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UNUSUAL COURSE OF THE REACTION OF 15(*S*)-BROMOISOSTEVIOL METHYL ESTER WITH SODIUM AZIDE

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*The reaction of 15(*S*)-bromoisosteviol methyl ester with sodium azide produced 15(*S*)-hydroxyisosteviol, the structure of which was elucidated by an x-ray structure analysis.*

Keywords: α-haloketones, azides, isosteviol, *ent*-beyerane, oxidation, 1,2-diketones.

The bromine atom in 3-methoxy-15-bromoestrone was shown to undergo facile replacement by azide in DMF in the presence of glacial AcOH at room temperature in 30 min to form the corresponding 3-methoxy-15-azidoestrone in quantitative yield [1].

We discovered that 15(*S*)-bromoisosteviol methyl ester (**1**) under analogous conditions did not form the corresponding azide **2** even after 1 d. Only heating the reaction mixture for several hours formed two major and several still unidentified minor products. The two major products were separated by column chromatography over silica gel (petroleum ether:benzene:Et_2O, 1:1:1). The less polar product was identified as isosteviol methyl ester **3** according to PMR, mass spectrometry, and melting point, which agreed with the literature [2]. The IR spectrum of the second more polar product showed bands at 1152 and 1720 (CO_2CH_3)) and 1742 cm^{-1} (C=O), indicating that isosteviol methyl ester was present, and at 1019, 1094, and 3528, characteristic of a secondary hydroxyl. This in addition to a peak in the mass spectrum at *m*/*z* 348 for the molecular ion indicated that a hydroxyl added to the *ent*-beyerane framework of **3**. Because proton H-15$_\alpha$ of **1** appeared in the PMR spectrum as a doublet at 4.44 ppm with SSCC 2.07 Hz [3], the presence in the PMR spectrum of the analyzed product of a doublet at 3.95 ppm with SSCC 2.3 Hz indicated that this was 15(*S*)-hydroxyisosteviol methyl ester (**4**). It is noteworthy that an analog of **4** was obtained previously by microbiological trnasformation of isosteviol (**5**) [4]. This derivative of *ent*-beyerane was obtained for the first time by a chemical route. The structure of **4** was solved by an x-ray structure analysis (XSA) (Table 1, Fig. 1a).

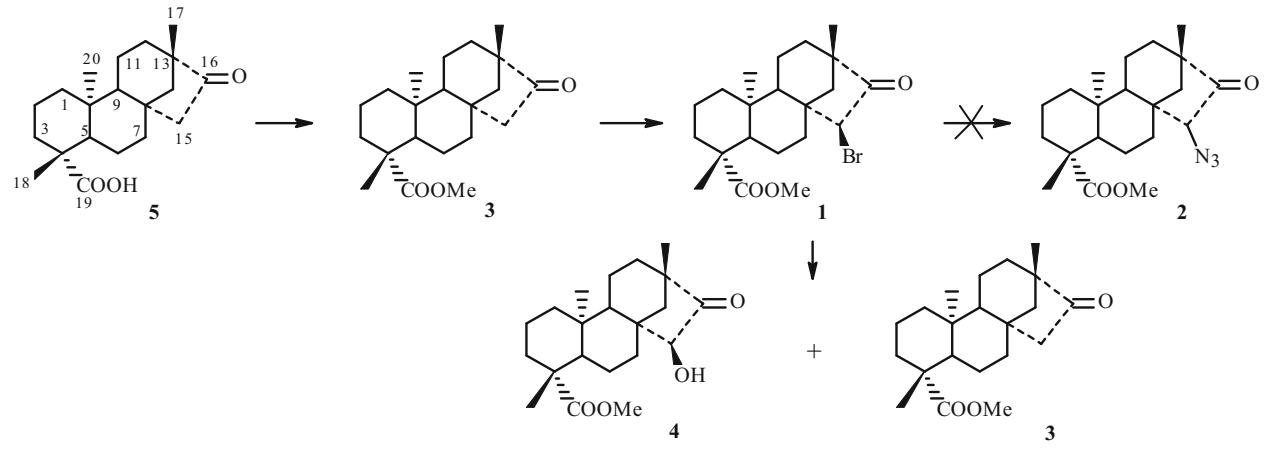

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TABLE 1. Crystallographic Parameters of **4** and **6** and X-ray Structure Conditions

