

## Ozonides of *N*-acyl-4-phenyl-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline

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Ozonation of *N*-acyl-4-phenyl-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline gave stable ozonides: a conformationally mobile isomer with the pseudoequatorial *N*-acyl group and a conformationally stable isomer with the pseudoaxial *N*-trifluoroacetyl group.

**Key words:** 4-phenyl-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline, ozonolysis, ozonides, X-ray diffraction analysis.

Discovery of valuable therapeutic properties in natural peroxy compounds has stimulated considerable interest in the chemistry and pharmacology of synthetic peroxides.<sup>1–3</sup> For instance, the unique peroxy sesquiterpenoid artemisinin has been introduced into medical practice for treatment of malaria.<sup>4,5</sup> This had a particular effect on the design of investigations. Artemisinin derivatives with nitrogen-containing structural fragments have proved to be highly active.<sup>6</sup> It has been found that ozonide-type agents, namely, interolane and its conjugate with 4-amino-7-chloroquinoline, are also highly active and are not inferior to artemisinin and its semisynthetic modifications.<sup>7</sup>

Here, with the aim to obtain ozonides of nitrogen-containing heterocyclic compounds, we studied ozonolysis of substituted 3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinolines prepared by the Povarov reaction.<sup>8</sup> The structures and stereochemistry of the starting *N*-acyltetrahydroquinolines **1** and **2** (Scheme 1) were determined by 1D (<sup>1</sup>H, <sup>13</sup>C, and DEPT-135°) and 2D (<sup>1</sup>H and <sup>13</sup>C NMR spectroscopy (COSY, HSQC, and HMBC)).

The relative configurations of the chiral C(3a), C(4), and C(9b) atoms in compound **1** are evident from the coupling constants  $J_{\text{H}(3a),\text{H}(9b)} = 10$  Hz (for the doublet of H(9b)) and  $J_{\text{H}(3a),\text{H}(4)} = 8$  Hz (for the doublet of H(4)) in the <sup>1</sup>H NMR spectrum recorded at –10 °C, which suggests that these protons are all *cis* to each other.

It should be noted that the H(3a) and H(4) protons in the deacetylated precursor of compound **1** are *trans* to

each other (X-ray diffraction data).<sup>9</sup> Apparently, epimerization at the chiral C(4) atom occurs under the acylation conditions.

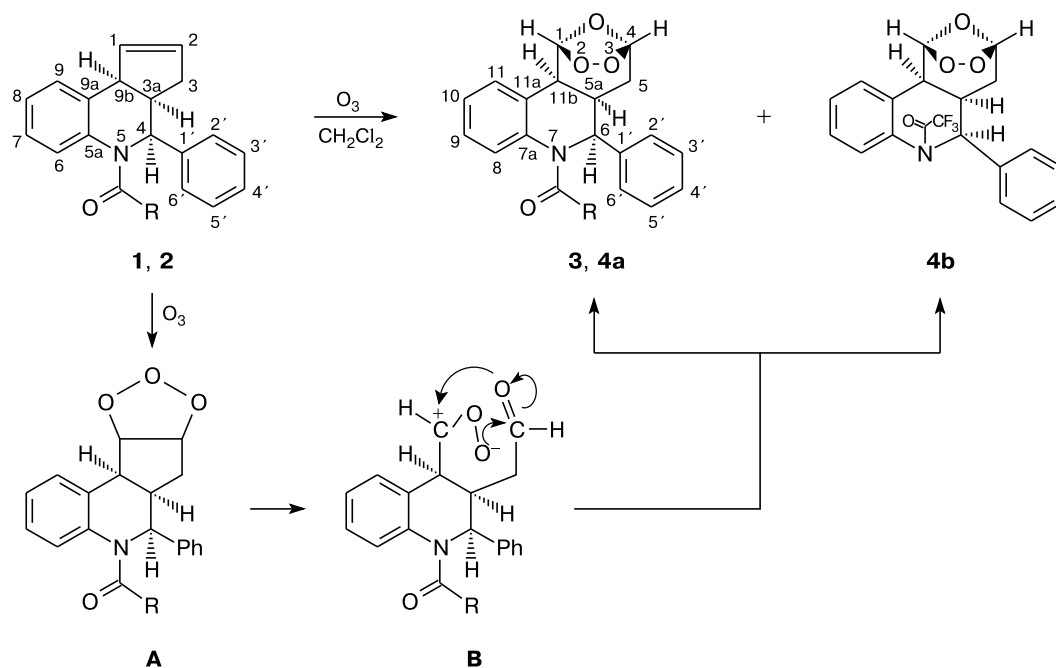
The broadened signals for the C(4) atom ( $\delta$  55.69) and its proton ( $\delta$  6.26) in the NMR spectra of compound **1** at ~20 °C (Table 1) suggest a slow (on the NMR time scale) interconversion of the conformers. At –10 °C, these signals appear as a narrow signal for the C(4) atom and a doublet for the H(4) proton, which provides evidence for stabilization of a thermodynamically more favorable conformer with the pseudoaxial Ph group at the C(4) atom and the *gauche*-oriented H(3a) and H(4) protons (the characteristic vicinal coupling constant is 8 Hz).

