REACTION OF TRIMETHYLSILYLIMIDAZOLE WITH 5,10β-EPOXY-3-KETOSTEROIDS: ENOLIZATION AND AROMATIZATION OF THE A-RING

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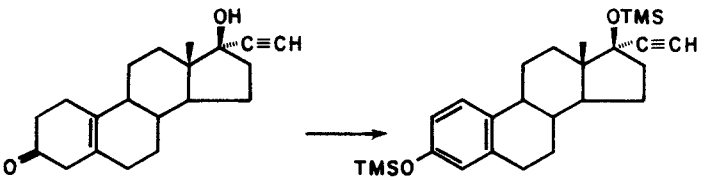
ABSTRACT

The reaction of trimethylsilylimidazole (TSIM) and 3-keto-5,10-epoxy-nor-19-methylandrostanone 3 and its 17-acetate analog 4 was examined at two different temperatures. In both compounds, reaction at 90°C gave predominantly a Δ^3-silyl-enol ether plus a minor product as a result of the epoxide ring opening. Under reflux conditions, besides the aforementioned products, aromatization of the A-ring was observed as a major process. The results suggest the potential use of silylation reactions with epoxy-ketones towards the synthesis of aromatic compounds.

INTRODUCTION

Recent studies in this laboratory have been concerned with the aromatization of the A-ring of nor-19-methyl steroids during trimethylsilylation reactions (1,2). It has been previously reported by Thompson and Horning (3) that reaction of norethynodrel 1 with trimethylsilylimidazole (TSIM) at 25°C resulted in 20-30% yield of a product bear-

ing A-ring aromatization as indicated by combined gas chromatographic/mass spectrometric (GC/MS) analysis. On the other hand, reaction at higher temperatures was found to produce a 100% yield of the aromatic product 2 (Scheme 1).



1 2

Scheme 1

An enol ether was proposed as intermediate leading to the aromatization, consistent with related reports by Chambaz et al. (4,5) regarding the behavior of ketonic compounds during silylation.

Recently we reported (2) that relative to the saturated analog, the presence of a double bond in ring "A" increases the yield of enol ether. In addition, the presence of an epoxide function in the 4,5 (α or β) or 1,2 (α) positions of ring "A" strongly favored the formation of the enol ether.

The rate of enolization was found to decrease in the order:

α,β-epoxyketone > α,β-unsaturated ketone > saturated ketone.

In an extension of this earlier work, we report here on the effect of 5,10-epoxy substitution in 19-nortestosterone on the formation of the enol ether and on the aromatization of ring "A," using TSIM as silylating reagent at different temperatures.

EXPERIMENTAL

Chemicals

TSIM was purchased from Pierce Chemical Co. (Rockford, IL). Steroids were purchased from Steraloids, Inc. (Wilton, NH).

Apparatus

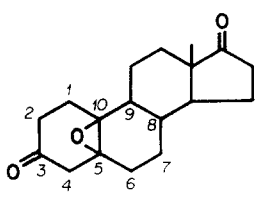
Electron impact (EI) mass spectra were obtained with a 12-90-G magnetic mass spectrometer (Nuclide, State College, PA) interfaced to a 2700 gas chromatograph (Varian Associates, Inc., Palo Alto, CA) via an open-split separator. The ionizing energy was 70 ev. The column was 3% OV-1, 6 ft × 2 mm inner diameter.

Reaction Procedure

Reactions were carried out by dissolving the steroid (10 μmol) in 1.0 mL of TSIM and heating at the desired temperature for 10 h. The products were isolated by evaporation of the excess reagent under a stream of nitrogen and reconstitution in methylene chloride.

RESULTS

Two steroidal compounds bearing a 5,10-epoxide function were examined. They were 3-keto-5,10β-epoxy-nor-19-methyl androstanone, 3, and 3-keto-5,10β-epoxy-nor-19-methyl androstanone-17-acetate, 4. The compounds were reacted with TSIM neat at 90°C and under reflux conditions (140°C). The silylation reaction was carried out in an inert (N_2) atmosphere. In the following we consider first the results obtained under mild reaction conditions at 90°C, followed by an examination of the effects of higher temperature (140°C) on the consistency of the reaction products.



