Steroids 104 (2015) 37–48

Contents lists available at ScienceDirect

Steroids

journal homepage: www.elsevier.com/locate/steroids

Solvolysis of 14,17-etheno-bridged 16α-nitroestratrienyl acetate and lactam formation pathways studied by LC–NMR and LC–MS. Structures of minor products

Alexander V. Baranovsky [a,*], Dmitry A. Bolibrukh [a], Bernd Schneider [b]

[a] Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus, Kuprevich Str. 5/2, 220143 Minsk, Belarus
[b] Max Planck Institute for Chemical Ecology, Beutenberg Campus, Hans Knöll Str. 8, D-07745 Jena, Germany

ARTICLE INFO

Article history:
Received 17 March 2015
Accepted 15 August 2015
Available online 19 August 2015

Keywords:
Bridged steroid cleavage
Rearrangement
Nitrile oxide
Alkoxynitrone
Lactam

ABSTRACT

The ethanol solvolysis of 3-methoxy-14,17-etheno-16α-nitroestra-1,3,5(10)-trien-17β-yl acetate in the presence of $NaHCO_3$ was studied by means of real-time NMR experiments, LC–SPE–NMR, and LC–MS. The pathway to form 3-methoxy-2′-oxopyrrolidino-[4′,5′:14β,15β]-estra-1,3,5(10)-trien-17-one was disclosed. The intermediacy of nitrile oxide and alkoxynitrone was postulated based on the analysis of the reaction products. The proposed mechanism of cleaving the bridge in the nitro compound is legal for the formation of *N*-acetoxylactams, nitriles, isoxazoles and isoxazolines.

1. Introduction

It was previously reported that the ethanol solvolysis of the bridged nitro compound **1** in the presence of $NaHCO_3$ led mainly to the formation of lactam **2** and *N*-hydroxylactam **3** [1]. Lactam **2** was the principal by-product in the cycloaddition reaction of dipolarophiles (acetylenes and alkyl vinyl ethers) with compound **1** as well as the major product of the alkaline hydrolysis of oxazine **8** [2,3]. The basic hypothesis for most of these reactions (Scheme 1) is the formation of a nitrile oxide intermediate **13** due to the cleavage of the C^{16}–C^{17} bond. This suggestion explains reaction products such as isoxazoles and isoxazolines **7**, **12** [2], nitriles **5**, **10**, oxime **11**, *N*-hydroxy- and *N*-acetoxylactams **3**, **4** [1,4], but not lactam **2**. Moreover, further study of the solvolysis reaction with both the same substrate and its androstane analogs [5] showed that the ratio of lactam **2** and *N*-hydroxylactam **3** can vary widely depending on the work-up procedure. In contrast, *N*-acetoxylactam **4** was the only isolable product in the reactions of compound **1** with acetic anhydride and $SnCl_4$, respectively.

Two products – namely, compounds **6** and **8** – are clearly the result of different reaction mechanisms. The formation of compound **6** is explained by the well-known pathway of the cleavage of bridgehead tertiary alcohols [6,7] with the hydrolysis of 17-acetate as the first step. In the case of the $NaHCO_3$-mediated cleavage, we suggest that the acetate hydrolysis is not the first step of the reaction [2]. Oxazine **8** is a product of a two-step reaction: the reduction of the nitro group into the nitroso group by $TiCl_3$ [4] or Bu_3SnH [8] followed by a sigmatropic rearrangement. It is worthwhile to mention that treating compounds **6** and **8** with $NaHCO_3$ in the presence Ph_3P or a dipolarophile in ethanol did not result in any reaction products such as **5** or **7** [4]. As for reactions mediated by the Lewis acids, we suspect a nitrile oxide derived species intermediacy due to the presence of the acetoxy group in the product that could be only the result of an intramolecular rearrangement and similar to the reaction mediated by $NaHCO_3$.

The present study was undertaken to provide additional evidence of the intermediacy of nitrile oxide by analyzing minor components of the reaction mixture and in attempt to understand the lactam formation mechanism as well as the variation in the ratio of lactam to *N*-hydroxylactam.