The broadened signals for the C(4) atom ( $\delta$  59.12) and its proton ( $\delta$  5.77) in the NMR spectra of compound **2** at ~20 °C (see Table 1) are transformed at –10 °C into two narrow signals for the C(4) atom ( $\delta$  58.41 and 60.14) and two signals for the H(4) proton (a doublet at  $\delta$  5.42 with  $J_{\text{H}(4),\text{H}(3a)} = 6$  Hz and a multiplet at  $\delta$  6.27). Therefore, both conformers (with the axial and equatorial Ph substituent at the C(4) atom) of compound **2** are stabilized at a lowered temperature and do not interconvert.

Ozonolysis of compound **1** in CH<sub>2</sub>Cl<sub>2</sub> at –10 °C gave ozonide **3\*** (see Scheme 1). The <sup>13</sup>C NMR spectrum of compound **3** (Table 2) shows signals at  $\delta$  99.37 (C(1)) and

\* Ozonolysis of a similar *N*-unacylated compound yielded a complex mixture of products.

Scheme 1

R = Me (**1**, **3**), CF<sub>3</sub> (**2**, **4a**)Table 1. <sup>1</sup>H and <sup>13</sup>C NMR spectra (δ) of alkenes **1** and **2**

Group or atom	Compound 1		Compound 2	
	δ <sub>C</sub>	δ <sub>H</sub>	δ <sub>C</sub>	δ <sub>H</sub>
C(1)H	131.29	5.72 (br.s)	130.72 <sup>a</sup>	5.77 (br.s)
C(2)H	132.00	6.15 (br.s)	132.20 <sup>a</sup>	6.19 (br.s)
C(3)H <sub>2</sub>	35.92	2.58 (m); 2.08 (m)	35.76	2.64 (m); 2.13 (m)
C(3a)H	40.30	3.55 (br.s)	40.43	3.67 (br.s)
C(4)H	55.69 <sup>b</sup>	6.26 (br.s) <sup>b</sup>	59.12 <sup>b</sup>	5.77 (br.s) <sup>b</sup>
C(5a)	135.50	—	— <sup>c</sup>	—
C(6)H—C(9)H	125.94, 126.09, 126.24, 127.21	7.01—7.43 (m)	126.16, 126.99, 127.67, 128.04	7.16—7.46 (m)
C(9a)	138.07	—	134.28	—
C(9b)H	45.38	4.10 (d, $J_{H(9b),H(3a)} = 10$ Hz)	45.34	4.19 (d, $J_{H(9b),H(3a)} = 9$ Hz)
C(1')	137.15	—	135.98	—
C(2')H—C(6')H	127.67, 127.76, 129.12	6.87—7.43 (m)	126.46, 127.91, 129.22	6.85—7.17 (m)
C=O	168.9	—	155.74 (q, ${}^2J_{CF} = 37$ Hz)	—
Me	22.85	2.20	—	—
CF <sub>3</sub>	—	—	116.80 (q, ${}^1J_{CF} = 289$ Hz)	—