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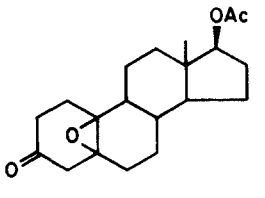

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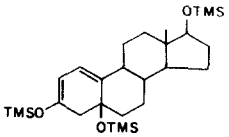
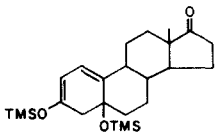
Reaction at 90°C

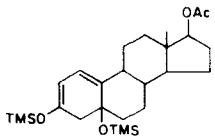
Both compounds 3 and 4 yielded two products each upon reaction with TSIM at 90°C, as determined by GC/MS analysis. In each case, the molecular weight of the first eluting compound was found to be 72U higher than that of the starting material. In accordance with the well known propensity of the carbonyl function to form a trimethylsilyl (TMS) enol ether, structures 3a and 4a are proposed for these compounds.* Formation of a 3,4- as opposed to a 2,3-enol ether is postulated due to resonance stabilization provided by the 5,10β-epoxide function (6). Two major fragmentation processes are noted in the mass spectra of 3a and 4a (Figures 2 and 3). They involve losses of CO and H_2O from the molecular ion and are substantially associated with the epoxide group. This is consistent with previous observations on the mass spectrometric behavior of 4,5-epoxy steroids (1,5), and was further confirmed by labeling of the 3- and 17-oxygens of compound 3 with oxygen-18. Plausible mechanisms for these fragmentations are proposed in Scheme 2.



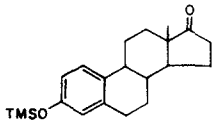
3d



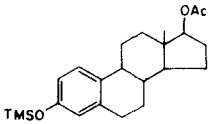
3c



4c



3b



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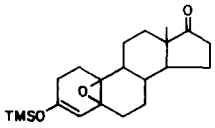
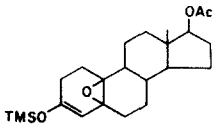


