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Prostanoids. LXXVIII.* New sp^2-Functionalized 4-Hydroxy-2-cyclopentenones from 6,7-Dichloro-1,4-dioxaspiro[4.4]non-6-en-8-one

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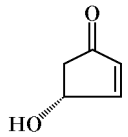
Abstract—Readily accessible 6,7-dichloro-1,4-dioxaspiro[4.4]non-6-en-8-one was converted into 2,3-dichloro-, 2-ethylthio-, and 3-chloro-2-ethylthio-4-hydroxy-2-cyclopentenones.

Protected derivatives of (4R)-4-hydroxy-2-cyclopentenones (**I**) are widely used in the synthesis of prostanoids, following the triply convergent scheme [2–4]. In the present communication we report on the synthesis of new 4-hydroxycyclopentenones on the basis of readily accessible 6,7-dichloro-1,4-dioxaspiro[4.4]non-6-en-8-one (**II**) [5]. Products **III**–**V** attract interest as potential starting compounds for alternative approaches (other than triply convergent synthesis) to vicinal 2,3-dialkyl derivatives of 4-hydroxy-2-cyclopentenones.



I

The transformations of compound **II** into products **III**–**V** are shown in Scheme 1. The reduction of **II** with $LiAlH_4$ gave alcohol **VI** which was treated with 15% hydrochloric acid in Me_2CO to obtain the desired 2,3-dichloro-4-hydroxy-2-cyclopentenone (**III**). The proposed procedure for preparation of 2-ethylthio derivative **V** is also simple. It includes nucleophilic substitution of the chlorine atom in **II**, exhaustive reduction of ketone **VII** to alcohol **VIII** with $LiAlH_4$, and acid hydrolysis to remove the acetal protection.

As a result, we isolated compound **IV** and ether **IX** as by-product in 52 and 26% yield, respectively (calculated on ethylthio derivative **VII**. Unlike lithium aluminum hydride, the reduction of **VII** with sodium tetrahydridoborate gave alcohol **X** in which the vinyl chlorine atom remained intact. Mild acid hydrolysis of **X** smoothly afforded 2,3-disubstituted hydroxycyclopentenone **V**. Presumably, extremely facile hydrolysis of the dioxolane moiety in compounds **IV**, **VIII**, and **X** is favored by intramolecular assistance by the hydroxy group (cf. [6, 7]).

EXPERIMENTAL

The IR spectra were recorded on a UR-20 instrument from samples prepared as thin films. The ^1H and ^{13}C NMR spectra were obtained on a Bruker AM-300 spectrometer at 300 and 75.47 MHz, respectively; $CDCl_3$ was used as solvent, and TMS, as internal reference.

2,3-Dichloro-4-hydroxy-2-cyclopentenone (III). To a solution of 0.11 g (0.5 mmol) of compound **VI** in 10 ml of acetone we added 0.1 ml of 15% hydrochloric acid. The mixture was kept for 30 min at 20°C and evaporated, and the residue was purified by chromatography on silica gel to obtain 60 mg (82%) of ketone **III**. IR spectrum, ν, cm^{-1}: 1620, 1745, 3400. ^1H NMR spectrum, δ, ppm: 3.13 d.d (1H, 5-H, J = 18.6, 6.4 Hz). 2.68 d.d (1H, 5-H, J = 18.6, 1.7 Hz), 4.0–4.25 m (1H, OH), 4.91 d.d (1H, 4-H, J = 1.7, 6.4 Hz). ^{13}C NMR spectrum, δ_C, ppm: 43.54 (C^5), 69.76 (C^4), 134.03 (C^2), 163.81 (C^3), 194.66 (C=O).

2-Ethylthio-4-hydroxy-2-cyclopentenone (IV) and bis(4-oxo-3-ethylthio-2-cyclopentenyl) ether (IX). To a solution of 120 mg of compound **VIII**

* For communication LXXVII, see [1].