<sup>a</sup> The signal is broadened.<sup>b</sup> At -10 °C, the broadened signals for the protons and the C atoms of the group HC(4) in compounds **1** and **2** are transformed into a narrow signal at δ 55.23 for olefin **1** and two narrow signals at δ 58.41 and 60.14 for olefin **2** (<sup>13</sup>C NMR) and into a doublet at δ 6.33 ( $J_{H(4),H(3a)} = 8$  Hz) for compound **1** and two signals at δ 5.42 (d,  $J_{H(4),H(3a)} = 6$  Hz) and 6.27 (m) for compound **2** (<sup>1</sup>H NMR). Similar changes are observed at -10 °C for other signals in the <sup>1</sup>H and <sup>13</sup>C NMR spectra of olefins **1** and **2**.<sup>c</sup> The signal expected to appear at δ 135 is absent (strong broadening due to the vicinity of the N atom).

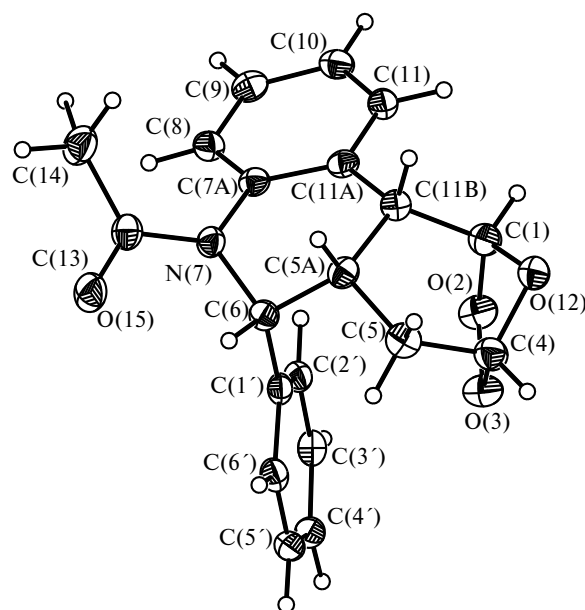
**Table 2.**  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra ( $\delta$ ) of ozonides **3**, **4a**, and **4b**

Group or atom	Compound <b>3</b>		Compound <b>4a</b>		Compound <b>4b</b> *	
	$\delta_{\text{C}}$	$\delta_{\text{H}}$	$\delta_{\text{C}}$	$\delta_{\text{H}}$	$\delta_{\text{C}}$	$\delta_{\text{H}}$
C(1)H	99.37	6.32 (d, $J_{\text{H}(1),\text{H}(11\text{b})} = 2$ Hz)	99.03	6.40 (d, $J_{\text{H}(1),\text{H}(11\text{b})} = 2$ Hz)	101.14	6.47 (d, $J_{\text{H}(1),\text{H}(11\text{b})} = 2$ Hz)
C(4)H	99.45	5.73 (d, $J_{\text{H}(4),\text{H}(5)} = 5$ Hz)	99.17	5.81 (d, $J_{\text{H}(4),\text{H}(5)} = 5$ Hz)	101.26	5.60 (br.s)
C(5)H <sub>2</sub>	30.47	1.78 (m); 2.21 (m)	30.45	1.79 (m); 2.24 (m)	31.26	1.79 (m); 2.24 (m)
C(5a)H	31.47	3.22 (m)	31.27	3.31 (m)	32.95	3.89 (m)
C(6)H	55.59 (br.s)	6.10 (br.s)	58.56 (br.s)	5.94 (br.s)	59.32	5.93 (d, $J_{\text{H}(6),\text{H}(5\text{a})} = 10$ Hz)
C(7a)	131.08	—	131.60	—	131.73	—
C(8)H—C(11)H	126.24, 126.63, 126.74, 127.23	6.90—7.50 (m)	126.66, 127.46, 127.79, 128.28	7.21—7.47 (m)	126.66, 127.52, 127.78, 128.40	7.21—7.47 (m)
C(11a)	138.80	—	135.40	—	138.19	—
C(11b)H	38.79	3.50 (dd, $J_{\text{H}(11\text{b}),\text{H}(5\text{a})} = 10$ Hz, $J_{\text{H}(11\text{b}),\text{H}(1)} = 2$ Hz)	38.68	3.58 (dd, $J_{\text{H}(11\text{b}),\text{H}(5\text{a})} = 11$ Hz, $J_{\text{H}(11\text{b}),\text{H}(1)} = 2$ Hz)	39.14	3.13 (dd, $J_{\text{H}(11\text{b}),\text{H}(5\text{a})} = 6$ Hz, $J_{\text{H}(11\text{b}),\text{H}(1)} = 2$ Hz)
C(1')	137.20	—	135.16	—	135.99	—
C(2')H—C(6')H	127.57, 127.77, 129.73	6.90—7.50 (m)	128.06, 128.28, 129.75	6.89—7.20 (m)	128.06, 128.28, 129.75	6.89—7.20 (m)
C=O	169.2	—	155.55 (q, $^2J_{\text{CF}} = 37$ Hz)	—	156.85 (q, $^2J_{\text{CF}} = 37$ Hz)	—
Me	22.72	2.17	—	—	—	—
CF <sub>3</sub>	—	—	116.54 (q, $^1J_{\text{CF}} = 289$ Hz)	—	116.42 (q, $^1J_{\text{CF}} = 289$ Hz)	—