3a



4a

Figure 1. Structures of Enolization Products

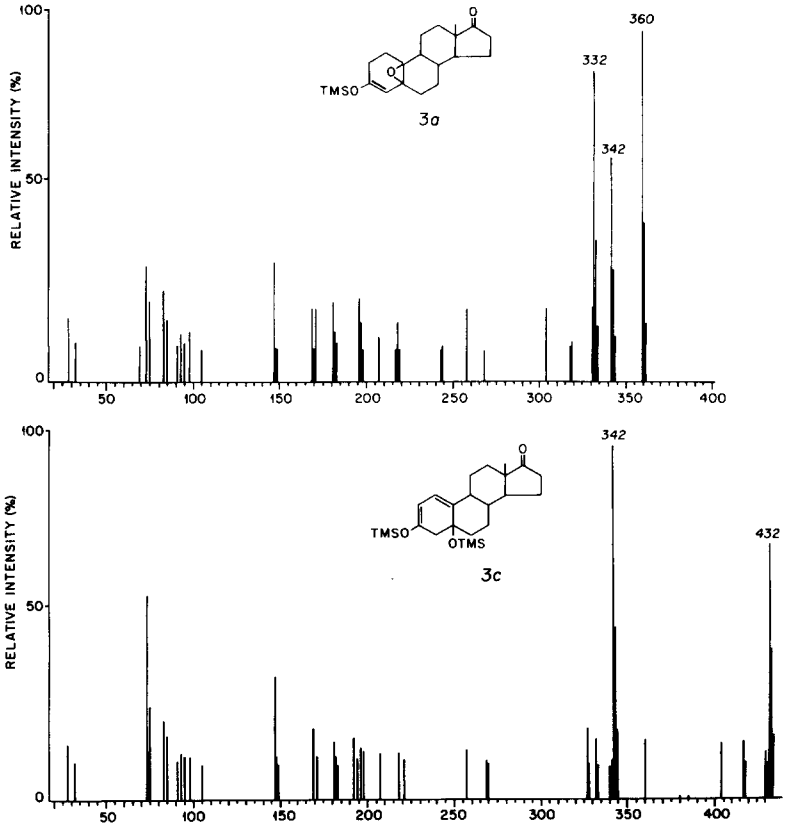


Figure 2. Electron Impact Mass Spectra of 3a and 3c

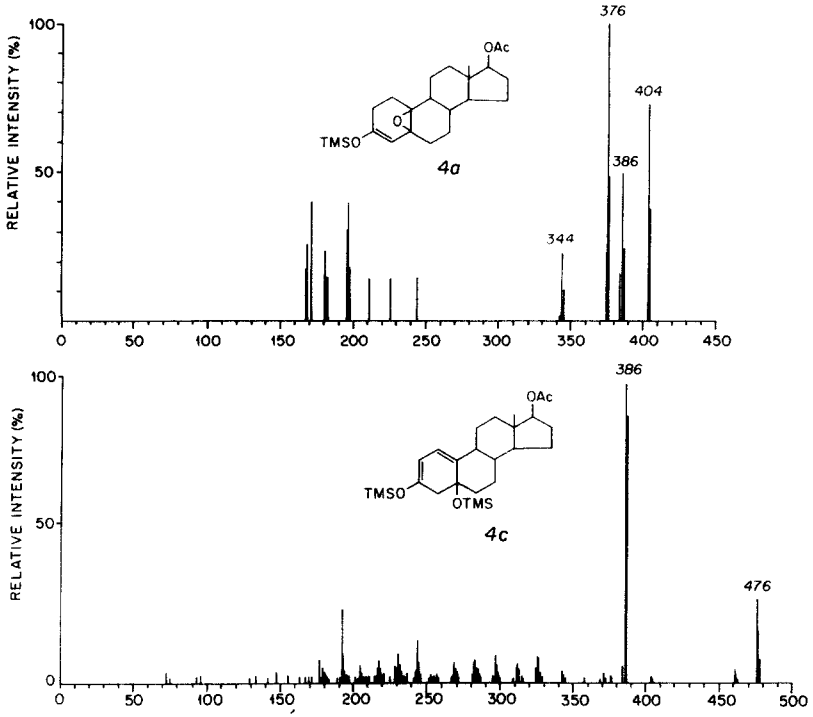
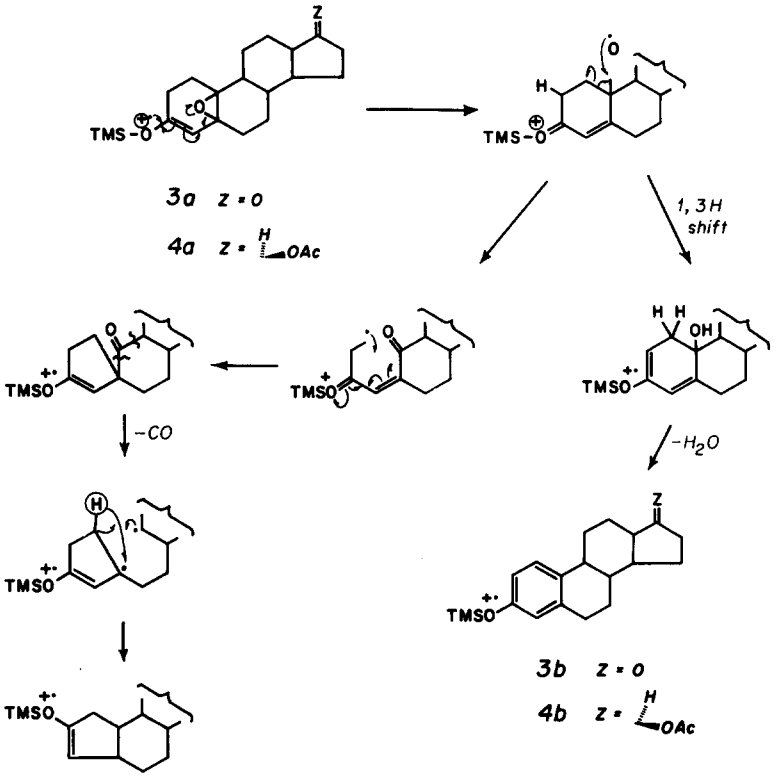


Figure 3. Electron Impact Mass Spectra of 4a and 4b



Scheme 2

Reaction at 140°C

Reaction under reflux conditions resulted in the formation of two new products, 3b and 3c, in the case of 3 and one additional product, 4b, in the case of 4. Aromatization of the A-ring yielded compounds having structures 3b and 4b, whose mass spectra are given in Figures 4 (top) and 5, respectively. This is consistent with the results of Thompson and Horning (1,2) and our own previous observations on the behavior of 3-keto-4,5β-(or α)-epoxy-nor-19-methylsteroids (3,4). Typical of estrogen derivatives, the mass spectra of 3b and 4b are dominated by the molecular ion peaks. Elimination of acetic acid from $[M]^{+\cdot}$ to give an ion of m/z 326 is one easily recognizable process in the EI decomposition of 4b.

