

The Crystal and Molecular Structure of 12-Keto-17-deoxy-8-azaestrone Methyl Ether Hydrobromide

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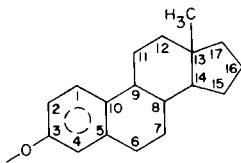
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The crystal and molecular structure of 12-keto-17-deoxy-8-azaestrone methyl ether hydrobromide ($C_{18}H_{24}BrNO_2$) has been determined by a single crystal, x-ray diffraction study. The compound crystallizes in the monoclinic space group $P2_1/n$ with unit cell constants $a = 12.024$ (2), $b = 10.340$ (1), $c = 14.269$ Å (2), $\beta = 104.12^\circ$ (1). The structure was solved by the heavy atom method and refined by block-diagonal least-squares to a final R-value = 0.03₆ for the 835 independently measured, statistically significant reflections. All hydrogen atoms, including methyl hydrogens, were located.

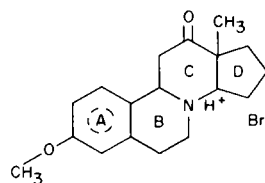
Introduction.

Estrogens are the essential hormones for the development of primary and secondary female sex characteristics. The structures of the primary estrogens found in humans have in common a ring skeleton as shown below with the customary numbering of positions indicated. In addition,



the "natural" conformation has α -hydrogens at the 9- and 14- positions and a β -hydrogen at the 8-position. The angular methyl at the 13-position defines the β -orientation.

To avoid unwanted pharmacological side-effects and in hopes of enhancing desirable medicinal properties (1), aza-analogues of the steroids have been synthesized (2,3). In the 8-azasteroid series, structural and conformational assignments were based on indirect evidence including: (A) ir studies (the presence of Bohlmann bands (4)); (B) synthetic evidence; (C) nmr chemical shifts; (D) nmr solvent shifts. The validity, in general, of these studies was confirmed by the previous structure determination of 8-azaestrone hydrobromide (5). However, the synthetic methods used in the various laboratories proceeded by different pathways (2,3) to the final azasteroid and so it became necessary to determine the structure of more than one member of the series in order that the entire series could be characterized. Consequently, the structure determination of the title compound (shown below) was undertaken.



Experimental and Structure Determination.

A sample of this compound was kindly furnished to us by Professor A. I. Meyers. Cylindrical single crystals of the compound were obtained by a solvent exchange technique (6) using diethyl ether and acetonitrile. One of these smaller cylindrical crystals (0.11 mm x 0.16 mm) was chosen and mounted with the long axis coincident with ϕ . The symmetry and cell data were determined on a G.E. XRD-5 diffractometer using Copper $K\alpha$ radiation. Extinctions with $h+l$ odd for $(h0l)$ and k odd for $(0k0)$ led uniquely to the space group $P2_1/n$ for a monoclinic angle reasonably near 90° . Lattice constants were then determined by a least-squares fit of forty-eight carefully measured two-theta values (1° take-off angle and 0.05° slit) at $2\theta > 60^\circ$ where the $Cu-K\alpha_1$ and $Cu-K\alpha_2$ doublet is resolvable. The resultant lattice constants and their estimated standard deviations are:

$$\begin{aligned} a &= 12.024 \pm 0.002 \text{ \AA} \\ b &= 10.340 \pm 0.001 \text{ \AA} \\ c &= 14.269 \pm 0.002 \text{ \AA} \\ \beta &= 104.12 \pm 0.01^\circ \end{aligned}$$

Intensity data were collected on a General Electric XRD-490 fully automated diffractometer by the stationary

TABLE I

Final Coordinates and Anisotropic Temperature Factors (a)

