sciences, 420088 Kazan, Russian Federation. Fax: +7 8432 73 2253; e-mail kataev@iopc.knc.ru

DOI: 10.1070/MC2005v015n01ABEH001946

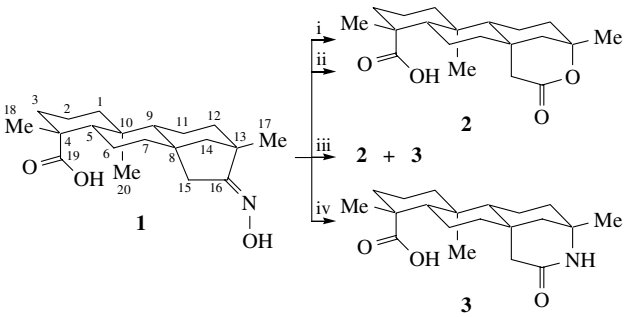
Heating the 16-*E*-oxime of isosteviol (*ent*-16-*E*-hydroxyiminobeyeran-19-oic acid) with concentrated hydrochloric acid (or 25% H_2SO_4) at 110 °C leads to the formation of lactone of 4α-carboxy-13α-hydroxy-13,16-seco-*ent*-19-norbeyeran-16-oic acid as the main product, whereas approximately equal quantities of this lactone and lactam of 4α-carboxy-13α-amino-13,16-seco-*ent*-19-norbeyeran-16-oic acid are formed by heating the 16-*E*-oxime of isosteviol with concentrated hydrochloric acid in an ampoule at 180 °C.

It is well known that certain oximes when subjected to Beckmann rearrangement conditions[1–3] do not rearrange into amides but undergo heterolytic fragmentation into a nitrile and a carbocation,[3] the latter being stabilised depending on the structure of the initial oxime and reaction conditions (Beckmann fragmentation reaction[3]). Among the oximes of cyclic ketones, only the oximes of α-trialkyl-substituted ketones are involved in this reaction. Thus, camphor oxime affords campholenic nitriles[1–6] under heating with 80–98% H_2SO_4 at 100–160 °C. The same nitriles are also formed as a result of the treatment of camphor oxime with concentrated hydrochloric acid,[7] 25% H_2SO_4, thionyl chloride, benzenesulfonyl chloride / sodium hydroxide, polyphosphoric acid or phosphorus pentoxide.[2,3] Norcamphor oxime reacts in the same way.[5]

We investigated the behaviour of the 16-*E*-oxime isosteviol (*ent*-16-*E*-hydroxyiminobeyeran-19-oic acid) **1**, which has

three alkyl substituents at the α-carbon atom of the oxime fragment, just as in camphor oxime. Isosteviol (*ent*-16-oxo-beyeran-19-oic acid), a diterpenoid of the beyeran (shachen) series,[8,9] is obtained by acid hydrolysis of the glycoside extracted from the plant *Stevia rebaudiana Bertoni*.[10–12]

We found that, under conditions of the Beckmann rearrangement, 16-*E*-oxime isosteviol **1**[13] reacts differently from camphor oxime. After heating with concentrated hydrochloric acid or 25% H_2SO_4 for 10 h, oxime **1** unexpectedly afforded lactone **2**† (Scheme 1) as the main reaction product in 53% yield (after chromatography on silica and recrystallization from AcOEt). The co-product of this reaction is isosteviol[8–12] formed as a result of hydrolysis of oxime **1**. No traces of lactam **3** were observed. It should be noted that we did not find in the literature any examples of lactone formation either under Beckmann rearrangement conditions or as the result of Beckmann fragmentation reactions. Lactone **2** was synthesised earlier by the oxidation of isosteviol with peracetic acid.[9]



Scheme 1 *Reagents and conditions*: i, 0.15 g (0.4 mmol) of oxime **1** and 3 ml of conc. HCl, 110 °C, 10 h; ii, 0.1 g (0.3 mmol) of oxime **1** and 3 ml of 25% H_2SO_4, 110 °C, 10 h; iii, 0.15 g (0.45 mmol) of oxime **1** and 2.5 ml of conc. HCl, ampoule, 180 °C, 10 h; iv, 0.08 g (0.6 mmol) of $SOCl_2$ was added to 0.1 g (0.3 mmol) of oxime **1** in 6 ml of $CHCl_3$, 60 °C, 10 h.