\* The spectra of ozonide **4b** were obtained by comparing the spectra of the mixture **4a** + **4b** and ozonide **4a**.

99.45 (C(4)) characteristic of ozonides<sup>10</sup> instead of the signals for the olefinic C atoms at  $\delta$  131.29 (C(1)) and 132.00 (C(2)) observed for alkene **1** (see Table 1), which confirms the transformation of its double bond into a 1,2,4-trioxolane ring. The coupling constants of the vicinal protons at the C(5a) and C(11b) atoms ( $J_{\text{H}(11\text{b}),\text{H}(5\text{a})} = 10$  Hz, see Table 2) suggest the *cis*-arrangement of these atoms and *cis*-fusion of the tetrahydroquinoline and dioxepane rings in compound **3**. This is confirmed by single-crystal X-ray diffraction data for ozonide **3** (Fig. 1). According to the crystallographic data, the Ph substituent at the C(6) atom in ozonide **3** is pseudoaxial with respect to the tetrahydropyridine ring, while the *N*-acetyl group is pseudoequatorial and the epoxy O atom linking the C(1) and C(4) atoms is *exo* to the molecular framework. The data obtained by 1D and 2D  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy and X-ray diffraction allow ozonide **3** to be formulated as (1*R*\*,4*S*\*,5*aR*\*,6*S*\*,11*bR*\*)-7-acetyl-6-phenyl-4,5,5*a*,6,7,11*b*-hexahydro-1*H*-1,4-epoxy[1,2]dioxepino[5,4-*c*]quinoline.

The  $^1\text{H}$  NMR spectra of both olefin **1** and its ozonide **3** show a broadened singlet for the proton near the N



**Fig. 1.** Molecular structure of ozonide **3** in the crystal with atomic thermal displacement ellipsoids (50% probability).

atom, which suggests a slow conformational transition. According to X-ray diffraction data (see Fig. 1), ozonide **3** exists in the crystal as a thermodynamically more favorable conformer with the pseudoaxial Ph group.

The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of a product obtained by ozonation of *N*-trifluoroacetyl derivative **2** contain a double set of signals. Therefore, the product is actually a mixture of two ozonides **4a** and **4b** (**4a** : **4b**  $\approx$  70 : 30; the ratio was determined from the relative intensities of the signals for the H(1) proton at  $\delta$  6.40 and 6.47 or for the H(4) proton at  $\delta$  5.81 and 5.60). Ozonides **4a** and **4b** were not separated by HPLC.\* Yet ozonide **4a** was isolated by column chromatography from the reaction mixture pretreated with dimethyl sulfide. By comparing its  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra with those of the mixture **4a** + **4b**, we identified the signals relating to either of the ozonides (see Table 2).

