

An unusual Bamford–Stevens reaction of 17-toluenesulfonylhydrazono-3 β -acetoxy-14 α -hydroxyandrost-5-ene

Vladimir A. Khripach,^{a*} Vladimir N. Zhabinskii,^a Anna I. Kotyatkina,^a Galina P. Fando,^a Alexander S. Lyakhov,^a Alla A. Govorova,^a Jaap van der Louw,^b Marinus B. Groen^b and Aede de Groot^c

^a Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus, 220141 Minsk, Belarus.

Fax: +375 17 264 8647; e-mail: vz@ns.iboch.ac.by

^b Department of Medicinal Chemistry, N. V. Organon, P.O. Box 20, 5340 BH Oss, The Netherlands

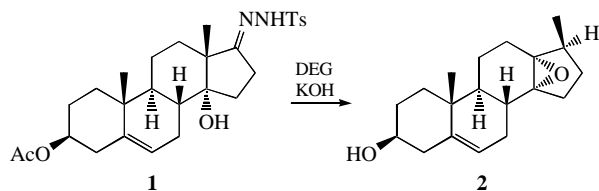
^c Laboratory of Organic Chemistry and Research Centre, Wageningen University, 6703 HB Wageningen, The Netherlands

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The Bamford–Stevens reaction of 17-toluenesulfonylhydrazono-3 β -acetoxy-14 α -hydroxyandrost-5-ene was found to proceed with migration of the 18-methyl group and formation of a 13,14-epoxide.

The cleavage of aliphatic tosyl hydrazones under basic conditions (Bamford–Stevens reaction¹) is widely used in organic chemistry for the generation of diazoalkanes and their transformation products. Many attempts have been done to study this reaction in steroids,^{2,3} including the reaction of 17-tosyl hydrazones,⁴ which was shown to give cyclopropane derivatives or a mixture of olefins.

We present here a detailed study of the Bamford–Stevens reaction of tosyl hydrazone **1**[†] containing a hydroxy group at C¹⁴.⁵



Scheme 1

It is known that the introduction of a functional group in the close vicinity of the reaction centre may result in formation of new products because of involvement of this group in the process. The heating of tosyl hydrazone **1** in diethylene glycol in the presence of KOH for 1.5 h at 110–120 °C followed by usual work-up and column chromatography gave epoxide **2** (Scheme 1).[‡] Its structure was assigned on the basis of the NMR data and confirmed by X-ray analysis.[§]

An ORTEP⁶ view of epoxide **2** with an atom-numbering scheme is shown in Figure 1. The bond distances and angles in

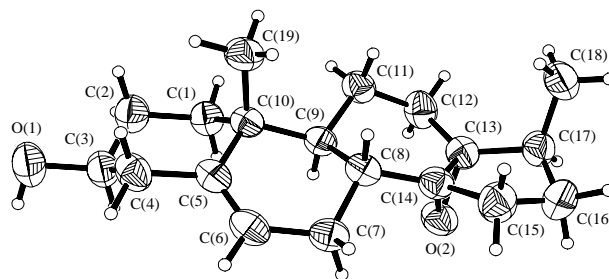
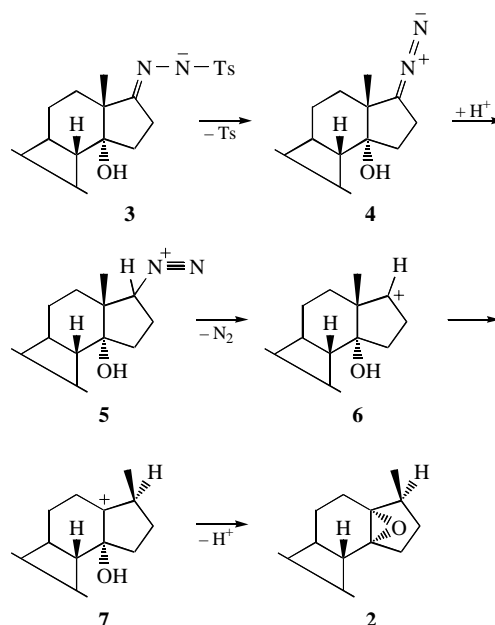


Figure 1 ORTEP drawing of the molecular structure of **2**. Displacement ellipsoids are shown at the 50% probability level; hydrogen atoms are represented by spheres of arbitrary radii.

2 are consistent with those observed previously for analogous compounds.⁷ A study of the molecular packing revealed that they are linked by O–H...O hydrogen bonds forming chains parallel with the *x* axis of the unit cell.

The proposed reaction mechanism is outlined in Scheme 2. The treatment of tosyl hydrazone **1** with a base gave anion **3**, which, on elimination of the tosyl group, was converted into the diazoalkane **4**. Under the reaction conditions, it was protonated to give cation **5**. The elimination of nitrogen led to cation **6**, which was subjected to a Wagner–Meerwein rearrangement⁸ to give **7**. Epoxide ring closure in **7** followed by deprotonation gave epoxide **2**.