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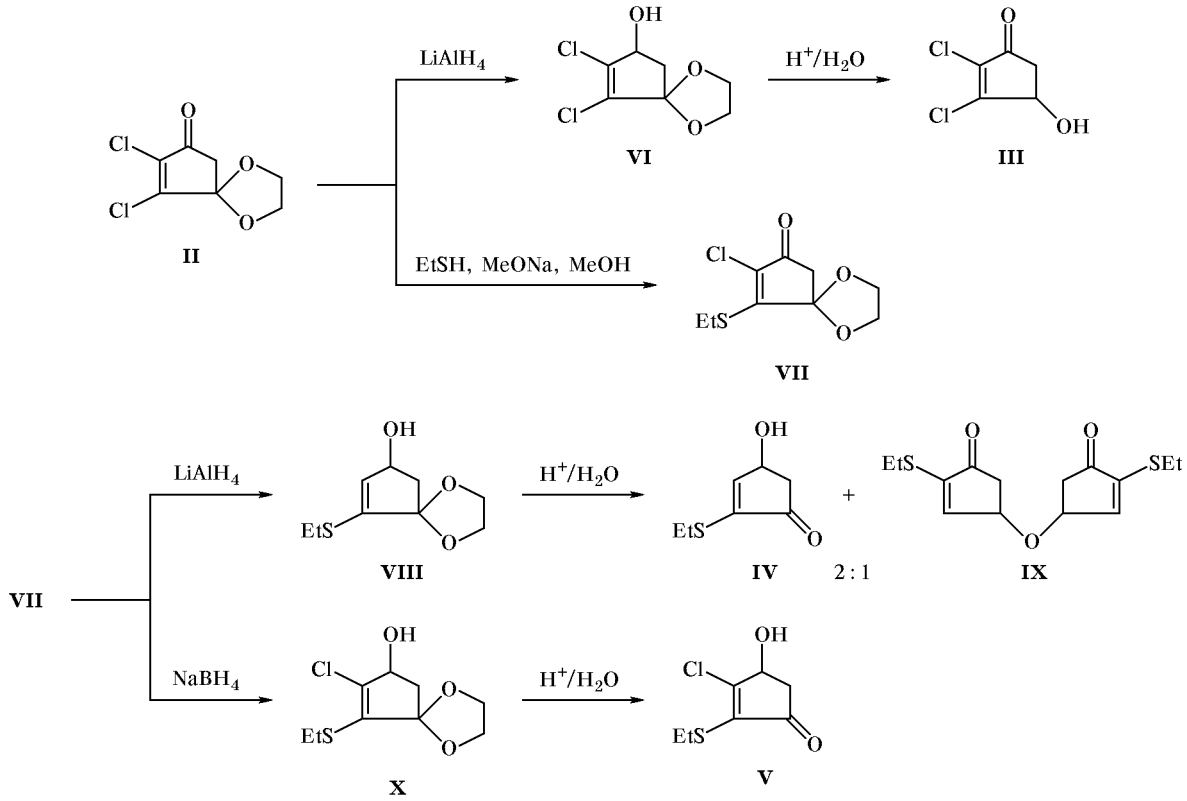
Scheme 1.



in 10 ml of acetone we added 0.1 ml of 15% hydrochloric acid. The mixture was stirred for 30 min at 20°C and evaporated, and the residue was subjected to chromatography on silica gel to isolate 60 mg (52%) of ketone **IV** and 30 mg (26%) of ether **IX**.

2-Ethylthio-4-hydroxy-2-cyclopentenone (IV). Oily liquid. IR spectrum, ν, cm^{-1}: 1604, 1712, 3424. ^1H NMR spectrum, δ, ppm: 1.35 t (3H, CH_3, J = 7.4 Hz), 2.00–2.30 m (1H, OH), 2.41 d.d (1H, CH_2, J = 18.7, 2.0 Hz), 2.86 q (2H, SCH_2, J = 7.4 Hz), 2.92 d.d (1H, CH_2, J = 18.7, 6.1 Hz), 5.00–5.04 m (1H, 4-H), 6.93 d (1H, 3-H, J = 2.6 Hz). ^{13}C NMR spectrum, δ_C, ppm: 13.56 (CH_3), 24.99 (SCH_2), 44.96 (C^5), 69.16 (C^4), 145.03 (C^2), 148.65 (C^3), 202.39 (C=O).