The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of ozonide **4a**, which is inert to dimethyl sulfide, and ozonide **3** are very similar because of their stereochemical similarity. This is not the case of ozonide **4b**. The  $^{13}\text{C}$  chemical shifts of the C atoms of the oxepane ring in ozonides **3** and **4a** as compared to those of the corresponding atoms (C(1), C(4), C(5), C(5a), and C(11b)) in ozonide **4b** demonstrate clearly that compounds **3** and **4a** are structurally similar. The broadened signals for the C(6) atom ( $\delta$  58.56) and the H(6) proton ( $\delta$  5.94) in the spectra of ozonide **4a** are also indicative. Such broadening also noted for the corresponding signals of the HC(6) group in ozonide **3** ( $\delta_{\text{C}}$  55.59,  $\delta_{\text{H}}$  6.10) provides evidence for an exchange process between conformers with close energies. In contrast, the  $^{13}\text{C}$  NMR spectrum of ozonide **4b** shows a narrow signal for the C(6) atom ( $\delta$  59.32), which is adjacent to the N atom, and its  $^1\text{H}$  NMR spectrum shows a distinct doublet for the H(6) proton ( $\delta$  5.93,  $J_{\text{H(6),H(5a)}} = 10$  Hz). Apparently, ozonide **4b** exists as a stable (hindered) conformer with donor–acceptor interactions of the *p* electrons of the O atoms of the trioxolane ring with the strongly electronegative F atoms of the trifluoromethyl group ( $\text{O}_2\text{F}_2$  coupling<sup>11</sup>), which is probably pseudoaxial in ozonide **4b**. Because of this, the  $\text{CF}_3$  group approaches the trioxolane ring and, accordingly, the Ph substituent at the C(6) atom is in the pseudoequatorial position. Ultimately, the structures of ozonides **4a** and **4b** were determined by 1D and 2D  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy: indeed, the phenyl group is pseudoaxial in isomer **4a** and pseudoequatorial in isomer **4b**.

The structures of ozonides **3**, **4a**, and **4b** suggest that their formation from olefins **1** and **2** proceed regio- and stereoselectively. According to the ozonolysis mechanism proposed by Criegee,<sup>12,13</sup> the anionic O site of zwitterion

**B** generated from molozone **A** (see Scheme 1) attacks the carbonyl C atom with accompanying formation of an epoxy bridge of the ozonide on the *exo*-side of its framework. Since compound **2** exists under the ozonolysis conditions ( $-10$  °C,  $\text{CH}_2\text{Cl}_2$ ) as a mixture of stable conformers with the pseudoaxial and pseudoequatorial Ph substituent at the C(6) atom, the resulting ozonide **4** is also a mixture of conformers. One of them (ozonide **4b**) is conformationally stable but is more sensitive to nucleophilic reducing agents (dimethyl sulfide), probably because of the peroxide bond polarization due to a donor–acceptor interaction with the strongly electronegative F atoms of the *N*-trifluoroacetyl group.

## Experimental

$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker Avance-400 instrument (400.13 ( $^1\text{H}$ ) and 100.62 MHz ( $^{13}\text{C}$ )) in  $\text{CDCl}_3$  with  $\text{Me}_4\text{Si}$  as the internal standard. The homo- and heteronuclear experiments DEPT-135°, COSY, HSQC, and HMBC were carried out according to standard Bruker procedures. Melting points were determined on a Boetius hot-stage microscope. Elemental analysis was performed on a Carlo Erba EA-1108 CHNS-O analyzer. HPLC was carried out on an HP-1050 instrument (Zorbax ODS  $\text{C}_{18}$ , acetonitrile–water (80 : 20) as an eluent). TLC on  $\text{SiO}_2$  (Silufol) was used for checking; spots were visualized in the iodine vapor.

X-ray diffraction analysis of ozonide **3** was carried out on a Bruker Smart 1000 CCD diffractometer (graphite monochromator,  $\lambda = 0.71073$  Å,  $\omega$  scan mode,  $2\theta = 54^\circ$ ). Crystals of compound **3** ( $\text{C}_{20}\text{H}_{19}\text{NO}_4$ ,  $M = 337.36$ ) grown from  $\text{EtOAc}-\text{CHCl}_3$  (1 : 1) are colorless prisms. At 120 K,  $a = 7.0476(7)$  Å,  $b = 13.2329(14)$  Å,  $c = 16.7764(17)$  Å,  $\beta = 91.306(3)^\circ$ ,  $V = 1564.2(3)$  Å<sup>3</sup>, space group  $P2(1)/n$ ,  $Z = 4$ ,  $d_{\text{calc}} = 1.433$  g cm<sup>-3</sup>,  $\mu(\text{Mo-K}\alpha) = 1.00$  cm<sup>-1</sup>. The structure was solved by the direct methods and refined by the full-matrix least-squares method on  $F^2_{\text{hkl}}$  in the anisotropic approximation for all non-hydrogen atoms. Final residuals are  $wR_2 = 0.1199$  (GOOF = 1.007) for all independent reflections and  $R_1 = 0.0460$  calculated on  $F_{\text{hkl}}$  for 2148 observed reflections with  $I > 2\sigma(I)$ . All PC-assisted calculations were performed with the SHELXTL program package.<sup>14</sup> The CIF file comprising the comprehensive crystallographic data for structure **3** has been deposited with the Cambridge Crystallographic Data Center (CCDC No. 728 592) and can be made available upon request on [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of compounds **1** and **2** are given in Table 1. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of compounds **3**, **4a**, and **4b** are presented in Table 2.

