LUMI-MESTRANOL AND EPI-LUMI-MESTRANOL

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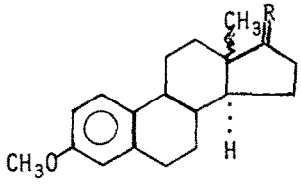
ABSTRACT

Treatment of lumi-estrone 3-methyl ether (I) with acetylene gave the C-17-epimeric compounds lumi-mestranol (3-methoxy-17α-ethynyl-13α-estra-1,3,5(10)-trien-17β-ol, III) and epi-lumi-mestranol (3-methoxy-17β-ethynyl-13α-estra-1,3,5(10)-trien-17α-ol, IV). The structures of the two isomers were assigned on the basis of their molecular rotations and shift-reagent experiments in the NMR. The irradiation of estrone 3-methyl ether (II) to provide compound I was investigated in two solvent systems. Minor products of these reactions were the seco-steroids VII, VIII and X.

INTRODUCTION

In the course of synthetic studies in our laboratories, we investigated the irradiation of estrone 3-methyl ether (II) under several conditions in order to prepare quantities of lumi-estrone 3-methyl ether (I) [1]. When the irradiation was conducted in anhydrous THF, the major product was compound I. However, we also obtained the seco-steroids VII and VIII as minor products. When ethanol containing a small amount of NaOH was used as the irradiation solvent, the seco-steroid X was formed as well as a number of highly polar unidentified compounds. Ethynylation of compound I gave the C-17 epimeric compounds lumi-mestranol (III) and epi-lumi-mestranol (IV). The structures of compounds III and IV were assigned on the basis of both molecular rotation comparisons and NMR $Eu(fod)_3$ shift reagent experiments. For the NMR studies, mestranol (3-methoxy-17α-ethynyl-1,3,5(10)-estratrien-17β-ol, V) and epi-mestranol (3-methoxy-17β-ethynyl-1,3,5(10)-estratrien-17α-ol, VI) [2] were used as model compounds.



I 13α, R = O

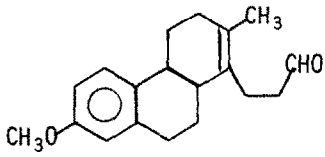
II 13β, R = O

III 13α, R = 

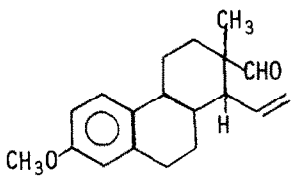
IV 13α, R = 

V 13β, R = 

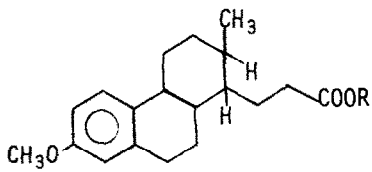
VI 13β, R = 



VII

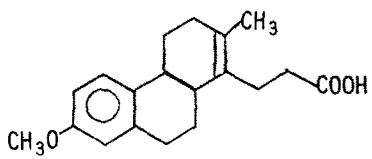


VIII



IX R = H

X R = Et



XI

MATERIALS AND METHODS

Estrone 3-methyl ether (II) was obtained from Organon, West Orange, New Jersey. All solvents used were J. T. Baker, reagent grade. THF was distilled over LAH under N_2 prior to use. A medium pressure mercury Hanovia lamp equipped with a Corex filter was used for the irradiation. Column chromatography was effected on SilicAR-CC-7 (Mallinckrodt Chemical Co.). $Eu(fod)_3$ was from Norell Chemical Co., Inc., Linden, New Jersey.

NMR spectra were run on a Varian A-60-A spectrometer. Mass spectra were obtained using a Finnigan 1015-D MS. Melting points were determined using a Thomas-Hoover capillary apparatus and are uncorrected. IR spectra were recorded on a Beckman IR-8 spectrophotometer as KBr pellets. Elemental analyses were performed on a Perkin-Elmer 240 Elemental Analyzer. Optical rotations were determined for 1% solutions in $CHCl_3$ on a Rudolph model 70 polarimeter with a model 200 photoelectric unit.