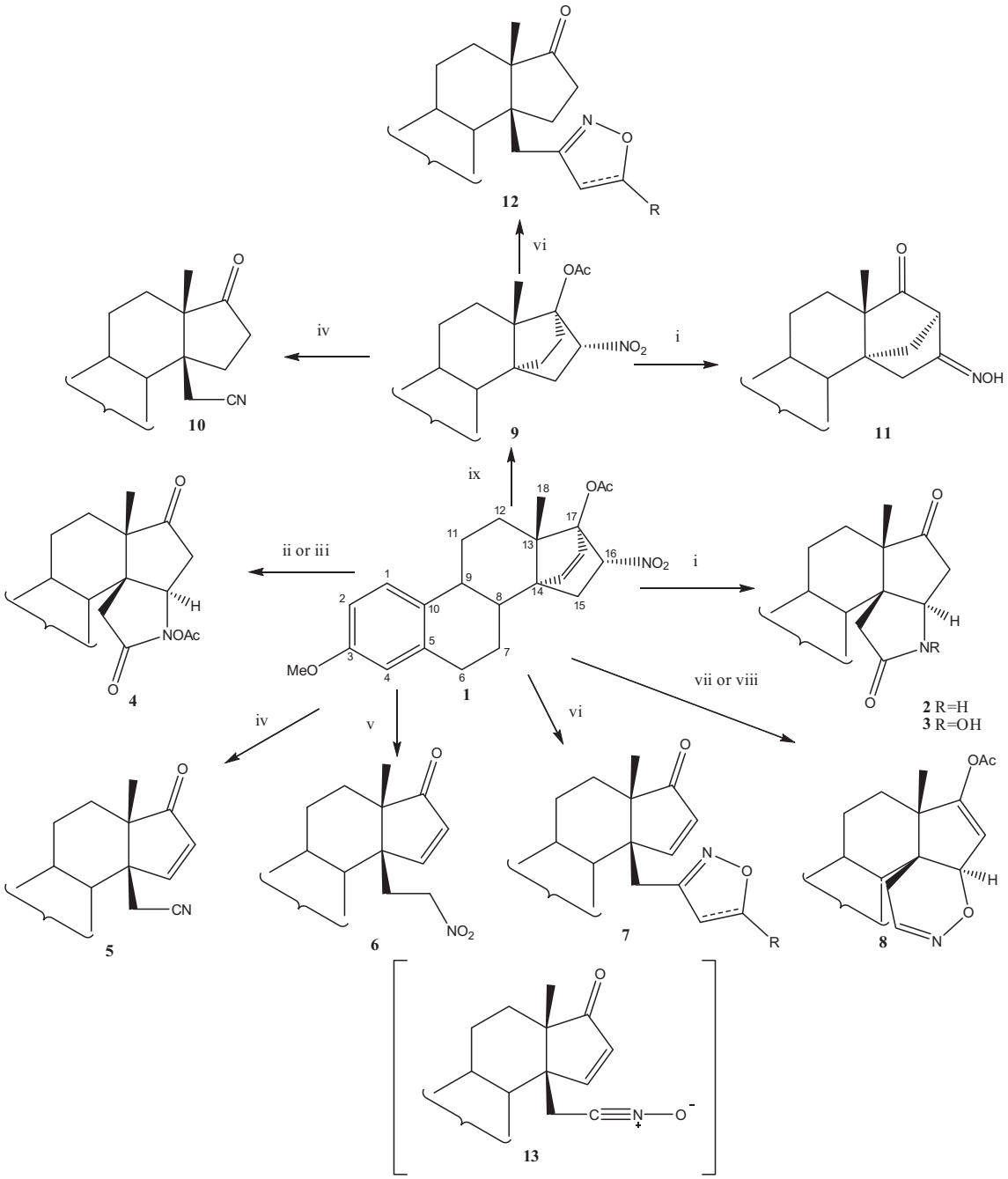
2. Experimental

2.1. General

The real-time experiment was carried out on a Bruker AVANCE 400 NMR spectrometer equipped with a 5 mm PABBI ^{1}H-BB Z-GRD probe. Ethanol-d_6 was used as a solvent and the residual signal of its methyl group (δ 1.11) served as an internal reference standard.

* Corresponding author.
E-mail address: baranovsky@iboch.bas-net.by (A.V. Baranovsky).

http://dx.doi.org/10.1016/j.steroids.2015.08.009
0039-128X/



Scheme 1. Transformation products of compound **1** [1,2,4,7]. *Reagents and conditions:* i: (1) $NaHCO_3$, EtOH, Δ, (2) HCl, H_2O; ii: (1) $SnCl_4$ or $TiCl_4$, CH_2Cl_2, (2) AcOH or HCl, H_2O; iii: Ac_2O, NaOAc; iv: Ph_3P, $NaHCO_3$, EtOH, Δ; v: KOH, MeOH; vi: dipolarophile (acetylene or alkyl vinyl ether), $NaHCO_3$, EtOH, Δ; vii, $TiCl_3$, THF, H_2O; viii: Bu_3SnH, AIBN, PhH, Δ; ix: H_2, Pd/C, EtOH, THF.

The liquid chromatography – photodiode array detection – solid phase extraction – nuclear magnetic resonance spectroscopy (LC–DAD–SPE–NMR) system consisted of an Agilent 1100 chromatography system (quaternary solvent delivery pump G1311A, autosampler G1313A; Agilent Technologies, Waldbronn, Germany) and a photodiode array detector (DAD, detection 200–700 nm; J&M Analytik AG, Aalen, Germany) connected to a Prospekt 2 solid-phase extraction (SPE) device (Spark Holland, Emmen, The Netherlands) containing HySphere resin GP cartridges (10 × 2 mm, 10 μm). UV profiles were obtained via DAD detection during analytical HPLC in the eluents $CDCl_3$ and MeCN-d_3. A make-up pump (Knauer, Berlin, Germany) was used to add water (2.5 ml min^{-1}) to the eluent after HPLC in order to reduce the eluotropic capacity. The system was controlled by Bruker software HyStar 3.2 (Bruker Biospin, Rheinstetten, Germany). A LiChrospher RP18 column (5 μm, 250 × 4 mm) was used for HPLC.

SPE cartridges loaded with the reaction products were dried in a stream of nitrogen. MeCN-d_3 or $CDCl_3$ was used to elute the analytes from the cartridges and transfer them through the connecting capillary into the CryoFIT™ flow system (30 μl), which was inserted into the 5 mm TCI Cryoprobe™ of the Bruker AVANCE 500 NMR spectrometer. ^{1}H NMR (500.13 MHz) and ^{13}C NMR (125.77 MHz), ^{1}H,^{1}H-COSY, HSQC, HMBC, TOCSY and NOESY spectra were recorded at 300 K using standard Bruker pulse sequences. $CDCl_3$