This reaction under conditions (iii) provides approximately equal quantities of lactone **2** and lactam **3** (30% yield each after chromatography on silica). As expected, under mild conditions of the Beckmann rearrangement (iv), lactam **3**† was isolated as the main reaction product in 70% yield (after chromatography on silica and recrystallization from methanol). The following explanation of the formation of lactone **2** can be proposed according to published data.[3,5,7] Nitrile carbocation **A** (Scheme 2) is formed as in the Beckmann fragmentation reaction of camphor oxime,[3,7] norcamphor oxime[5] or fenchone oxime.[3] However, it is further stabilised not by losing α-proton but by attaching a hydroxyl group and subsequent cyclization in imidate **B**, which, as well as other imidates,[3] is unstable under conditions (i), (ii) and (iii) and easily hydrolyses to lactone **2**.

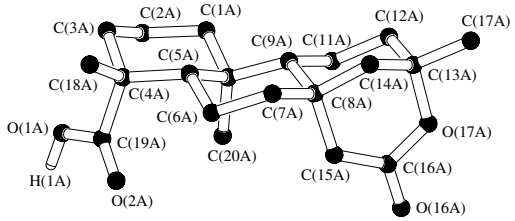
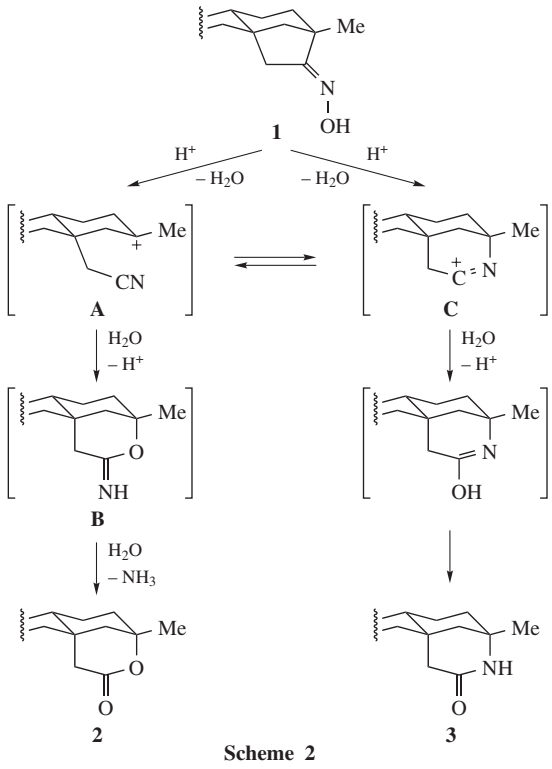


Figure 1 Molecular geometry of lactone **2** according to X-ray data (only the hydrogen atom of the carboxylic group is shown).

† **2**: mp 272 °C (from AcOEt) (lit.,[9] mp 262–264 °C). ^{1}H NMR ($CDCl_3$) δ: 0.87 (s, 3H, 20-H_3), 1.25 (s, 3H, 17-H_3), 1.35 (s, 3H, 18-H_3), 2.17 (d, 1H, 3-H, *J* 12.9 Hz), 3.12 (dd, 1H, 15-H, *J* 18.56 and 2.2 Hz). IR (mineral oil, ν/cm^{-1}): 1156 (C–O), 1690 (CO_2H), 1722 (lactone). EIMS, *m*/*z*: 334.2162 [calc. for $C_{20}H_{30}O_4$ (M^+) *m*/*z* 334.2144]. Found (%): C, 72.03; H, 9.50. Calc. for $C_{20}H_{30}O_4$ (%): C, 71.82; H, 9.04.

3: mp 377 °C (from MeOH). ^{1}H NMR (CD_3OD) δ: 0.82 (s, 3H, 20-H_3), 1.10 (s, 3H, 17-H_3), 1.21 (s, 3H, 18-H_3), 2.79 (d, 1H, 15-H, *J* 18.24 Hz). IR (mineral oil, ν/cm^{-1}): 1633 (O=C–NH), 1713 (CO_2H). EIMS, *m*/*z*: 333.2307 [calc. for $C_{20}H_{31}O_3N$ (M^+) *m*/*z* 333.2304]. Found (%): C, 72.05; H, 9.78; N, 4.22. Calc. for $C_{20}H_{31}O_3N$ (%): C, 72.02; H, 9.39; N, 4.2.



Scheme 2

One can assume that carbocation **C** (Scheme 2) is also formed under conditions (iii) and undergoes usual transformation[2,3,5] into lactam **3**.

X-ray data‡ observed for lactone **2** (Figure 1) and lactam **3** (Figure 2) demonstrate that the reactions proceed stereoselectively with cleavage of the C^{13}–C^{16} bond of cyclopentane ring D of the isosteviol framework, which is in the *anti* position in respect to the OH group of the oxime moiety (Scheme 2).