Irradiation of estrone 3-methyl ether (II)

A. In anhydrous THF

Estrone 3-methyl ether (II, 100 g) was irradiated for 16 hours as a 0.1 molar solution in anhydrous THF with stirring under an N_2 atmosphere. The solvent was removed under vacuum and the residue chromatographed on a column 30 times the weight of the residue using an ethyl acetate/hexane gradient. The first major component to be eluted from the column was identified as 3-methoxy-13,17-seco-estra-1,3,5(10)-13-tetraene-17-al (VII, 14%): M^+ 284, m.p. 127-128°. $\delta_{TMS}^{CDCl_3}$ 1.7 (s,3H), 2.5 (s,4H), 3.75 (s,3H), 6.6 (s,1H), 6.7 (d,d,J = 2,8Hz,1H), 7.21 (d,J = 8Hz,1H), 9.73 (1H). IR 2700, 1724 cm^{-1}. Anal. Calc'd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.37; H, 8.83. Further elution gave lumi-estrone 3-methyl ether (I,37%): m.p. 126-128°. $\delta_{TMS}^{CDCl_3}$ 1.0 (s,3H), 3.75 (s,3H), 6.6 (s,1H), 6.7 (d,d,J = 2,8Hz,1H), 7.21 (d,J = 8Hz,1H) [3]. The spectral data corresponded to that previously reported for this compound. In addition, a minor product (~ 1%), the seco-aldehyde VIII, was also isolated and its structure assigned on the basis of spectral evidence: M^+ 284, m.p. 135°. $\delta_{TMS}^{CDCl_3}$ 1.26 (s,3H), 3.75 (s,3H), 4.8-5.9 (m,3H), 6.6 (s,1H), 6.7 (d,d,J = 2,8Hz,1H), 7.21 (d,J = 8Hz,1H), 9.73 (1H). In addition, unreacted starting material (18%) was eluted from the column.

B. In EtOH containing NaOH

Steroid II (0.5 g) was irradiated for five hours in 95% EtOH (1.5 l) containing 0.3% NaOH (10 ml) in a reaction vessel open to the atmosphere. The solvent was removed under vacuum, the residue dissolved in CH_2Cl_2, washed (H_2O) and dried (Na_2SO_4). The crude yield after solvent evaporation was 60%. The residue was chromatographed on a column 80 times its weight using an ethyl acetate/benzene gradient. The first component to be eluted from the column was ethyl 3-methoxy-13,17-seco-estra-1,3,5(10)-trien-17-oic acid (X,10%): M^+ 330. $\delta_{TMS}^{CDCl_3}$ 0.97 (distorted doublet,3H), 1.23 (t,J = 8Hz,3H), 3.75 (s,3H), 4.13 (q,J = 8Hz,2H), 6.6 (s,1H), 6.7 (d,d,J = 2,8Hz,1H), 7.21 (d,J = 8Hz,1H). The remaining products eluted from the column consisted of a number of highly polar compounds which were not identified.

Synthesis of lumi- and epi-lumi-mestranol

Lumi-estrone 3-methyl ether (I) was ethynylated using methyl magnesium bromide in the presence of acetylene in THF as described by Crabbé [3] with the modification that the reaction mixture was refluxed for 18 hours. The reaction was incomplete and 56% of the starting material was recovered. Silica gel chromatography using a $CHCl_3$/hexane gradient separated lumi-mestranol (III, 17%) and epi-lumi-mestranol (IV, 10%). Lumi-mestranol (III) had a M^+ 310, m.p. 130-132°. $[\alpha]_D^{24.8}$ = + 18.9° $\delta_{TMS}^{CDCl_3}$ 1.06 (s,3H), 2.48 (s,1H), 2.7-3.0 (m,3H), 3.75 (s,3H), 6.6 (s,1H), 6.7 (d,d,J = 2,8Hz,1H), 7.21 (d,J = 8Hz,1H). IR 3549, 3280 cm^{-1}. Anal. Calc'd for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 81.19; H, 8.69. Epi-lumi-mestranol (IV) had a M^+ 310, m.p. 154-156.5°. $[\alpha]_D^{25}$ = + 129° $\delta_{TMS}^{CDCl_3}$ 1.16 (s,3H), 2.48 (s,1H), 2.7-3.0 (m,3H), 3.73 (s,3H), 6.6 (s,1H), 6.7 (d,d,J = 2,8Hz,1H), 7.21 (d,J = 8Hz,1H). IR 3520, 3240 cm^{-1}. Anal. Calc'd for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 81.02; H, 8.43.

