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Unexpected formation of an oxetane cycle by oxidation of diacetonide of 20-hydroxyecdysone with oxygen in an alkaline medium

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The diacetonides of 9α,14α-epoxy-14-deoxy-20-hydroxyecdysone and 14α-hydroperoxy-14-deoxy-20-hydroxyecdysone have been obtained by the interaction of diacetonide of 20-hydroxyecdysone with a solution of lithium in liquid ammonia and following treatment with ammonia chloride and atmospheric oxygen.

The reaction of α,β-unsaturated ketones with alkali metals in liquid ammonia is widely used in steroid chemistry for the selective reduction of conjugated double bonds.[1,2]

We found that reduction of diacetonide of 20-hydroxyecdysone **1** by lithium in liquid ammonia and subsequent treatment of the reaction mixture with ammonium chloride and evaporation of ammonia on air leads to unusual transformation with the formation of 9,14-epoxy derivative (oxetane) **2** and 14α-hydroperoxide **3**† (Scheme 1). It was reported earlier[3] that 14α-hydroperoxide **3** with a yield of 82% had been obtained by analogous reduction of diacetonide **1** and subsequent slow evaporation of NH_3 'without hard exception of oxygen' and treatment with water solution of NH_4Cl. Oxetane **2** was not formed.

Formation of oxygen bridge between C^9 and C^{14} in compound **2** accounted for appearing singlets (^{13}C NMR, JMOD) in the region of δ 92.7 and 106.7 ppm, respectively, instead of 34.3 (dublet C^9) and 84.7 ppm (singlet C^{14}) in the ^{13}C NMR spectrum of initial compound **1**.[4] In the ^1H NMR spectrum of oxetane **2** the HC^9 proton signal was absent and the HC^7 proton signal was transformed from a doublet ($^4J_{7,9}$ 2 Hz in spectrum of **1**) to a singlet. The structure of oxetane **2** was established by a combination of 1D and 2D NMR procedures and confirmed

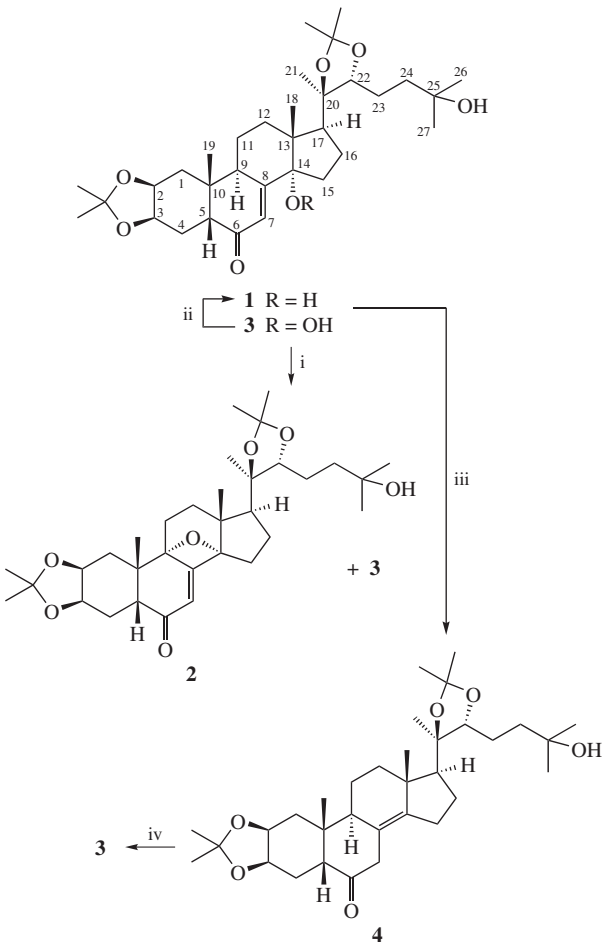
† IR spectra were recorded on a Specord 75-IR spectrometer. UV spectra were measured on a Specord M-40 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance-500 spectrometer (500.13 MHz for ^1H and 125.76 MHz for ^{13}C) and a Bruker Avance-400 spectrometer (400.13 MHz for ^1H and 100.62 MHz for ^{13}C). Chemical shifts are given in ppm from TMS as an internal standard. Mass spectra were measured on a VG ZAB-E high-resolution instrument. Specific rotations were measured on a Perkin-Elmer-141 polarimeter. Elemental analysis was determined on element analysator of Karlo Erba, model 1106. Melting points were determined on a Boetius hot stage. Column chromatography and TLC were carried out using silica gel (< 0.06 mm) and precoated silica gel 60 F_{254} plates, respectively.