Apart from **2**, the formation of diol **8**[†] was also observed as a result of epoxide ring opening under the reaction conditions (Scheme 3). It should be noted that the reductive opening of



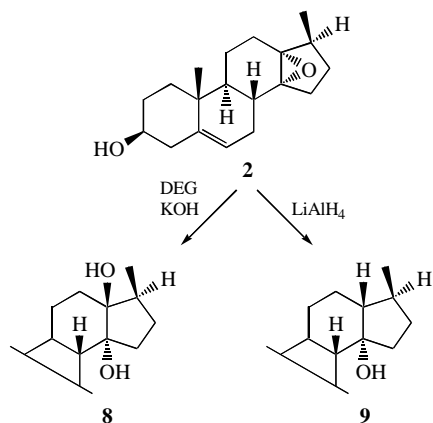
Scheme 2

[†] 17-Toluenesulfonylhydrazono-3 β -acetoxy-14 α -hydroxyandrost-5-ene **1** was prepared from 3 β -acetoxy-14 α -hydroxyandrost-5-ene (Organon N.V.) in 95% yield, mp 264–266 °C (EtOH). ¹H NMR, δ : 1.06 (s, 3H, 18-Me), 1.14 (s, 3H, 19-Me), 2.04 (s, 3H, OAc), 2.20 (s, 3H, Ts), 4.60 (m, 1H, C³-H), 5.44 (br. s, 1H, C⁶-H), 7.10 (s, 1H, Ts), 7.36 (s, 1H, Ts), 7.82 (s, 1H, Ts). IR, ν /cm⁻¹: 1730, 1710, 1480, 1300, 1190, 1070.

[‡] 13 α ,14 α -Epoxy-3 β -hydroxy-19-nor-17 β -methylandrost-5-ene **2**. Yield 69%, mp 141–144 °C (hexane–EtOAc) (lit.⁵ mp 139–142 °C). ¹H NMR, δ : 0.92 (s, 3H, 19-Me), 0.94 (d, 3H, C¹⁷-Me, *J* 7 Hz), 3.54 (m, 1H, C³-H), 5.44 (t, 1H, C⁶-H, *J* 3 Hz). ¹³C NMR, δ : 16.7, 18.5, 23.2, 23.6, 27.6, 28.0, 28.4, 31.4, 34.3, 36.2, 36.3, 37.2, 42.1, 43.6, 70.4, 71.7, 71.9, 121.5, 140.5. IR, ν /cm⁻¹: 1460, 1440, 1380, 1330, 1315, 1230, 1060, 970, 910.

[§] Crystal data for **2**: C₁₉H₂₈O₂, *M* = 288.41, orthorhombic, space group *P*2₁2₁2₁, *a* = 8.433(2) Å, *b* = 9.045(2) Å, *c* = 21.119(4) Å, *V* = 1610.9 Å³, *Z* = 4, *d*_{calc} = 1.189 g cm⁻³, μ (MoK α) = 0.75 cm⁻¹. Data collection (1.93 $\leq \theta \leq 30.06^\circ$) was performed on a Nicolet R3m diffractometer (MoK α , graphite monochromator, $\omega/2\theta$ scan) at 293 K. The structure was solved using direct methods (SIR97)⁹ and refined by full-matrix least-squares (SHELXL-97),¹⁰ giving *R*₁ = 0.0460 for 194 parameters and 2125 reflections with *I* > 2 σ (*I*) and *wR*₂ = 0.1505 for all 2796 unique reflections (GOOF = 1.026). The positional parameters of all the H atoms were calculated geometrically and refined using a riding model with *U*(H) = 1.2*U*_{eq} of attached atom [for methyl groups *U*(H) = 1.5*U*_{eq}]. 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, 2001. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/93.

epoxide **2** afforded 14 α -alcohol **9**,^{††} *i.e.*, the ultimate result of this reaction sequence is a 1,2-shift of the 18-methyl group.



Scheme 3

[†] 3 β ,13 β ,14 α -Trihydroxy-19-nor-17 β -methylandrost-5-ene **8**: yield 9.3%, mp 187–190 ° (hexane–EtOAc). ¹H NMR, δ : 0.94 (d, 1H, C¹⁷-Me, *J* 7 Hz), 1.00 (s, 3H, 19-Me), 3.50 (m, 1H, C³-H), 5.40 (m, 1H, C⁶-H). ¹³C NMR (600 MHz) δ : 12.8, 19.8, 20.0, 25.5, 28.3, 29.0, 32.0, 34.0, 35.1, 37.0, 37.8, 39.0, 42.6, 43.4, 72.1, 81.4, 83.8, 122.0, 140.5.

^{††} 3 β ,14 α -Dihydroxy-19-nor-17 β -methylandrost-5-ene **9**: yield 63%, mp 186–188 °C (hexane–EtOAc). ¹H NMR, δ : 0.96 (s, 3H, 19-Me), 0.99 (d, 3H, 18-Me, *J* 6 Hz), 3.43–3.60 (m, 1H, C³-H), 5.35–5.42 (m, 1H, C⁶-H). ¹³C NMR, δ : 19.0, 19.5, 23.0, 25.4, 25.5, 30.5, 31.7, 35.3, 36.2, 36.5, 41.3, 42.2, 44.0, 56.0, 71.6, 81.4, 121.6, 139.9.

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