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# THERMAL DEGRADATION OF MESTRANOL AND ETHINYL ESTRADIOL

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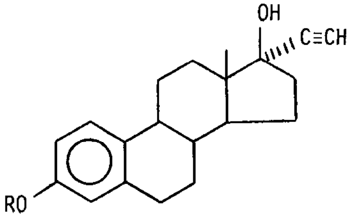
Although mestranol (MEE, 1) and ethinyl estradiol (EE, 7) have been available for a number of years[1], there is no information in the literature concerning the nature of the products formed upon their degradation. This work was undertaken in order to provide fundamental information concerning the degradation pathways of these two compounds.

The accelerated decomposition of MEE and EE in the solid state at elevated temperatures in the presence of air was investigated. It was assumed that the major pathway of degradation under these conditions would be the result of auto-oxidation[2]. Preparative tlc was used to separate the thermal decomposition mixtures and the various fractions examined by gc-ms.



1 R = Me Mestranol

7 R = H Ethinyl Estradiol

The major degradation products from the three hour thermal (147°) decomposition of MEE were shown to be 6α-hydroxy (3) and 6β-hydroxy MEE (4). The apparent $M^+$ for both compounds was 326, which could be rationalized to result from the addition of one oxygen atom to the MEE molecule. Prominent fragments in the mass spectrum at 308, 243, 225 and 171 supported the assigned structures. The presence of the 308 fragment ($M-H_2O$) suggested that the oxygen was incorporated in the form of a hydroxyl group. The 243 (M-83) and 225 ($M-H_2O-83$) fragments were indicative of an intact D ring, while the 171 fragment was rationalized to arise from rings A and B after initial dehydration. From these data it appeared that the new alcohol was located in the B ring. The C-6 benzylic position appeared to be one most likely for attack by oxygen and the hydroxyl group was tentatively placed there.

One of the two isomers was separated by preparative tlc on silica gel using benzene-ethyl acetate (7:3) as the developing solvent. On the basis of its NMR spectrum ($CDCl_3$), this isolated compound appeared to be 6α-hydroxy MEE (3)[3]. The C-6 benzylic protons had disappeared and the C-4 proton appeared at $\delta$ = 7.1 (0.5 ppm downfield from the position of the C-4 proton in MEE). This large downfield shift of the C-4 proton supported the assignment of the alcohol to the C-6 position and required that the alcohol be close to the plane of the aromatic ring and therefore equatorial (6α). These suppositions proved correct when the authentic compound was made available through synthesis and its spectrum compared to that of the thermal degradation product.

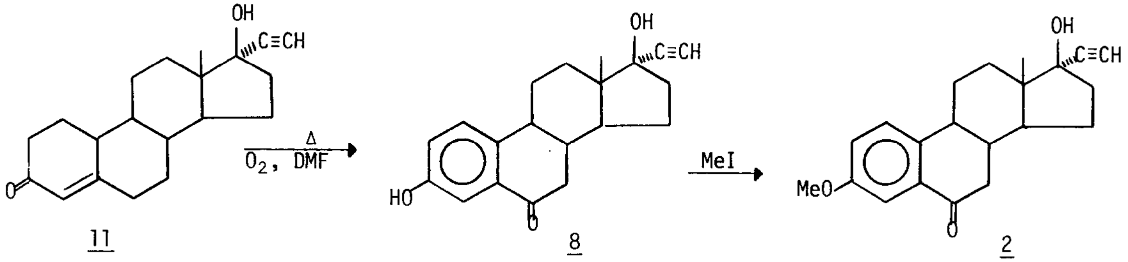
The second isomeric alcohol had the same fragmentation pattern in the mass spectrum as 3. The differences between the two isomers appeared to be only the intensity of several fragments, most particularly in the ratio of the $M^+$ ion (326) to the M-$H_2O$ ion (308). This evidence supported the assignment of the epimeric 6β configuration to this alcohol (4).

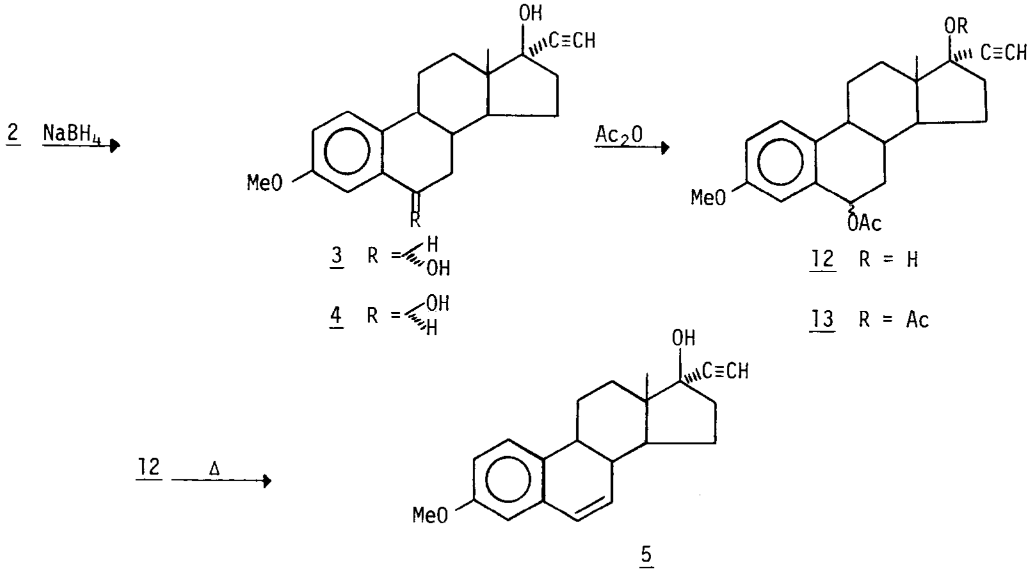
The minor degradation products included $\Delta^6$ MEE (5) and 6-keto MEE (2). The $\Delta^6$ MEE had a mass spectral fragmentation pattern very similar to that of the epimeric alcohols 3 and 4. Since the mass spectra of 3 and 4 may be rationalized as arising from a dehydro compound after initial loss of water, this result was not surprising. The 6-keto compound (2) was identified by its fragmentation pattern as well as its $R_f$ value compared to an authentic sample.