3-Chloro-2-ethylthio-4-hydroxy-2-cyclopentenone (V) was synthesized by hydrolysis of compound **X**, following the procedure described above for ketone **IV**. Oily substance. Yield 84%. IR spectrum, ν, cm^{-1}: 1570, 1712, 3416. ^1H NMR spectrum, δ, ppm: 1.25 t (3H, CH_3, J = 7.4 Hz), 2.57 d.d (1H, CH_2, J = 18.5, 2.1 Hz), 2.85–3.15 m (1H, OH), 2.98 d.d (1H, CH_2, J = 18.5, 6.5 Hz), 3.15 q (2H, SCH_2, J = 7.4 Hz), 4.73 d.d (1H, 4-H, J = 6.5, 2.1 Hz). ^{13}C NMR spectrum, δ_C, ppm: 15.60 (CH_3), 24.37 (SCH_2), 44.71 (C^5), 70.62 (C^4), 137.63 (C^2), 162.70 (C^3), 198.02 (C=O).

6,7-Dichloro-1,4-dioxaspiro[4.4]non-6-en-8-ol (VI). A solution of 0.42 g (2 mmol) of ketone **II** in 10 ml of THF was added dropwise with vigorous stirring at room temperature to a suspension of 0.08 g of $LAlH_4$ in 10 ml of THF. The mixture was stirred for 15 min and diluted with 30 ml of diethyl ether, and 1 ml of a 10% aqueous solution of KOH was added. The organic phase was dried over $MgSO_4$ and evaporated, and the residue was subjected to chromatography on silica gel using 4 : 1 pentane–ethyl acetate as eluent. Product **VI** was isolated as an oily substance. Yield 0.35 g (83%). IR spectrum, ν, cm^{-1}: 1636, 3440. ^1H NMR spectrum, δ, ppm: 2.09 d.d (1H, 9-H, J = 14.2, 3.5 Hz), 2.60 d.d (1H, 9-H, J = 14.2, 7.3 Hz), 3.70–3.90 m (1H, OH), 3.90–4.25 m (4H, CH_2O), 4.50–4.60 m (1H, 8-H). ^{13}C NMR spectrum, δ_C, ppm: 44.45 (C^9), 65.70 (CH_2O), 66.03 (CH_2O), 71.54 (C^8), 112.50 (C^5), 132.57 (C^6), 134.13 (C^7).

7-Chloro-6-ethylthio-1,4-dioxaspiro[4.4]non-6-en-8-one (VII). To a solution of sodium methoxide, prepared from 0.03 g (1.3 mmol) of metallic sodium and 5 ml of anhydrous methanol, we added with stirring 0.81 g (1.3 mmol) of ethanethiol and 0.3 g

(1.2 mmol) of ketone **II**. The mixture was stirred for 0.5 h at 20°C, 10 ml of water was added, and the mixture was extracted with CH_2Cl_2 (3 × 20 ml). The combined extracts were washed with a saturated aqueous solution of sodium chloride until neutral reaction, dried over $MgSO_4$, and evaporated to obtain 0.37 g of a crude product which was purified by column chromatography on silica gel using 2:1 pentane–ethyl acetate as eluent. Yield 0.27 g (81%), oily substance. IR spectrum, ν, cm^{-1}: 1570, 1720. ^1H NMR spectrum, δ, ppm: 1.33 t (3H, CH_3, J = 7.1 Hz), 2.70 s (2H, 9-H_2), 3.40 m (2H, SCH_2), 4.00–4.20 m (4H, CH_2O). ^{13}C NMR spectrum, δ_C, ppm: 14.97 (CH_3), 25.16 (SCH_2), 65.77 (CH_2O), 110.51 (C^5), 130.99 (C^7), 164.73 (C^6), 191.94 (C=O). Found, %: C 45.80; H 4.58; Cl 15.40; S 13.40. $C_9H_{11}ClO_3S$. Calculated, %: C 46.06; H 4.72; Cl 15.11; S 13.66.