Lithium (purity ≥ 99%) was from Fluka, liquid ammonia from balloon was distilled under sodium, diacetonide of 20-hydroxyecdysone was obtained according to ref. 4.

*Synthesis of (20*R,22R*)-9α,14α-epoxy-2β,3β:20,22-bis[(dimethylmethylene)dioxy]-25-hydroxy-5β-cholest-7-en-6-one* **2** *and (20*R,22R*)-14α-hydroperoxy-2β,3β:20,22-bis[(dimethylmethylene)dioxy]-25-hydroxy-5β-cholest-7-en-6-one* **3**. A solution of compound **1** (2 g, 3.6 mmol) in anhydrous THF (10 ml) was added to a solution of Li (0.3 g, 43 mmol) in ammonia (50 ml). The mixture was stirred at –33 °C for 0.5 h, NH_4Cl (4.0 g) was added and the ammonia allowed to evaporate NH_3 on air before obtaining solid residue without ammonia smell. The crude product was dissolved with water (30 ml) and extracted with EtOAc (3×50 ml). Evaporation of the solvent afforded a solid residue, that was chromatographed on a column (100 g SiO_2, eluted with $CHCl_3$–MeOH, 100:1, v/v) to give compound **2** [1.5 g, 75%, R_f 0.60 ($CHCl_3$–MeOH, 8:1, v/v)] and compound **3** [0.4 g, 19%, R_f 0.49 ($CHCl_3$–MeOH, 8:1, v/v)].

For **2**: mp 232–233 °C, $[\alpha]_D^{18}$ +75 (*c* 1.0, $CHCl_3$). IR (KBr, ν/cm^{-1}): 3400, 2900, 1650, 1450, 1370. UV (MeOH, λ_{max}/nm): 242. HR-FAB-MS (positive-ion mode), *m/z*: 559.3641 $[M + H]^+$ (calc. for $C_{33}H_{50}O_7$ + H, 559.3635). ^1H NMR (500 MHz, $CDCl_3$) δ: 0.97 (s, 3H, H_3C^{18}), 1.16 (s, 3H, H_3C^{21}), 1.21 (s, 3H, H_3C^{26}), 1.22 (s, 3H, H_3C^{27}), 1.26 and 1.28 (2s, 6H, 2,3-Me_2C), 1.33 (s, 3H, H_3C^{19}), 1.41 and 1.48 (2s, 6H, 20,22-Me_2C), 1.46 and 1.55 (2m, 2H, H_2C^{23}), 1.52 and 1.69 (2m, 2H, H_2C^{24}), 1.56 (m, 1H, H_aC^4), 1.76 and 1.98 (2m, 2H, H_2C^{16}), 1.89 and 2.10 (2m, 2H, H_2C^{15}), 1.89 and 2.47 (2m, 2H, H_2C^{11}), 1.90 and 1.99 (2m, 2H, H_2C^{12}), 1.92 and 2.12 (2m, 2H, H_2C^1), 2.08 (m, 1H, HC^{17}), 2.19 (m, 1H, HC^5), 2.54 (m, 1H, H_eC^4), 3.71 (d, 1H, HC^{22}, *J* 9.4 Hz), 4.01 (m, $w_{1/2}$ 25 Hz, 1H, HC^3), 4.20 (m, 1H, HC^2), 5.61 (br. s, 1H, HC^7). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 17.5 (C^{18}), 21.1 (C^{21}), 21.5 (C^{19}), 22.9 (C^{16}), 23.5 (C^{23}), 24.2 (C^4), 25.9 and 28.4 (2,3-C*Me*$_2$), 26.3 and 28.7 (20,22-C*Me*$_2$), 26.4 (C^{11}), 28.0 (C^{15}), 28.8 (C^{26}), 29.2 (C^1), 29.6 (C^{27}), 33.9 (C^{12}), 40.6 (C^{10}), 41.3 (C^{24}), 50.4 (C^5), 50.6 (C^{13}), 52.7 (C^{17}), 70.8 (C^{25}), 70.9 (C^2), 72.7 (C^3), 81.7 (C^{22}), 82.9 (C^{20}), 92.7 (C^9), 106.7 (C^{14}), 107.1 (20,22-*C*Me$_2$), 108.0 (2,3-*C*Me$_2$), 110.8 (C^7), 168.3 (C^8), 196.7 (C^6).