Parameter	**4**	**6**
Color, habit	Colorless prisms	Colorless prisms
	0.40 × 0.40 × 0.20 мм	0.35 × 0.12 × 0.07мм
Empirical formula	$C_{21}H_{32}O_4$	$C_{21}H_{30}O_4$
System	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
Unit-cell constants	a = 7.522 (2)	a = 6.464(6),
	b = 8.8570 (10)	b =13.15(2),
	c = 27.492 (7) Å	c = 22.30(3) Å
Volume, Å^3	1831.6 (7)	1896 (4)
Z	4	4
Molecular weight	348.47	346.45
Density (calcd), g/cm^3	1.264	1.213
Absorption coefficient, см$^{-1}$	0.85	6.59
F (000)	760	752
Radiation (λ, Å)	MoK$_\alpha$, 0.71073	CuK$_\alpha$, 1.54184
Scan range	1.48 ≤ θ ≤ 26.33	3.90 ≤ θ ≤ 74.54
Index measurement range	0 ≤ h ≤ 9,	–7 ≤ h ≤ 7,
	0 ≤ k ≤ 11,	0 ≤ k ≤ 15,
	0 ≤ l ≤ 34	–26 ≤ l ≤ 26
Measured reflections total/independent	2098/2098	6484/3491
Observed reflections with $I > 2\sigma(I)$	1975	1531
Final values of agreement factors	R = 0.0559,	R = 0.0860,
	Rw = 0.1473	Rw = 0.1881
	over F$^2 \geq 2\sigma$	over F$^2 \geq 2\sigma$
Fitting parameter	1.049	0.927
Number of refined parameters	354	227

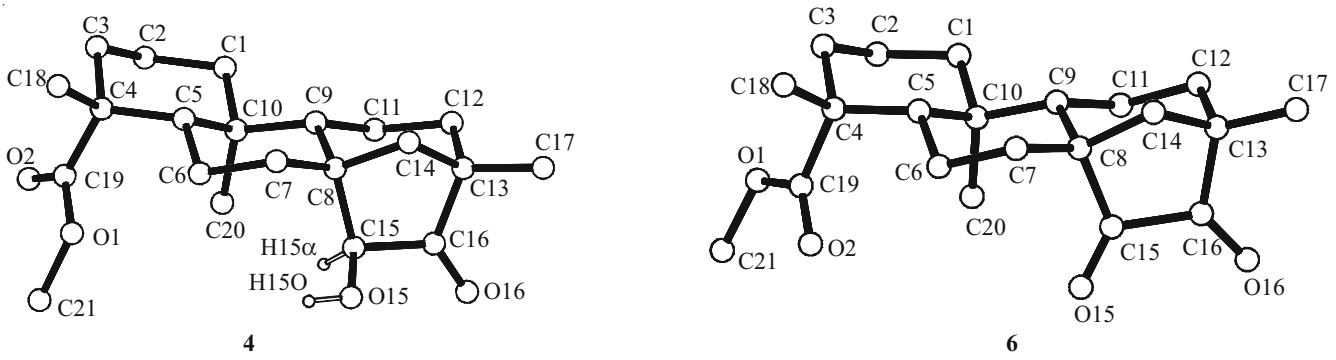
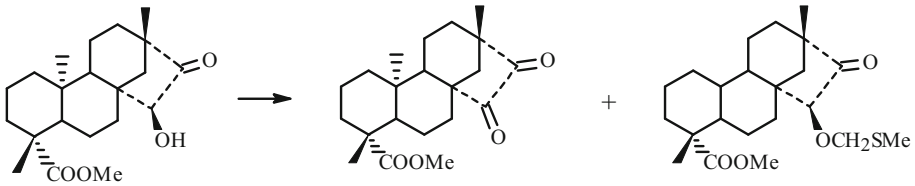


Fig.1. Molecular structures of 15(*S*)-hydroxyisosteviol (**4**) (selected H atoms are shown) and 15-oxoisosteviol methyl ester (**6**) (H atoms are not shown).

Substitution of the Br atom by hydroxyl in the reaction of **1** with sodium azide is unusual. It order to explain its role, **1** was heated without NaN_3 in pure DMF and in the presence of KOH. 15(*S*)-Hydroxyisosteviol (**4**) was not observed. Bromide **1** was practically completely converted to isosteviol methyl ester (**3**). We found the optimal conditions for synthesizing **4** by changing the ratio of reagents and reaction time and temperature. Traces of moisture in the reaction mixture are required for its preparation. Performing the reaction in pure DMF formed only **3**. The reaction mechanism is still unclear; however, steric hindrance to the C-15 Br atom of **1** from the *re*-side (i.e., atom H-15$_\alpha$) by the CH_3-20 group [3] probably plays an important role. This can be seen in Fig. 1a.