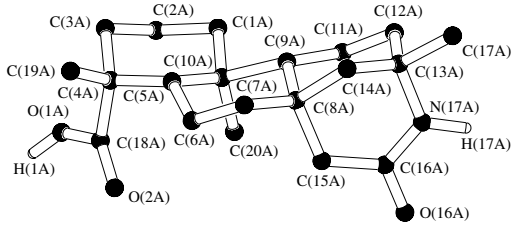


Figure 2 Molecular geometry of lactam **3** according to X-ray data (only the hydrogen atoms of carboxylic and amide groups are shown).

‡ *X-Ray crystallography of* **2** *and* **3**: $C_{20}H_{30}O_4$ **2**, orthorhombic, space group $P2_12_12_1$, a = 12.139(4), b = 14.029(3) and c = 20.890(10) Å, V = = 3559(2) Å^3, Z = 8, d_{calc} = 1.253 g cm^{-3}, 4081 independent reflections, final residues R_1 = 0.068 and wR_2 = 0.143.

$C_{20}H_{31}N_1O_3$ **3**, monoclinic, space group $P2_1$, a = 11.728(2), b = = 13.997(2) and c = 12.385(2) Å, β = 116.91(2)°, V = 1813(1) Å^3, Z = 8, d_{calc} = 1.22 g cm^{-3}, 3767 independent reflections (710 reflections with $F^2 \geq 3\sigma$), final residues R_1 = 0.064 and wR_2 = 0.053.

Cell parameters and intensities of reflections were measured on an Enraf-Nonius CAD-4 diffractometer in the $\omega/2\theta$-scan mode ($\theta \leq 22.76°$, MoKα radiation with a graphite monochromator). The structure was solved by a direct method using the SIR program and refined by the full matrix least-squares using the MOLEN program package. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were solved from difference Fourier maps, and the contribution of structural factors was included with fixed positional and thermal parameters in the last cycles.

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference numbers 242202 and 242203. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2005.

This work was supported by the Russian Foundation for Basic Research (grant no. 04-03-32133).

References

1 L. G. Donoruma and V. Z. Heldt, in *Organic Reactions*, Wiley, New York, 1960, vol. 11, p. 30.
2 P. A. S. Smith, in *Molecular Rearrangements*, ed. P. de Mayo, Interscience, New York, 1962, Part I, p. 483.
3 C. G. McCarty, in *The Chemistry of the Carbon–Nitrogen Double Bond*, ed. S. Patai, Interscience, London, 1970, p. 363.
4 G. R. Krow and S. Szczepanski, *Tetrahedron Lett*., 1980, **21**, 4593.
5 G. R. Krow, *Tetrahedron*, 1981, **37**, 1283.
6 J. Soloducho and A. Zabza, *Pol. J. Chem*., 1979, **53**, 1497.
7 N. G. Kozlov and T. I. Pehk, *Zh. Org. Khim*., 1982, **18**, 1118 [*J. Org. Chem. USSR* (*Engl. Transl.*), 1982, **18**, 968].
8 J. R. Hanson, *The Tetracyclic Diterpenes*, Pergamon Press, Oxford, 1968, p. 132.
9 J. MacMillan and M. H. Beale, in *Comprehensive Natural Products Chemistry*, ed. D. E. Cane, Elsevier, Amsterdam, 1999, vol. 2, p. 217.
10 R. M. Coates and E. F. Bertram, *J. Org. Chem*., 1971, **36**, 2625.
11 V. A. Alfonsov, G. A. Bakaleynik, A. T. Gubaidullin, V. E. Kataev, G. I. Kovyljaeva, A. I. Konovalov, I. A. Litvinov and I. Yu. Strobykina, *Zh. Obshch. Khim*., 1998, **68**, 1813 (*Russ. J. Gen. Chem*., 1998, **68**, 1735).
12 B. H. de Oliveira, M. C. dos Santos and P. C. Leal, *Phytochemistry*, 1999, **51**, 737.
13 V. A. Alfonsov, O. V. Andreeva, G. A. Bakaleynik, D. V. Beskrovny, A. T. Gubaidullin, V. E. Kataev, G. I. Kovyljaeva, A. I. Konovalov, M. G. Korochkina, I. A. Litvinov, O. I. Militsina and I. Yu. Strobykina, *Zh. Obshch. Khim*., 2003, **73**, 1330 (*Russ. J. Gen. Chem.*, 2003, **73**, 1255).

Received: 26th May 2004; Com. 04/2271