For **3**: mp 139–141 °C (lit.,[3] an amorphous solid), $[\alpha]_D^{18}$ +17.2 (*c* 5.2, $CHCl_3$). IR (KBr, ν/cm^{-1}): 3400, 2965, 1650. UV (MeOH, λ_{max}/nm): 242. HR-FAB-MS (positive-ion mode), *m/z*: 561.3795 $[M - O + H]^+$ (calc. for $C_{33}H_{52}O_8$ – O + H, 561.3791). ^1H NMR (500 MHz, $CDCl_3$) δ: 0.85 (s, 3H, H_3C^{18}), 1.02 (s, 3H, H_3C^{19}), 1.12 (s, 3H, H_3C^{21}), 1.24 (s, 3H, H_3C^{26}), 1.25 (s, 3H, H_3C^{27}), 1.33 (s, 6H, 2,3-Me_2C), 1.41 and 1.49 (2s, 6H, 20,22-Me_2C), 1.48 and 1.59 (2m, 2H, H_2C^{23}), 1.58 and 1.72 (2m, 2H, H_2C^{24}), 1.64 and 1.78 (2m, 2H, H_2C^{11}), 1.77 and 1.94 (2m, 2H, H_2C^{12}), 1.78 and 2.05 (2m, 2H, H_2C^{16}), 1.81 and 2.06 (2m, 2H, H_2C^{15}), 1.99 (m, 1H, H_aC^4), 2.05 (m, 1H, H_eC^4), 2.12 (m, 1H, HC^{17}), 2.36 (dd, 1H, HC^5, *J* 10.0 and 7.0 Hz), 3.64 (m, $w_{1/2}$ 15 Hz, 1H, HC^{22}), 4.25 (m, $w_{1/2}$ 21 Hz, 1H, HC^2), 4.28 (m, $w_{1/2}$ 12 Hz, 1H, HC^3), 5.83 (d, 1H, HC^7, *J* 2.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 17.9 (C^{18}), 21.1 (C^{11}), 21.3 (C^{16}), 21.8 (C^{21}), 23.8 (C^{19}), 23.8 (C^{23}), 24.5 (C^{15}), 26.4 (C^4), 26.6 and 28.5 (2,3-C*Me*$_2$), 26.6 and 28.9 (20,22-C*Me*$_2$), 29.5 (C^{26}), 29.5 (C^{27}), 31.1 (C^{12}), 35.7 (C^9), 37.6 (C^1), 37.7 (C^{10}), 41.5 (C^{24}), 49.2 (C^{13}), 49.9 (C^{17}), 50.9 (C^5), 70.7 (C^{25}), 71.7 (C^3), 72.3 (C^2), 82.0 (C^{22}), 84.1 (C^{20}), 96.8 (C^{14}), 107.5 (20,22-*C*Me$_2$), 108.6 (2,3-*C*Me$_2$), 125.1 (C^7), 158.9 (C^8), 202.2 (C^6).