Next **4** was reacted with a mixture of DMSO:Ac_2O, which was previously used successfully to oxidize a sterically hindered hydroxyl in α-hydroxycarbonyl compounds [5, 6] and diols [7, 8], including sugars [7]. Column chromatography over silica gel isolated 15-oxoisosteviol methyl ester (**6**) in addition to a product (29% yield) that was characterized as the 15(*S*)-methylthiomethyl ether **7** based on spectral (IR and PMR) and mass spectral data. The formation of side products of such structure was noted previously [5, 7, 8]. The reaction mechanism is unknown [5].



4 **6** **7**

Based on the appearance in the PMR spectrum of **4** of a doublet at 4.0 ppm with SSCC 1.7 Hz, which according to the aforementioned arguments is the resonance of H-15α, C-15 was assigned the *S*-configuration.

The molecular structure of **6** was elucidated by an XSA (Fig. 1b).

EXPERIMENTAL

XSA of single crystals of **4** and **6** were performed in the X-ray Structure Department of the Center for Collective Use Spectral Analytical Center in the Laboratory of Diffraction Methods at Arbuzov IOPC, Kazan SC, RAS. Table 1 presents crystallographic parameters, experimental conditions, and structure refinement data. The experiments were carried out on CAD-4 automated four-circle diffractometers (Nonius B. V.) at 23°C with a graphite monochromator. Data were processed initially using the MolEN program [9] on an AlphaStation 200 computer. The intensities of three control reflections remained constant during the experimental exposures. The structures of **4** and **6** were solved by direct methods using the SIR program [10] and were refined initially isotropically then anisotropically using the SHELXL-97 [11] and WinGX [12] programs. H atoms in the structure of **4** were found in difference electron-density syntheses and refined isotropically; in **6**, calculated stereochemically and refined by corresponding rider models. Intermolecular interactions were analyzed and figures were drawn using the PLATON program [13]. Atomic coordinates of **4** and **6** and their thermal parameters were deposited in the Cambridge Crystallographic Database Centre (http://www.ccdc.cam.ac.uk; 729202 and 729203).

IR spectra were recorded on a UR-20 spectrophotometer (400–3600 cm^{-1}) and a Vector 22 Fourier-spectrometer (Bruker) (400–4000 cm^{-1}). Samples were studied as mineral-oil emulsions and in KBr pellets.

Mass spectra were obtained on an MX-1310 instrument at ionizing potential 60 eV and collector electron current 30 μA with direct sample insertion into the ion source at 120°C. The vaporization ampul was heated to 120–250°C. PMR spectra were taken on an Avance 600 instrument (Bruker). Column chromatography was performed over silica gel (Chemapol). Reaction mixtures were analyzed by TLC on Silufol UV-254 plates.

15(*S*)-Bromo-16-oxo-*ent*-beyeran-19-oic acid (1) was synthesized as before [3], mp 247°C (MeOH) (lit. [3] mp 246–248°C). Its spectral characteristics agreed with the literature [3].

15(*S*)-Hydroxy-16-oxo-*ent*-beyeran-19-oic Acid Methyl Ester (4). Compound **1** (0.41 g, 1 mmol) and NaN_3 (0.2 g, 3.1 mmol) were dissolved in DMF (25 mL), heated for 10 h on a water bath (90–100°C), treated with water (250 mL) and glacial AcOH (1 mL), and left for 72 h. The resulting precipitate was filtered off, washed with water, and dried in air. Chromatography over silica gel (petroleum ether:benzene:Et_2O, 1:1:1) isolated isosteviol methyl ester (**3**, 0.07 g, 18%), the constants and spectral characteristics of which agreed with the literature [2], and compound **4** (0.19 g, 54%), mp 221–224°C (petroleum ether:EtOAc). IR spectrum (KBr, ν, cm^{-1}): 1019, 1094 (>CH–OH), 1152, 1720 ($COOCH_3$), 1742 (C=O), 3528 (>CH–OH). PMR spectrum (600 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.74–3.94 (28H, m, *ent*-beyerane skeleton), 0.74 (3H, s, H_3-20), 1.02 (3H, s, H_3-17), 1.20 (3H, s, H_3-18), 3.63 (3H, s, OCH_3), 3.95 (H, d, $J_{20,15\alpha}$ = 2.3, H-15α), $C_{21}H_{32}O_4$.