	X	Y	Z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Br	0.0919 (1)	0.0359 (1)	0.1963 (1)	77 (1)	87 (1)	53 (1)	1 (2)	14 (1)	- 5 (1)
C1	0.6582 (9)	0.1815 (11)	0.5523 (7)	86 (12)	107 (15)	30 (7)	14 (11)	20 (7)	- 6 (9)
C2	0.7607 (9)	0.1342 (12)	0.5422 (7)	69 (11)	145 (17)	29 (6)	23 (11)	3 (7)	13 (9)
C3	0.7762 (8)	0.1073 (11)	0.4502 (7)	41 (9)	101 (14)	49 (7)	-25 (9)	7 (7)	4 (8)
C4	0.6851 (9)	0.1275 (11)	0.3723 (8)	60 (10)	87 (14)	50 (7)	3 (10)	8 (7)	-11 (9)
C5	0.5782 (9)	0.1747 (9)	0.3837 (7)	78 (11)	37 (11)	40 (6)	6 (9)	0 (7)	- 3 (7)
C6	0.4817 (9)	0.1886 (11)	0.2972 (7)	49 (10)	102 (14)	47 (7)	- 6 (10)	31 (7)	-12 (8)
C7	0.3704 (9)	0.1758 (11)	0.3249 (7)	77 (11)	82 (14)	36 (7)	- 8 (10)	- 2 (7)	-14 (8)
N8	0.3620 (7)	0.2729 (8)	0.4019 (6)	57 (8)	61 (10)	42 (6)	-13 (7)	11 (5)	- 7 (6)
C9	0.4565 (8)	0.2573 (10)	0.4944 (7)	65 (11)	85 (14)	25 (6)	20 (10)	11 (7)	- 8 (7)
C10	0.5654 (8)	0.2002 (10)	0.4751 (7)	49 (9)	61 (12)	29 (6)	- 3 (9)	8 (6)	4 (7)
C11	0.4108 (9)	0.1824 (11)	0.5702 (8)	63 (11)	102 (15)	43 (7)	30 (11)	7 (7)	20 (9)
C12	0.3103 (9)	0.2468 (11)	0.5993 (8)	63 (11)	92 (14)	58 (8)	-30 (10)	16 (8)	-14 (9)
C13	0.2386 (9)	0.3278 (11)	0.5190 (8)	44 (10)	104 (16)	55 (8)	10 (10)	10 (7)	-13 (9)
C14	0.2430 (9)	0.2711 (10)	0.4212 (8)	51 (10)	86 (14)	53 (8)	6 (10)	5 (7)	-28 (9)
C15	0.1490 (9)	0.3376 (12)	0.3484 (8)	56 (11)	130 (18)	56 (8)	22 (11)	5 (8)	1 (10)
C16	0.0593 (10)	0.3640 (13)	0.4072 (9)	57 (11)	153 (19)	92 (11)	44 (12)	22 (9)	22 (12)
C17	0.1074 (11)	0.3200 (13)	0.5058 (9)	127 (15)	146 (20)	66 (9)	10 (14)	45 (10)	10 (11)
M13	0.2787 (10)	0.4701 (14)	0.5352 (8)	99 (12)	118 (15)	65 (8)	41 (14)	22 (8)	- 9 (12)
O3	0.8800 (6)	0.0612 (9)	0.4470 (5)	61 (7)	202 (15)	70 (6)	41 (9)	25 (5)	14 (8)
M3	0.9010 (10)	0.0296 (15)	0.3571 (9)	81 (12)	188 (20)	89 (20)	47 (15)	52 (9)	6 (14)
O12	0.2919 (7)	0.2290 (9)	0.6761 (6)	122 (10)	205 (15)	57 (6)	- 3 (9)	44 (6)	4 (8)