Scheme 1 *Reagents and conditions*: i, Li/$NH_{3\ liq}$–THF, then NH_4Cl, evaporation of NH_3 on air; ii, H_2/Pd-C, EtOH; iii, Li/$NH_{3\ liq}$–THF, then NH_4Cl, evaporation of NH_3 (Ar); iv, O_2.

by a high-resolution mass spectrum. Evidence of 9,14-position of oxetane cycle synonymously ensued from HMBC experiments and ^1H–^{13}C correlation of Me^{19} and Me^{18} with C^9 (δ 92.7 ppm) and C^{14} (δ 106.7 ppm), respectively.

The X-ray diffraction study of crystals **2**‡ (Figure 1) showed, that by transformation of compound **1** to the oxetane **2** inversion of configuration of chiral centers did not take place, and oxetane **2** has a structure of 2,3:20,22-diacetonide of 9α,14α-epoxy-14-deoxy-20-hydroxyecdysone. In the crystal, molecules of oxetane **2** form H-bonded dimers [intermolecular hydrogen bond O(25)–H···O(9,14)$_{-x+1,\,y,\,-z+1}$, distance O···O 2.873(4) Å, angle O–H···O 165(5)°].

The structure of 14α-hydroperoxide **3** was confirmed with data of 1D and 2D ^1H and ^{13}C NMR spectra. Correlation of Me^{19} with HC^5 (NOESY experiment) testified about β-configuration of HC^5. For C^{14} signal in ^{13}C NMR spectrum typical of hydroperoxides downfield shift ($\Delta\delta$ 12.1 ppm) is characteristic.[3,7]

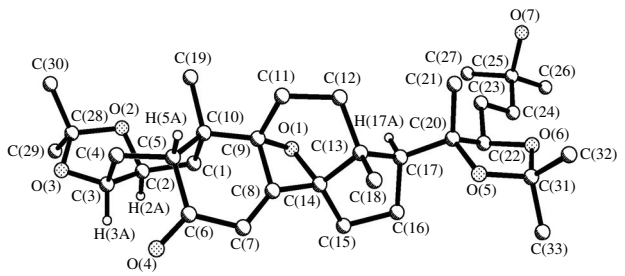


Figure 1 Molecular structure of oxetane **2** in crystal.

The unusual transformations of compound **1** are caused apparently by characteristic of γ-hydroxy-α,β-enones easiness of reduce elimination of hydroxyl group with forming 6(7),8(14)-dienolate **A**.[3,8] At the same time, initial α,β-connected ketone under the action of base ($LiNH_2$) can be deprotonated to give 6(7),8(9)-dienolate **B** (14-hydroxy group is not eliminated due to transformation in 14-alkoxide of lithium).[9,10] Dienolates **A**[3,8] and **B**[9,10] underwent autooxidation (apparently, in the process of evaporation of NH_3 on air) with the formation of 14α-hydroperoxide **3**[3,8] or 14α-hydroxy-9α-hydroperoxide **C**,[9,10] respectively. Splitting in latest 9α-hydroperoxy group (probably, involving the O–O homolytic fission) with detachment of H_2O_2 [by analogy with destruction of (α-hydroxy)hydroperoxides[11]] leads to oxetane **2** (Scheme 2).

Note that, for described transformations of compound **1** 14α-hydroxy group has to be free: 14,25-bis(trimethylsilyl ether) of compound **1** (its synthesis was described[12]) was isolated from reaction without change.

