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Synthesis and molecular structure of 14,15-pyrrolidino-and 14,16-ethano derivatives of estrone

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ABSTRACT

Hydrolysis of 3-methoxy-16α-nitro-14,17-ethenoestra-1,3,5(10)-trien-17β-yl acetate under weakly basic conditions leads to formation of 3-methoxy-2′-oxopyrrolidino-[4′,5′:14β,15β]-estra-1,3,5 (10)-trien-17-one, the structure of which has been confirmed by X-ray analysis and some chemical transformations. The reactivity of 3-methoxy-16α-nitro-14,17-ethanoestra-1,3,5(10)-trien-17β-yl acetate under various conditions of basic hydrolysis has been investigated. The derived compounds have been identified by means of NMR spectroscopy and X-ray analysis.

1. Introduction

It has previously been established [1] that compound **1**, which is a product of cycloaddition of nitroethylene to the dienyl acetate **2**, undergoes cleavage of the C16–C17 bond in the presence of Lewis acids or inorganic bases, and secondary reactions of the derived intermediate(s). Analysis of reaction products has led us to the conclusion that a nitrile oxide features as such an intermediate in certain cases. This hypothesis is supported by reactions of the cycloadduct **1** outlined in Scheme 1. Thus, reduction of the cycloadduct **1** with triphenylphosphine gives nitrile **3**, and isoxazole **4** when the reaction is carried out in the presence of propargyl alcohol [1]. The cyclic derivative of hydroxamic acid **5** is a major product arising from treatment of **1** with Lewis acids.

In this paper we report the results of hydrolytic transformation of nitro acetate **1** and its dihydro derivative **13** with sodium bicarbonate in aqueous ethanol.

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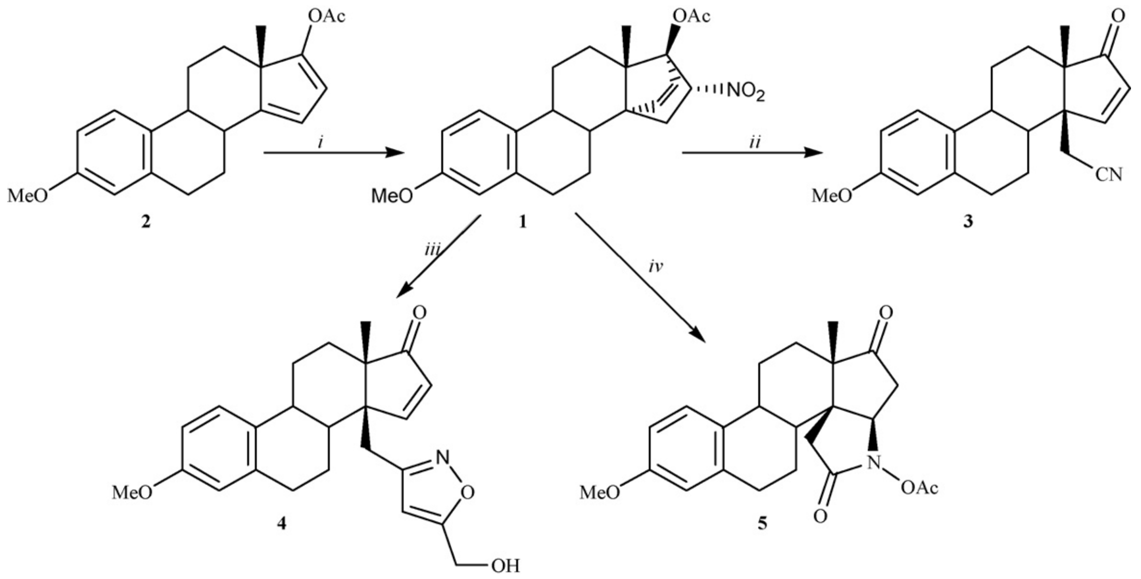

Scheme 1 – Reagents: (*i*) nitroethylene, benzene, 80 °C; (*ii*) $NaHCO_3$, Ph_3P, EtOH, 75 °C; (*iii*) $NaHCO_3$, propargyl alcohol, EtOH, 75 °C; (*iv*) $SnCl_4$, CH_2Cl_2, 0 °C.