Synthesis of the seco-steroid X

A chromatography fraction (2.45 g) containing a mixture of compounds VII and I (∿ 2:1) was stirred with Ag_2O (3.0 g), 10% NaOH (5 ml) and 90% THF (50 ml) for 20 hours. The THF was evaporated and the residue treated with H_2O and ethyl acetate. The aqueous layer was acidified with dilute HCl and extracted with ether. The ether layer was evaporated and the residue recrystallized from ethyl acetate/hexane, giving the seco-acid XI (31.6%); m.p. 126°. Anal. Calc'd for $C_{19}H_{24}O_3$: C, 75.79; H, 8.32. Found: C, 75.97; H, 8.05. A solution of compound XI (150 mg) in anhydrous EtOH (75 ml) was hydrogenated for 18 hours in a Parr shaker using 250 mg of 5% Pd/C catalyst. The catalyst was filtered and the

filtrate evaporated giving compound IX (84%): $\delta_{TMS}^{CDCl_3}$ 0.9 (broad, ~ 3H), 3.75 (s,3H), 6.6 (s,1H) 6.7 (d,d,J = 2,8Hz,1H), 7.21 (d,J = 8Hz). A solution of compound IX (125 mg) in EtOH (4 ml) containing four drops of HCl was stirred at room temperature for 18 hours. The solvent was evaporated and the sample triturated with $CHCl_3$ to give a mixture of the 13,14-cis and trans isomers containing compound X (NMR). The mass spectrum of the mixture was identical to compound X obtained by irradiation.

Eu(fod)$_3$ shift reagent experiments

Eu(fod)$_3$ shift reagent experiments were used to determine the stereochemistry of lumi-mestranol (III) and epi-lumi-mestranol (IV) using mestranol (V) and epi-mestranol (VI) as model compounds. The magnitude of the shift of the 18-methyl group upon the addition of Eu(fod)$_3$ was used as the probe. Since the 3-methoxy groups were not expected to compete successfully with the 17-hydroxyl group for the Eu(fod)$_3$ [4], the major shifts in the spectrum would appear in the groups adjacent to this hydroxyl group [5]. Due to the limited quantity of compound IV it was decided to obtain Eu(fod)$_3$ shifted spectra at only one concentration with respect to substrate. To ensure that we would be operating in a region that showed linear shifts with respect to relative concentration [6], mestranol (V) was used as a model system. Shifts of the 18-methyl group and the 17-ethynyl proton were found to be linear with respect to the concentration of Eu(fod)$_3$ in the range of 0.1 to 1.0 M Eu(fod)$_3$ to compound V.

The NMR Eu(fod)$_3$ shifted spectra of compounds III, IV, V and VI were obtained using the same technique. Each compound (35 mg) was dissolved in $CDCl_3$ (0.2 ml) and added to an NMR tube containing a 20% stock solution (0.5 ml) of Eu(fod)$_3$ in $CDCl_3$. This was a molar ratio of 0.85 moles of Eu(fod)$_3$ per mole of substrate, a region shown to yield linear shifts with respect to concentration. The spectrum of each isomer was then obtained and the shifts for the relevant protons in Hz were observed to be:

Compound	Shift in Hz for Functional Groups		
	3-OCH_3	17-C≡CH	18-CH_3
III	23	22	59
IV	23	44	120
V	24	60	149
VI	20	35	72