A second minor component in each of the chromatograms was found to contain two TMS groups as evidenced from the molecular ions at m/z 432 and 476 for the reaction products from the silylation of 3 (Figure 2, bottom) and 4 (Figure 3, bottom), respectively. While enolization of the 17-keto group in the case of 3 is possible, it is more reasonable to postulate an opening of the 5,10-epoxide ring, in

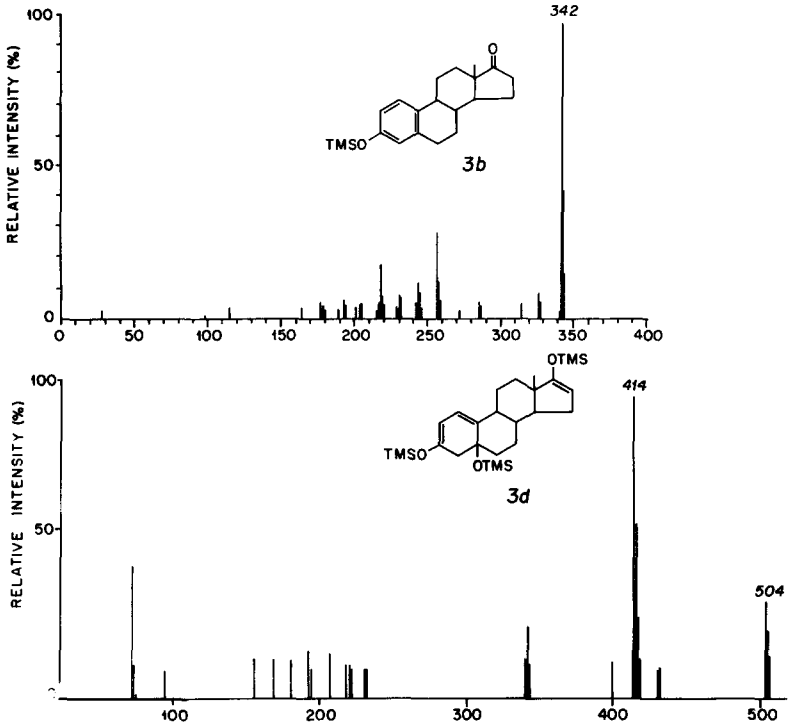


Figure 4. Electron Impact Mass Spectra of 3b and 3d

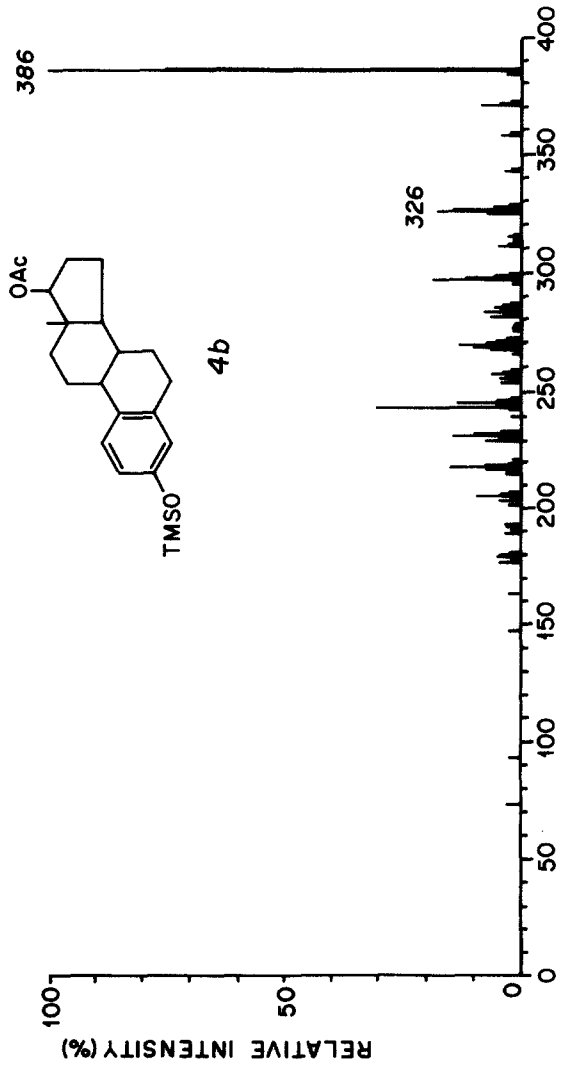


Figure 5. Electron Impact Mass Spectrum of 4b

view of the formation of a product of the same mass increment for the 17-acetyl derivative, 4. Two isomers can be formed upon epoxide ring opening: a 5β- or a 10β-TMS ether. The 5β-TMS ethers, structures 3c and 4c, are preferred because they are thermodynamically more stable due to the lower steric hindrance of the trimethylsilyloxy function with the methylene group at C_{11}. The mass spectra of 3c and 4c (Figures 2 and 3, bottom) are characterized by intense peaks at $[M-90]^{+\cdot}$, corresponding to a favorable elimination of trimethylsilanol from the molecular ion. This conforms with the postulated structures 3c and 4c, since the loss of trimethylsilanol yields a fragment ion bearing an aromatized A-ring.

