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Crystal structures of 10α-gon-5-enes from the synthetic pathway to desogestrel

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Abstract

X-ray crystallographic studies performed on the product of the ketalization reaction of 13β-ethyl-11α-hydroxy-gon-5-ene-3,17-dione have lead to the unequivocal assignment of the 10α stereochemistry to C10, showing that an inversion of configuration occurred during formation of the 3,17-diketal. From the Swern oxidation of this compound, 11α-(methylthio)methoxy-10α-gonene was obtained as the major product instead of the desired 11-ketone. Modeling studies showed that the configurational instability at C10 is determined by the presence of the 11α-hydroxyl group.

Keywords: Crystal structures; 10α-Steroids; Ketalization; Desogestrel; Swern oxidation

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1. Introduction

During our studies [1,2] on the synthesis of 13-ethyl-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-17-ol, desogestrel (**1**), the most prescribed third generation oral contraceptive [3–5], the 13β-ethyl-11α-hydroxy-gon-4-ene-3,17-dione intermediate (**2**) [6] was submitted to a ketalization reaction in order to protect the 3- and 17-keto functions as described by Gao et al. [7], who reported the formation of the bisdiethyleneketal **3**, easily recovered in high yield from the reaction mixture.

In our hands, after crystallization, the acetalization afforded 13β-ethyl-11α-hydroxy-10α-gon-5-ene-3,17-dione-3,17-diethyleneketal (**4**), in which the 10-hydrogen atom was on the α-side of the molecule. The "unnatural" stereochemistry at C10 of **4** was unambiguously assigned by X-ray diffraction.

Moreover, in order to readdress the synthetic approach towards the synthesis of the 10α-analogue of desogestrel [8], Swern oxidation [9], a mild oxidative method widely used in the case of steroidal compounds [10,11], was applied to the ketal **4**. Under Swern conditions, instead of the expected 11-keto compound, the major product of the reaction was found to be the (methylthio)methyl ether **5**.

In this paper, we report the structures (Scheme 1) of the 10α-gonenes **4** and **5**, together with that of compound **3**, which has the "natural" 10β-stereochemistry at C10, and we describe modeling studies to explain the configurational instability at C10.

2. Experimental

2.1. General

Uncorrected melting points were determined on a Büchi apparatus. Optical rotations were determined on a Perkin-Elmer 241 polarimeter in a 1 dm cell at 20 °C using chloro-

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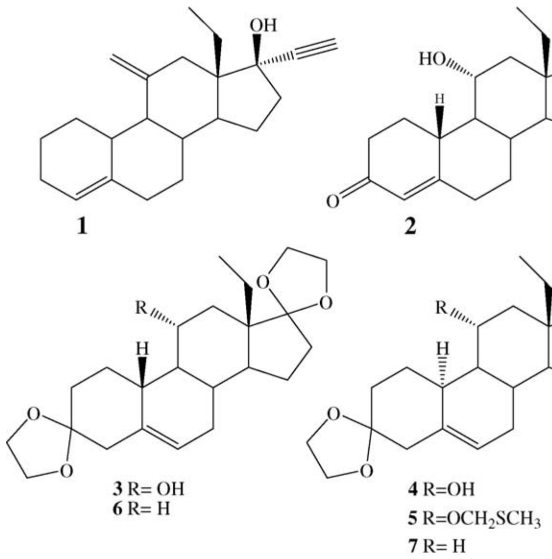

Scheme 1.

form solutions. Dry solvents and liquid reagents were distilled prior to use; triethylamine and pyridine were distilled from calcium hydride, and DMSO was dried over 4 Å molecular sieves. All reagents were purchased from Aldrich. All reactions were monitored by TLC on Silica Gel 60 F-254 plates (Merck) with detection by spraying with 50% H_2SO_4 solution and heating to 110 °C. Flash column chromatography was performed on Silica Gel 60 (230–400 mesh, Merck).

Mass spectrometry was performed on a particle beam quadrupolar mass spectrometer Hewlett-Packard HP 5988A equipped with an interface PB 5998A and a low pressure HPLC HP 1050. The mass spectrometric analyses were performed in electron impact (EI-MS) ionization mode at an electron energy of 70 eV with a source temperature of 250 °C. Samples were dissolved in methanol and introduced into the mass spectrometer via the particle beam LC–MS interface directly connected with the HPLC system. Elution was performed with methanol (0.4 ml/min).

The HPLC system consisted of an L-6200 Single pump (Merck-Hitachi), an L-4250 UV–vis detector (Merck-Hitachi), and a T-6300 Column Thermostat (Merck). The recorder was a Shimadzu C-R6A Chromatopac.

All NMR spectra were recorded at 303 K with a Bruker FT-NMR Avance DRX500 spectrometer in $CDCl_3$ solution; chemical shifts are reported as δ (ppm) relative to $CHCl_3$ fixed at 7.24 ppm for ^1H NMR spectra and relative to $CDCl_3$ fixed at 77.00 ppm for ^{13}C NMR spectra.