DISCUSSION

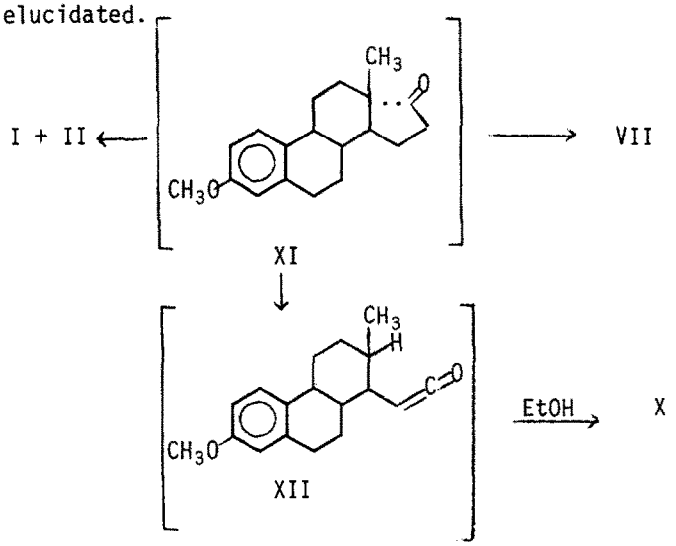
Ethynylation of lumi-estrone 3-methyl ether (I) gave an approximately 50:50 mixture of epimers III and IV. These results are consistent with previously reported ethynylation reactions of cis C/D ring steroids [7].

Tentative assignment of structures to the isolated epimers III and IV could be made on the basis of comparison of their respective molecular rotations. In both the 13β- and 13α-series of 17-ethynyl, 17-hydroxyl-steroids, the isomer with the 17β-hydroxyl group exhibits a more negative molecular rotation than the epimer with the 17α-hydroxyl group [8,9]. On the basis of their molecular rotations, it appeared likely that compound III, $[\phi]_D^{24.8}$ = +58.6°, was lumi-mestranol and compound IV, $[\phi]_D^{25}$ = +400° was epi-lumi-mestranol.

This assignment was confirmed by the NMR Eu(fod)$_3$ shift reagent experiments. The magnitude of the observed downfield shift of the 18-methyl group in each epimer upon addition of shift reagent was used to assign stereochemistry to the isomers. Eu(fod)$_3$ complexed preferentially with the 17-hydroxyl group. Protons adjacent to this group were shifted, downfield depending upon their relative distance from the Eu^{+3} ion.

In mestranol (V) and epi-lumi-mestranol (IV) the 17-hydroxyl group is cis to the 18-methyl protons. In these two isomers the magnitude of the downfield shift of the 18-methyl protons was observed to be much larger than in the two isomers lumi-mestranol (III) and epi-mestranol (VI) in which the 17-hydroxyl group and the 18-methyl protons are trans. The magnitude of the Eu(fod)$_3$ shift of the 18-methyl protons allowed us to conclusively assign the lumi-mestranol structure to compound III and the epi-lumi-mestranol structure to compound IV.

During the preparation of lumi-estrone 3-methyl ether (I), we investigated the UV-irradiation of estrone 3-methyl ether (II) in solution under several conditions. Compound I was the major product when anhydrous THF was used as a solvent. However, we also observed as minor products the previously unreported seco-steroids VII and VIII. When ethanol containing a small amount of NaOH was used, the related seco-steroid X was isolated. Formation of the seco-steroids VII, VIII and X although previously unreported for this system are not unexpected. Irradiation of cyclic ketones is known to give unsaturated aldehydes [10], ketenes [11] or ketene adducts as products [12]. The seco-ester X is presumed to have been formed by the addition of ethanol to an initially formed ketene XII. The stereochemistry of compound X, which, according to an NMR analysis, represents essentially a single isomer, was not elucidated.



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TRIVIAL NAMES

epi-lumi-mestranol - 3-methoxy-17β-ethynyl-13α-estra-1,3,5(10)-trien-17α-ol.
epi-mestranol - 3-methoxy-17β-ethynyl-1,3,5(10)-estratrien-17α-ol.
lumi-mestranol - 3-methoxy-17α-ethynyl-13α-estra-1,3,5(10)-trien-17β-ol.
mestranol - 3-methoxy-17α-ethynyl-1,3,5(10)-estratrien-17β-ol.

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