(a) Anisotropic Temperature Factors of the Form

$$\text{EXP} - [\beta(11)h^2 + \beta(22)k^2 + \beta(33)l^2 + 2\beta(12)hk + 2\beta(13)h\ell + 2\beta(23)k\ell]$$

crystal-stationary counter method using balanced zirconium and yttrium filters and molybdenum $K\alpha$ radiation. A total of 3184 independent reflections were measured to a two-theta maximum of 50° ($d = 0.840 \text{ \AA}$). Of these, 835 reflections were considered observed by the criterion

$$(I_{Zr} - 2\sigma(I_{Zr})) - (I_Y + 2\sigma(I_Y)) > 50$$

10 second counting time. The low percentage (26%) of observed reflections may be attributed to a relatively small crystal, a high background count, and to the relatively high 50 count difference. A phi scan at $\chi = 90^\circ$ showed no more than a 3% difference; therefore no absorption correction was made (linear absorption coefficient with Mo radiation is 28.8 cm^{-1}). Lorentz-polarization corrections were applied, and the corrected intensities were then reduced to structure amplitudes in the usual manner.

The coordinates of the bromine, located from a three-dimensional Patterson map, were refined by block-diagonal least-squares to a value of $R = 0.36$. An electron density map, phased by the bromine position, revealed the five-membered ring clearly while various other ring fragments were less clearly resolved. A second electron

density map phased from just these six atoms (bromine and five-membered ring) showed all the remaining non-hydrogen peaks. These twenty-two atoms were refined isotropically, using unit weights and ultimately converged at a value of $R = 0.06_6$. After conversion to anisotropic temperature factors for all atoms, further least-squares refinement lowered the value of the reliability index to $R = 0.05_6$.

At this stage, a difference Fourier map was calculated which showed reasonably well-formed peaks, with heights ranging from $0.5 - 0.8 \text{ e/\AA}^3$, in the regions where non-methyl hydrogen atoms were anticipated. There were three distinct peaks of height 0.4 e/\AA^3 around the methoxy carbon M3. In the region of the methyl carbon, M13, there was one distinct peak (0.5 e/\AA^3) and a diffuse region of general height 0.2 e/\AA^3 . Calculated hydrogen coordinates assuming a C-H distance of 1.03 \AA and chemically reasonable angles led to positions which coincided in all cases to the peak positions found in the map. The remaining two hydrogens about methyl carbon M13 fell well within the diffuse positive region found about that atom