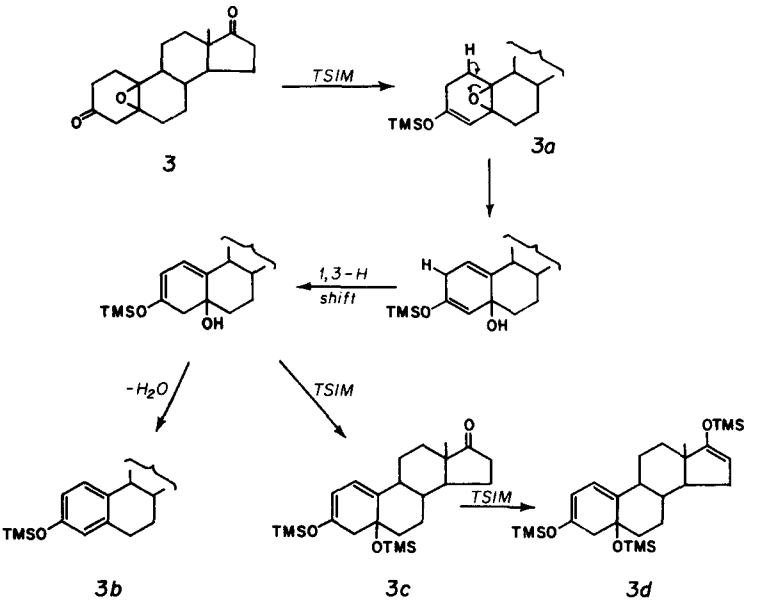
In addition to the formation of 3a and 4a, the reaction at high temperature is characterized by a decrease in the yields of the enol ethers 3a and 4a, and a corresponding increase in the yields of the dienol ethers 3c and 4c. Moreover, GC/MS analysis of the reaction mixture from the silylation of 3 revealed the formation in relatively small yield of a fourth product of molecular weight 504. This can be explained by enolization of the 17-keto group to

produce a compound bearing the formulation 3d. As expected, the mass spectrum of 3d (Figure 4, bottom) shows favorable elimination of trimethylsilanol, presumably from the 5β-position, to give a fragment ion of m/z 414 bearing A-ring aromatization.

DISCUSSION

The data described above further demonstrate a similarity in the behavior of the epoxide function and a double bond. In fact, when the same silylation reactions (140°C) were also conducted with 3-keto-5,10-estr-ene-17-one and 3-keto-5,10-estr-ene-17-acetate, the olefinic analogs of 3 and 4, only the product containing an aromatized A-ring was found in each of the reaction mixtures, identified respectively as 3b and 4b. An estradiene intermediate detected under milder reaction conditions (60°C) presumably precedes the aromatization of the A-ring, but is rapidly converted to the estratriene due to the high reactivity of the double bond. On the other hand, the presence of an epoxide function apparently provides more favorable conditions than in the olefin for stabilization and detection of the estradiene intermediates even when the reactions are

conducted at elevated temperatures. On the basis of these observations, a likely pathway for the formation of the different reaction products is outlined in Scheme 3 using compound 3 as an example.



Scheme 3

It is postulated that, after enolization, an aromatic product 3b can be formed by simple dehydration. Alternatively, opening of the epoxide ring and deprotonation can lead to the formation of the estradiene-TMS ether, 3c, which can also produce an aromatic product via elimination of trimethylsilanol. In the case of compound 3, the presence of a 17-keto group induced a further enolization process to yield an additional product 3d.

In conclusion, these results illustrate further the similarities in the chemical behavior of epoxide groups and double bonds. More specifically, they point out the susceptibility for epoxide ring opening and rearrangements during silylation reactions, in particular when epoxide rings are present in the vicinity of unprotected carbonyl groups or other related functionalities.

ACKNOWLEDGMENT

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NOTE

*Their structures, along with those of other enolization products encountered in this study, are shown in Figure 1.

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