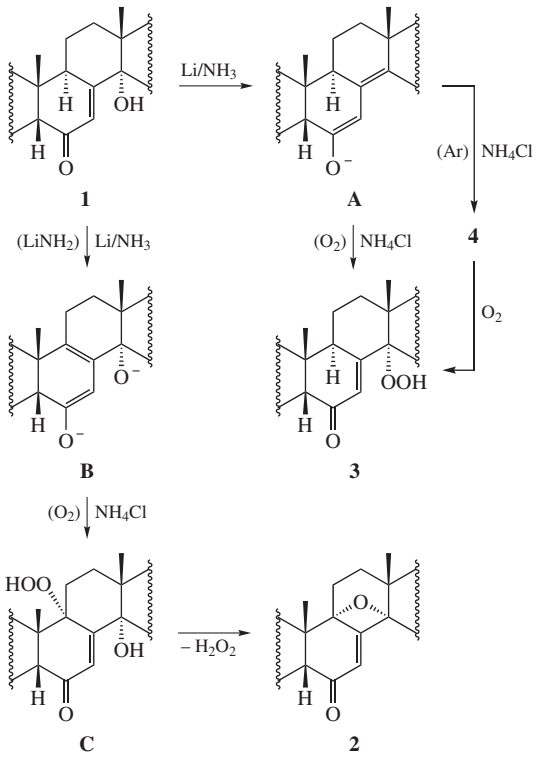
Passing of autooxidation reaction on the stage of NH_3 evaporation on air is confirmed by obtaining compound **4**§ when NH_3 was removed in argon stream (Scheme 1). The structure of compound **4** was established by 1D and 2D ^1H and ^{13}C NMR spectra (HHCOSY, HSQC, HMBC and NOESY). Singlet signals in ^{13}C NMR spectrum of compound **4** (JMOD) δ 121.4 (C^8) and 145.2 ppm (C^{14}) corresponded to a tetrasubstituted double bond. The 8(14)-position of it was confirmed with cross peaks of H_2C^7 and H_3C^{18} protons with sp^2 C^8 and C^{14} atoms, respectively.

Compound **4** in a solid state on air or in $CDCl_3$ solution is gradual oxidized with transforming to 14α-hydroperoxide **3**. We did not succeed in obtaining oxetane **2** from compound **4** under conditions of its synthesis from compound **1**, and the product of its transformation is only hydroperoxide **3**. Easily oxidizable compound **4** is stable to reduction and catalytic hydrogenation (10% Pd-C).

Hydroperoxide **3** is quantitatively transformed to compound **1** by treatment with Me_2S[3] or catalytic hydrogenation (10% Pd-C). Oxetane **2** was not produced from compound **3** under conditions of synthesis of the latter from diacetonide **1** (equimolar mixture of compounds **1** and **3** was obtained from reaction, according to the intensity ratio of C^8 signals at 163.7 and 158.9 ppm in

‡ *Crystallographic data for* **2**. X-ray structure of single crystals of oxetane **2** (were grown from an ether solution at room temperature) was determinated on a Bruker SMART APEX II[5] diffractometer (graphite monochromated MoKα radiation, λ = 0.71073 Å, ω-scan technique, $2\theta_{max}$ = = 52°, T = 100 K). The crystals of $C_{33}H_{50}O_7$ (M = 558.73, crystal size of 0.05×0.06×0.50 mm) are monoclinic, space group C_2, at 100 K a = 25.754(4), b = 6.6209(11) and c = 20.260(3) Å, β = 114.991(3)°, V = 3131.1(9) Å^3, Z = 4, d_{calc} = 1.185 g cm^{-3}, μ(MoKα) = 0.82 cm^{-1}. The intensities of 14976 reflections (3331 independent reflections, R_{int} = = 0.1091) were measured. The APEX II software[5] was used for collecting frames of data, indexing reflections, determination of lattice constants, integration of intensities of reflections, and SHELXTL[5] for space group and structure determination, refinements, graphics, and structure reporting. The structure was solved by direct methods and refined by the full-matrix least-squares technique against F^2 with the anisotropic temperature factors for all non-hydrogen atoms. The H atom of O(7)H(7) group was located from difference Fourier synthesis and refined in isotropic approximation, the rest hydrogen atoms were placed geometrically and included in the structure factors calculations in the riding motion approximation. The refinement converged to wR_2 = 0.0962 and GOF = = 1.016 for all independent reflections [R_1 = 0.0477 was calculated against F for 2272 observed reflections with $I > 2\sigma(I)$], 374 refined parameters.