**(3a*R*\*, 4*S*\*, 9*bS*\*)-5-Acetyl-4-phenyl-3a,4,5,9*b*-tetrahydro-3*H*-cyclopenta[*c*]quinoline (1).** Acetic anhydride (0.15 mL, 1.48 mmol) and DMAP (10 mg, 14 mol. %) were added to a solution of 4-phenyl-3a,4,5,9*b*-tetrahydro-3*H*-cyclopenta[*c*]quinoline (0.2 g, 0.81 mmol; m.p. 120–121 °C, prepared as described earlier<sup>9</sup>) in anhydrous toluene (10 mL) and pyridine (5 mL). The reaction mixture was refluxed for 4 h until the starting compound was completely consumed (TLC) and poured into cold water (30 mL). The product was extracted with  $\text{CH}_2\text{Cl}_2$  (30 mL) and the extract was washed with 10% HCl (3×15 mL)

\* On heating of the mixture **4a** + **4b** at 55 °C in the spectrometer cell, the spectrum contained a narrow signal for the C(6) atom at  $\delta$  58.70 instead of two original signals at  $\delta$  55.59 and 59.32.

(until the odor of pyridine was removed) and neutralized with a saturated aqueous solution of NaHCO<sub>3</sub> (15 mL). The organic layer was concentrated and the residue was chromatographed (column 25 mm in diameter, SiO<sub>2</sub> (KSKG), 10 g, *n*-hexane—ethyl acetate (19 : 1)). The yield of compound **1** was 0.19 g (82%), *R<sub>f</sub>* 0.42 (*n*-hexane—ethyl acetate (1 : 1)), m.p. 127–129 °C (from *n*-hexane). Found (%): C, 82.85; H, 6.68; N, 4.57; O, 5.90. C<sub>20</sub>H<sub>19</sub>NO. Calculated (%): C, 83.05; H, 6.57; N, 4.84; O, 5.54.

**(3aR\*,4S\*,9bS\*)-4-Phenyl-5-trifluoroacetyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[*c*]quinoline (2)** was obtained analogously from the same starting reactant (0.2 g, 0.81 mmol) and trifluoroacetic anhydride (0.22 mL, 1.07 mmol). The yield was 0.22 g (82%), m.p. 74–76 °C, *R<sub>f</sub>* 0.65 (*n*-hexane—ethyl acetate (1 : 1)). Found (%): C, 69.26; H, 4.88; N, 4.56; O, 4.68. C<sub>20</sub>H<sub>16</sub>F<sub>3</sub>NO. Calculated (%): C, 69.97; H, 4.66; N, 4.08; O, 4.66.

**(1R\*,4S\*,5aR\*,6S\*,11bR\*)-7-Acetyl-6-phenyl-4,5,5a,6,7,11b-hexahydro-1H-1,4-epoxy[1,2]dioxepino[5,4-*c*]quinoline (3)**. An ozone—oxygen mixture was bubbled at –10 °C through a stirred solution of compound **1** (0.3 g, 1.02 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) for 10 min (5 mmol of O<sub>3</sub>; the ozonizer output is 30 (mmol of O<sub>3</sub>) h<sup>-1</sup>). After the starting compound was completely consumed (TLC), the reaction mixture was purged with argon and concentrated. The residue was chromatographed on SiO<sub>2</sub> (10 g, KSKG) with CHCl<sub>3</sub> as an eluent. The yield of ozonide **3** was 0.16 g (45%), m.p. 82–84 °C, *R<sub>f</sub>* 0.55 (CHCl<sub>3</sub>—MeOH (20 : 1)). Found (%): C, 71.43; H, 5.84; N, 3.65; O, 19.08. C<sub>20</sub>H<sub>19</sub>NO<sub>4</sub>. Calculated (%): C, 71.22; H, 5.64; N, 4.15; O, 18.99.