2. Experimental

2.1. *General*

Melting points were measured using a Boetius apparatus and are uncorrected. Optical rotations were measured on a PerkinElmer 141 polarimeter in $CHCl_3$. IR spectra were recorded using a UR-20 or a PerkinElmer 983 IR spectrometers. Mass spectra (EI) were recorded on a VG Micromass 16F spectrometer, ratio *m*/z and relative intensities (%) are indicated for the significant peaks. Accurate mass (EI) were obtained with a VG-70E mass spectrometer. ^1H NMR (500,13 MHz) and ^{13}C NMR (125,75 MHz) spectra were recorded as a $CDCl_3$ solutions using residual signal of solvent (δ 7.26 ppm and 77.16 ppm for ^1H and ^{13}C respectively) as an internal standard on a Bruker AVANCE-500 instrument. COSY, HSQC, HMBC and NOESY experiments were carried out with the use of the standard Bruker program package.

TLC was performed on aluminum backed silica gel 60 F_{254} plates and visualized by UV and/or exposure to $Ce(NH_4)_4(SO_4)_4$ in 8 M H_2SO_4. Column chromatography was conducted with Merck Kieselgel 60: 70–230 mesh. Solvents were dried and freshly distilled according to common practice [2]. All reactions were conducted under positive nitrogen pressure.

2.2. *Crystal structure determination*

Single crystal X-ray data for **7** and **15** were collected on a Nicolet R3m diffractometer, graphite-monochromated Mo Kα radiation, ω–2θ scans, $2\theta_{max} = 55°$ for **7** and 58° for **15**. The structures were solved by direct methods using program SIR2004 [3]. Refinement on F^2 was carried out by full matrix least-squares technique as implemented in SHELXL-97 [4]. Anisotropic displacement parameters were used for all non-hydrogen atoms. All the hydrogen atoms were introduced in calculated positions and refined using riding model, with $U_{iso}(H)$ equal to $1.2U_{eq}$ of the corresponding carrier atom and $1.5U_{eq}$ for the methyl groups. Crystal data and refinement details are given in Table 5. Other details of crystal structure determination can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk) on request. Deposition numbers CCDC 661273 (**7**) and CCDC 661274 (**15**).

2.2.1. *3-Methoxy-2′-oxopyrrolidino-[4′,5′:14β,15β]-estra-1,3,5(10)-trien-17-one*

(7)

(*A*) A mixture of nitro compound **1** (0.119 g, 0.3 mmol) and $NaHCO_3$ (0.176 g, 2.1 mmol) in aqueous ethanol (33 ml, 10:1) was refluxed for 1 h. The yellow solution was cooled to 0 °C and poured into a cooled 1.5 M HCl solution (40 ml). The resulted mixture was stirred for 1 h and extracted with chloroform. The combined organic phase was washed with water, brine, dried ($MgSO_4$), and concentrated. The oily residue (0.11 g) was chromatographed on a silica gel column with ethyl acetate as eluent, affording hydroxy amide **6** [1] (0.025 g, 23%), and lactam **7** (0.043 g, 40%), mp 141–142 °C ($CHCl_3$). $[\alpha]_D^{20}$ +55.75° (*c* 0.64). IR ν_{max} ($CHCl_3$), cm^{-1}: 1694 (C=O, amide), 1732 (C=O), 3427 br (NH). EIMS, *m*/*z* (relative intensity, %): 339 (90) $[M]^+$, 321 (51) $[M-18]^+$, 187 (100) $[M-152]^+$. Exact mass calcd. for $C_{21}H_{25}NO_3$: 339.1834, found: 339.1836. Anal. calcd. for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N 4.13. Found. C, 73.39; H, 7.50; N, 4.02.

(*B*) Nitrile **3** [1] (0.063 g, 0.196 mmol) was dissolved in aqueous THF (15 ml, 7:3 v/v) and KOH (0.054 g, 0.98 mmol) was added. The resulting mixture was refluxed for 8 h, cooled and solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2, and the solution was washed with brine, dried (Na_2SO_4) and concentrated. The resulting oil was