CCDC 661563 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2008.



Scheme 2

§ *Synthesis of (20*R*,22*R*)-2β,3β:20,22-bis[(dimethylmethylene)dioxy]-25-hydroxy-5β-cholestene-8(14)-en-6-one* **4**. A solution of compound **1** (1.5 g, 2.7 mmol) in anhydrous THF (10 ml) was added to a solution of Li (0.22 g, 31 mmol) in ammonia (50 ml). The mixture was stirred at –33 °C for 25 min, NH_4Cl (3.0 g) was added and the ammonia was evaporated (Ar). The crude product was extracted with Et_2O (3×50 ml). Evaporation of the solvent afforded a solid residue, that was chromatographed on a column (40 g SiO_2, eluted with $CHCl_3$–MeOH, 100:1, v/v) to give compound **4** [0.85 g, 58%, R_f 0.38 ($CHCl_3$–MeOH, 6:1, v/v)] and compound **3** [0.6 g, 38.5%, R_f 0.3 ($CHCl_3$–MeOH, 6:1, v/v)].

For **4**: mp 105–110 °C, $[\alpha]_D^{20}$ +0.7 (*c* 1.6 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.77 (s, 3H, H_3C^{18}), 0.93 (s, 3H, H_3C^{19}), 1.12 (s, 3H, H_3C^{21}), 1.15 and 1.18 (2m, 2H, H_3C^{23}), 1.18 (s, 3H, H_3C^{26}), 1.18 (s, 3H, H_3C^{27}), 1.18 (m, 1H, HC^{17}), 1.23 and 1.75 (2m, 2H, H_2C^{12}), 1.29 (m, 1H, H_aC^1), 1.49 and 1.66 (2m, 2H, H_2C^{24}), 1.59 (m, 2H, H_2C^{11}), 1.65 and 1.98 (2m, 2H, H_2C^{16}), 1.78 (m, 1H, H_eC^1), 1.99 (m, 1H, H_eC^4), 2.02 and 2.23 (2m, 2H, H_2C^{15}), 2.09 (m, 1H, H_aC^4), 2.25 (t, 1H, HC^9), 2.35 (dd, 1H, HC^5, *J* 12.4 and 4.4 Hz), 2.91 and 2.93 (2d, 2H, HC^7, ^2J 14.0 Hz), 3.71 (m, 1H, HC^{22}), 4.19 (m, 1H, HC^2), 4.22 (m, 1H, HC^3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.8 (C^{18}), 20.6 (C^{11}), 22.0 (C^{21}), 22.6 (C^{23}), 24.0 (C^{16}), 25.1 (C^{15}), 26.0 (C^{19}), 26.0 and 28.2 (2,3-C*Me*$_2$), 26.9 and 29.1 (20,22-C*Me*$_2$), 27.0 (C^4), 29.3 (C^{26}), 29.8 (C^{27}), 37.1 (C^1), 37.3 (C^{12}), 37.4 (C^9), 38.2 (C^{13}), 41.5 (C^{24}), 42.2 (C^7), 44.0 (C^{10}), 53.2 (C^5), 55.6 (C^{17}), 70.5 (C^{25}), 71.6 (C^3), 72.5 (C^2), 81.8 (C^{22}), 84.1 (C^{20}), 107.1 (20,22-*C*Me$_2$), 107.9 (2,3-*C*Me$_2$), 121.6 (C^8), 145.4 (C^{14}), 213.0 (C^6). Found (%): C, 72.07; H, 9.38. Calc. for $C_{33}H_{52}O_6$ (%): C, 72.76; H, 9.62.

^{13}C NMR spectrum, respectively). Compound **4** and 14α-hydroperoxide **3** are not intermediate products for oxetane **2**, and the way of its formation is, probably, the consequence of transformations **1** → **B** → **C** → **2** (Scheme 2).

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