6-Ethylthio-8-hydroxy-1,4-dioxaspiro[4.4]non-6-ene (VIII) was synthesized by reduction of ketone **VII**, following the procedure described above for compound **VI**. Oily substance, yield 83%. IR spectrum, ν, cm^{-1}: 1610, 3450. ^1H NMR spectrum, δ, ppm: 1.33 t (3H, CH_3, J = 7.4 Hz), 1.97 d.d (1H, CH_2, J = 14.0, 3.2 Hz), 2.53 d.d (1H, CH_2, J = 14.0, 4.8 Hz), 2.30–2.50 m (1H, OH), 2.79 q (2H, SCH_2, J = 7.4 Hz), 3.90–4.13 m (4H, CH_2O), 4.65–4.78 m (1H, 8-H), 5.62 d (1H, 7-H, J = 2.5 Hz). ^{13}C NMR spectrum, δ_C, ppm: 13.47 (CH_3), 25.12 (SCH_2), 46.74 (C^9), 65.71 (CH_2O), 65.92 (CH_2O), 72.21 (C^8), 117.02 (C^5), 128.06 (C^7), 145.37 (C^6).

Bis(3-ethylthio-4-oxo-2-cyclopentenyl) ether (IX). Oily liquid. IR spectrum, ν, cm^{-1}: 1572, 1712. ^1H NMR spectrum, δ, ppm: 1.35 t and 1.37 t (6H, CH_3, J = 7.4 Hz), 2.47 d.d and 2.50 d.d (2H, 5-H, 5′-H, J = 18.4, 1.8 Hz), 2.70–3.00 m (6H, CH_2S, 5-H, 5′-H), 4.75–4.90 m (2H, 4-H, 4′-H), 6.89 d and 6.95 d (2H, 3-H, 3′-H, J = 2.6, 2.8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 13.60 (CH_3), 25.05 (SCH_2), 42.76 (C^5), 74.90 and 75.25 (C^4, $C^{4'}$), 145.52 and 145.64 (C^2, $C^{2'}$), 146.59 and 146.63 (C^3, $C^{3'}$), 201.09 (C=O).

7-Chloro-6-ethylthio-8-hydroxy-1,4-dioxaspiro-[4.4]non-6-ene (X). To a solution of 0.46 g (2 mmol) of ketone **VII** in 10 ml of ethanol we added at 0°C 0.03 g (0.8 mmol) of sodium tetrahydridoborate. The mixture was stirred for 1 h, 3 ml of acetone was added to decompose excess reducing agent, and the mixture was evaporated. The residue was dissolved in 10 ml of water, the solution was extracted with methylene chloride (3 × 20 ml), the extract was dried over $MgSO_4$ and evaporated, and the residue was subjected to chromatography on silica gel using 4:1 pentane–ethyl acetate as eluent. Yield 0.45 g (96%). IR spectrum, ν, cm^{-1}: 1570, 1712, 3430. ^1H NMR spectrum, δ, ppm: 1.19 t (3H, CH_3, J = 7.4 Hz), 2.01 d.d (1H, CH_2, J = 14.0, 3.8 Hz), 2.01 q (2H, SCH_2, J = 7.4 Hz), 2.52 d.d (1H, CH_2, J = 14.0, 7.2 Hz), 3.60–4.00 m (1H, OH), 3.80–4.20 m (4H, CH_2O), 4.54 d.d (1H, 8-H, J = 7.2, 3.8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 14.08 (CH_3), 26.64 (SCH_2), 44.88 (C^9), 65.54 (CH_2O), 65.66 (CH_2O), 73.51 (C^8), 115.46 (C^5), 135.47 (C^6), 143.58 (C^7).

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