Oxidation of 15(*S*)-Hydroxyisosteviol by DMSO:Ac_2O. 15(*S*)-Hydroxyisosteviol (**4**, 0.094 g, 0.3 mmol) was dissolved in DMSO (3 mL), treated with Ac_2O (2 mL), left for 24 h at room temperature, treated with water (40 mL), and extracted with EtOAc. The extract was washed with water and dried over $MgSO_4$. Solvent was removed. The solid (0.09 g) was chromatographed over silica gel (petroleum ether:Et_2O:benzene, 1:1:1) to isolate **6** (0.045 g, 48%) and **7** (0.032 g, 29%).

15,16-Dioxo-*ent*-beyeran-19-oic acid methyl ester (6), mp 201–203°C (benzene:DMSO) (lit. [14] mp 190°C). Its spectral characteristics agreed with the literature [14].

15-Methylthiomethyleneoxy-16-oxo-*ent*-beyeran-19-oic acid methyl ester (7), mp 100–102°C. IR spectrum (KBr, ν, cm^{-1}): 683, 730, 803 (C–S), 1720 ($COOCH_3$), 1742 (C=O). PMR spectrum (600 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.84–3.99

(28H, *ent*-beyerane skeleton), 0.84 (3H, s, H_3-20), 1.0 (3H, s, H_3-17), 1.18 (3H, s, H_3-18) 2.20 (3H, s, SCH_3), 3.62 (3H, s, OCH_3), 3.99 (H, d, $J_{20,15\alpha}$ = 1.7, H-15α), 4.78 (H, d, J_{AB} = 12, OCH_AS), 4.98 (H, d, J_{AB} = 12, OCH_BS). Mass spectrum (EI, 60 eV): $[M]^+$ *m*/*z* 408 (m/z_{calcd} 408.6039). $C_{23}H_{36}O_4S$.

REFERENCES

1. B. Schonecker and K. Ponsold, *J. Prakt. Chem.*, **313**, 817 (1971).
2. E. Mosetting and W. R. Nes, *J. Org. Chem.*, **20**, 884 (1955).
3. V. A. Mamedov, V. A. Al′fonsov, G. A. Bakaleinik, V. E. Kataev, G. I. Kovylyaeva, O. I. Militsina, I. Yu. Strobykina, D. V. Beskrovnyi, A. T. Gubaidullin, I. A. Litvinov, I. Kh. Rizvanov, and R. Z. Musin, *Zh. Obshch. Khim.*, **75**, 622 (2005).
4. S. F. Chang, L.-M. Yang, C.-H. Lo, J.-H. Liaw, L.-H. Wang, and S.-J. Lin, *J. Nat. Prod.*, **71**, 87 (2008).
5. J. D. Albright and L. Goldman, *J. Am. Chem. Soc.*, **87**, 4214 (1965).
6. M. Van Dyk and N. D. Pretchard, *J. Org. Chem.*, **32**, 3204 (1967).
7. W. Sorva and G. H. S. Thomas, *Can. J. Chem.*, **44**, 836 (1966).
8. M. S. Newman and C. C. Davis, *J. Org. Chem.*, **32**, 66 (1967).
9. L. H. Straver and A. J. Schierbeek, *MoIEN. Structure Determination System*, **1**, Program Description, Nonius B. V., Delft, 1994.
10. A. Altomare, G. Cascarano, C. Giacovazzo, and D. Viterbo, *Acta Crystallogr. Sect. A: Found. Crystallogr.*, **47**, 744 (1991).
11. G. M. Sheldrick, *SHELX-97. Programs for Crystal Structure Analysis (Release 97-2)*, University of Goettingen, Goettingen, 1997.
12. L. J. Farrugia, *J. Appl. Crystallogr.*, **32**, 837 (1999).
13. A. L. Spek, *Acta Crystallogr. Sect. A: Found. Crystallogr. (Suppl.)*, **46**, 34 (1990).
14. M. Bomkamp, K. Gottfried, O. Kataeva, and S. R. Waldvogel, *Synthesis*, 1443 (2008).