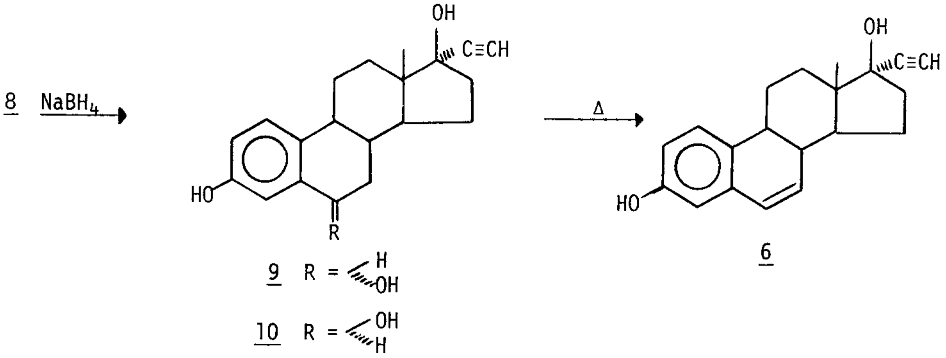
The thermal (178°) degradation products of EE were identified in a similar manner. The derived fractions were examined by gc-ms and compounds 6 and 8-10 identified by their retention time as well as their fragmentation patterns when compared to synthesized samples[4]. The mass spectra in the EE series were very similar to the analogous MEE compounds, in some cases differing only by 14 mass units.

The identity of the degradation products was confirmed by comparison to authentic samples prepared by synthesis in the following manner. Norethindrone (11) was oxidized to 6-keto EE (8)[5] in 40% yield by treatment with oxygen in DMF containing potassium acetate at 120°. Reaction of 8 with methyl iodide and potassium carbonate in acetone afforded the corresponding MEE derivative (2)[6]. Reduction of 2 with sodium borohydride in methanol-methylene chloride (1:1) afforded a mixture of the known 6α-hydroxy isomer (3, 90-95% yield)[6] and the 6β-hydroxy compound (4, mp 199-200°, 5-10% yield) which was separated by chromatography on neutral silicic gel. Acetylation of the crude reduction mixture at 120-135° with acetic anhydride afforded a mixture of the monoacetate (12) and the diacetate (13) which were separable by chromatography. When 12 was heated at 230°, the C-6 secondary acetate was eliminated to afford $\Delta^6$ MEE (5, oil) after chromatography.

Reduction of 8 with sodium borohydride in methanol afforded a mixture of the known 6α-hydroxy isomer (9, mp 138-139°, lit. 158-161°)[6] and the 6β-hydroxy compound (10, mp 120°-acetone solvate) which was separated by chromatography. Heating a mixture of 9 and 10 at 230° effected elimina-


OH
C≡CH
O
11
Δ
$O_2$, DMF
OH
C≡CH
HO
O
8
MeI
OH
C≡CH
MeO
O
2


2 $NaBH_4$
OH
C≡CH
MeO
R
3 R = H, OH
4 R = OH, H
$Ac_2O$
OR
C≡CH
MeO
OAc
12 R = H
13 R = Ac
12 Δ
OH
C≡CH
MeO
5


8 $NaBH_4$
OH
C≡CH
HO
R
9 R = H, OH
10 R = OH, H
Δ
OH
C≡CH
HO
6

tion of the secondary alcohol to afford $\Delta^6$ EE (6, mp 182-184°) after purification by chromatography[7].

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## References and Footnotes

1. EE has been known for 40 years, H. H. Inhoffen, W. Logemann, W. Hohlweg, and A. Serini, Chem. Ber., 71, 1024 (1938) and MEE for 24 years, F. B. Colton, U.S. Patent 2,666,769 January 19, 1954).
2. Charles E. Frank, Chem. Rev., 46, 162 (1950).
3. Satisfactory analyses were obtained for all new crystalline compounds. NMR spectra were determined on a Varian T-60-A and gc-ms spectra on an OV-1 column with a Finnigan 1015C equipped with a 6100 data system. Spectral data were consistent with the assigned structures. Melting points were taken on a Fisher-Johns apparatus and are uncorrected.
4. Additional compounds are formed from MEE and EE under the thermal degradation conditions and studies are underway to elucidate their structure.
5. H. Hofmeister, H. Laurent and R. Wiechert, Chem. Ber., 106, 723 (1973).
6. P. N. Rao, Steroids, 173 (1974). A sample of 6α-hydroxy MEE (3) was provided to us by Dr. Rao and was shown to contain the 6β-ol (4) as an impurity by gc-ms. This explains the reported mp (121-123°) since our pure sample melted higher (144-146°). A similar impurity (6β-ol) was found in Rao's sample of 6α-hydroxy EE (9) by gc-ms.
7. In contrast to $\Delta^6$ MEE (5), $\Delta^6$ EE (6) proved to be an unstable compound. In a period of two weeks at room temperature, several impurities were detected in the sample by gc-ms and tlc.