**(1R\*,4S\*,5aR\*,6S\*,11bR\*)-6-Phenyl-7-trifluoroacetyl-4,5,5a,6,7,11b-hexahydro-1H-1,4-epoxy[1,2]dioxepino[5,4-*c*]quinoline (4)**. A solution of compound **2** (0.4 g, 1.15 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) was ozonated as described above. The reaction mixture was purged with argon, stirred with Me<sub>2</sub>S (0.6 mL) at ~20 °C for 3 h, and concentrated under reduced pressure. The residue was chromatographed to give ozonide **4a** (0.11 g, 25%), m.p. 126–128 °C, *R<sub>f</sub>* 0.58 (CHCl<sub>3</sub>—MeOH (30 : 1)). Found (%): C, 61.70; H, 4.27; N, 3.47; O, 16.42. C<sub>20</sub>H<sub>16</sub>F<sub>3</sub>NO<sub>4</sub>. Calculated (%): C, 61.38; H, 4.09; N, 3.58; O, 16.37.

**Mixture of ozonides 4a and 4b**. A solution of compound **2** (0.3 g, 0.86 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was ozonated and treated as described for the synthesis of ozonide **3**. The yield of the mixture **4a** + **4b** (70 : 30, <sup>1</sup>H NMR) was 0.15 g (45%), *R<sub>f</sub>* 0.58

for both the isomers (CHCl<sub>3</sub>—MeOH (30 : 1)). Found (%): C, 61.65; H, 4.19; N, 3.49; O, 16.47. C<sub>20</sub>H<sub>16</sub>F<sub>3</sub>NO<sub>4</sub>. Calculated (%): C, 61.38; H, 4.09; N, 3.58; O, 16.37.

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## References

1. G. A. Tolstikov, A. G. Tolstikov, O. V. Tolstikova, *Usp. Khim.*, 1996, **65**, 836 [*Russ. Chem. Rev. (Engl. Transl.)*, 1996, **65**].
2. V. M. Dembisky, T. A. Glorizova, V. V. Poroikov, *Mini-Rev. Med. Chem.*, 2007, **7**, 571.
3. V. M. Dembisky, *Eur. J. Med. Chem.*, 2008, **43**, 223.
4. P. M. OrNeil, G. H. Posner, *J. Med. Chem.*, 2004, **47**, 2945.
5. L. Ying, H. Hao, W. Yu-Lin, in *Medicinal Chemistry of Bioactive Natural Products*, Eds X.-T. Liang, W.-Sh. Fang, John Wiley, New York, 2006, 183.
6. V. K. Kapour, K. Kumar, *Prog. Med. Chem.*, Eds F. D. King, G. Lawton, Elsevier, Amsterdam, 2005, **43**, 190.
7. P. M. OrNeil, *Expert Opin. Investig. Drugs*, 2005, **14**, 1117.
8. V. A. Glushkov, A. G. Tolstikov, *Usp. Khim.*, 2008, **77**, 138 [*Russ. Chem. Rev. (Engl. Transl.)*, 2008, **77**].
9. P. A. Grieco, A. Bahsas, *Tetrahedron Lett.*, 1988, **29**, 5855.
10. Sh. Kawamura, R. Takeuchi, A. Masuyama, M. Nojima, K. J. McCullough, *J. Org. Chem.*, 1998, **63**, 5617.
11. F. A. Cotton, G. Wilkinson, in *Advanced Inorganic Chemistry*, John Wiley, New York, 1966, 2nd ed.
12. R. Criegee, *Rec. Chem. Prog.*, 1957, **18**, 111.
13. P. S. Bailey, *Ozonation in Organic Chemistry*, Academic Press, New York—San Francisco, 1978, **1**.
14. *SHELXTL v. 5.10, Structure Determination Software Suite*, Bruker AXS, Madison, Wisconsin, USA, 1998.

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