2.2. Chemistry

2.2.1. 13β-Ethyl-11α-hydroxy-10α-gon-5-ene-3,17-dione-3,17-diethylene ketal (4)

Ethylene glycol (40 ml, 717 mmol), triethyl orthoformate (20 ml, 120 mmol) and *p*-toluenesulfonic acid hydrate (0.7 g, 3.7 mmol) were added to a solution of 13β-ethyl-11α-hydroxy-gon-5-ene-3,17-dione (**2**) (5 g, 16.6 mmol) in CH_2Cl_2 (90 ml), and the mixture was refluxed for 6 h under argon. The reaction was worked up by washing with aqueous $NaHCO_3$, and the organic layer was washed with brine, dried over anhydrous sodium sulfate, and evaporated to dryness. From the reaction mixture, pure compound **4** (3.5 g) was obtained after crystallization from methanol. Mp 158–160 °C; $[\alpha]_D$ −204.0° (c 1); selected ^1H NMR signals: δ 1.00 (3H, t, $J = 8$ Hz, $-CH_2CH_3$), 3.70 (1H, ddd, $J = 10$, 10, and 4 Hz, 11-H), 3.82–3.98 (8H, broad, 3- and 17-ethyleneketal), 5.42 (1H, dd, $J = 6$ and 1 Hz, 6-H); ^{13}C NMR: δ 9.5, 21.2, 22.3, 25.7, 31.1, 31.8, 35.5, 36.0, 37.1, 38.0, 46.2, 48.9, 49.6, 51.9, 65.0, 65.1, 65.2, 66.0, 68.6, 110.2, 120.5, 121.0, 138.1. EI-MS *m/z* 390 $[M]^+$. $C_{23}H_{34}O_5$ (390.50): calcd. C 70.74, H 8.78; found C 71.10, H 8.84.

2.2.2. 13β-Ethyl-11α-hydroxy-gon-5-ene-3,17-dione-3,17-diethylene ketal (3)

An analytical sample of pure compound **3** was obtained, from the mother liquors of the reaction mixture described above, using reversed-phase HPLC on a 25 cm × 4 mm column packed with 5 μm LiChrosorb RP-18. Initial conditions for the chromatography were 65% solvent A (water) and 35% solvent B (CH_3CN). A gradient was initiated after 5 min; the concentration of solvent B was increased linearly from 35 to 70% over a period of 20 min and these conditions were maintained for an additional 10 min. The flow-rate was 1.2 ml/min, $T = 30$ °C, UV detector 215 nm. The retention times were 19.03 min for compound **3** and 16.34 min for compound **4**.

3: Mp 186–188 °C (from methanol); $[\alpha]_D$ −23.0° (c 1); selected ^1H NMR signals: δ 1.0 (3H, t, $J = 8$ Hz, $-CH_2CH_3$), 2.68 (1H, m, 10-H), 3.56 (1H, m, 11-H), 3.80–4.00 (8H, broad, 3- and 17-ethylene ketal), 5.50 (1H, dd, $J = 6$ and 1 Hz, 6-H); ^{13}C NMR: δ 9.7, 21.4, 22.3, 30.2, 32.6, 35.6, 35.7, 36.0, 38.5, 43.9, 45.7, 49.1, 51.1, 52.7, 65.0, 65.1, 65.2, 66.0, 75.7, 110.3, 120.0, 120.4, 138.4. EI-MS *m/z* 390 $[M]^+$. $C_{23}H_{34}O_5$ (390.50): calcd. C 70.74, H 8.78; found C 71.27, H 8.86.

2.2.3. 13β-Ethyl-11α- (methylthio)methoxy-10α-gon-5-ene-3,17-dione-3,17-diethylene ketal (5)

Triethylamine (8.6 ml, 61 mmol) and pyridine (0.5 ml, 5 mmol) were added to a solution of **4** (1 g, 2.6 mmol) dissolved in dimethyl sulfoxide (5.7 ml, 80.5 mmol) under argon.The mixture was cooled to 10 °C, and sulfur trioxide pyridine complex (2 g, 12.6 mmol) was added over a period of 4 h. The mixture was stirred for another 3 h at 10 °C and then diluted with water (25 ml). The solution was extracted with toluene (3 × 20 ml), and the combined organic phases were washed with brine, dried over sodium sulphate, and evaporated to dryness. The resulting crude reaction mixture was purified by flash chromatography hexane/ethyl acetate (8:2) affording **5** (702 mg, 60%). Mp 126–128 °C (from methanol); $[\alpha]_D$ −285.5° (c 1); selected ^1H NMR signals: δ 1.0 (3H, t, $J = 8$ Hz, $-CH_2CH_3$), 3.75 (1H, ddd, $J = 10$, 10, and 4 Hz,