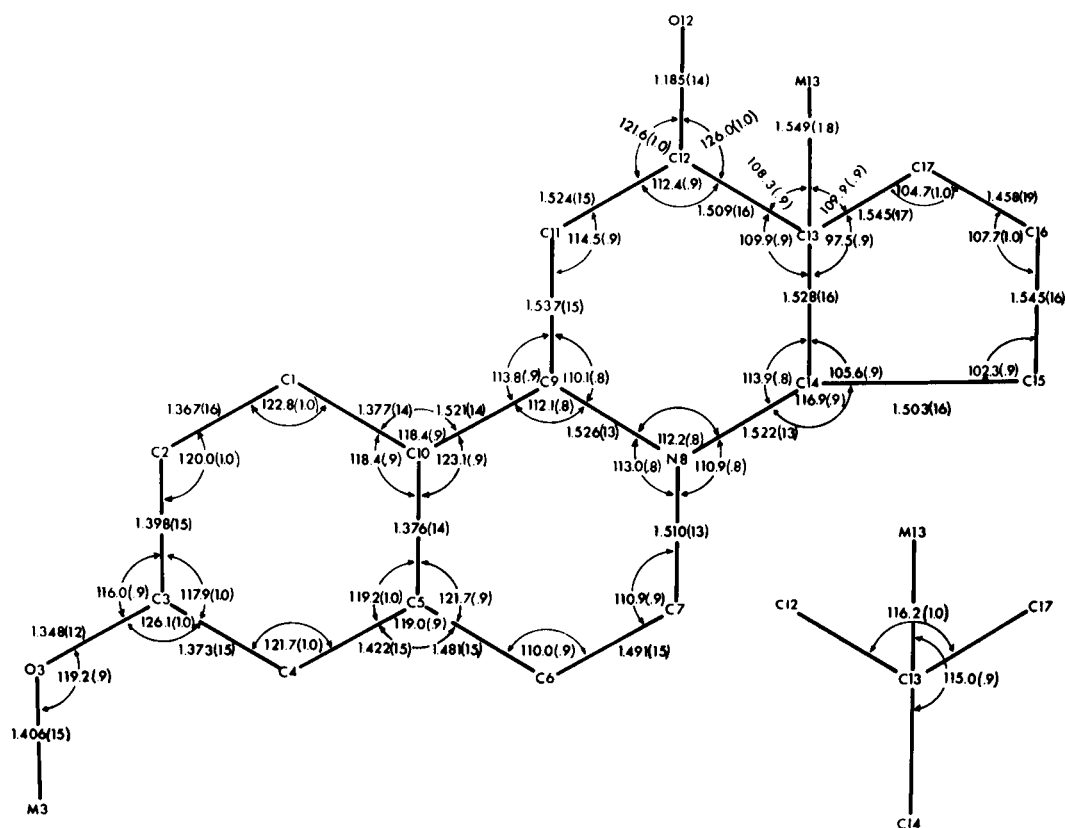


Figure I. Schematic View of Molecule, Bond Distances and Bond Angles indicated with Estimated Standard Deviations.

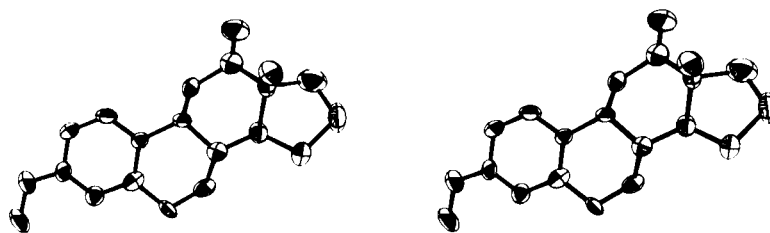


Figure II. ORTEP Stereo Projection of Molecule.

in the map. All peaks (or regions) of height greater than $0.1 \text{ e}/\text{\AA}^3$ in the map—with the exception of one peak ($0.5 \text{ e}/\text{\AA}^3$) which was only 1 \AA from the bromine—were thus taken into account.

Five cycles of block-diagonal least-squares refinement

were then carried out. All of the non-hydrogen atoms were refined anisotropically, while only the coordinates of the hydrogen atoms were allowed to vary. The non-methyl hydrogen atoms were assigned fixed isotropic temperature factors of 3.5 \AA^2 ; whereas the methyl

TABLE II

Final Hydrogen Coordinates
and Fixed Isotropic Temperature Factors

	X	Y	Z
Isotropic Temperature Factors fixed at 3.5			
H11	0.651 (7)	0.215 (8)	0.607 (6)
H12	0.816 (7)	0.127 (8)	0.589 (6)
H14	0.689 (7)	0.098 (8)	0.315 (6)
H16'	0.481 (7)	0.119 (8)	0.256 (6)
H16''	0.494 (7)	0.278 (8)	0.279 (6)
H17'	0.352 (7)	0.101 (8)	0.356 (6)
H17''	0.305 (7)	0.198 (8)	0.274 (6)
H18	0.377 (7)	0.352 (8)	0.382 (6)
H19	0.472 (7)	0.347 (9)	0.520 (6)
H111'	0.463 (7)	0.176 (8)	0.628 (6)
H111''	0.407 (7)	0.084 (8)	0.564 (6)
H114	0.224 (7)	0.191 (8)	0.421 (6)
H115'	0.125 (7)	0.293 (8)	0.278 (6)
H115''	0.168 (7)	0.417 (8)	0.330 (6)
H116'	-0.005 (7)	0.331 (9)	0.376 (6)
H116''	0.032 (7)	0.459 (9)	0.387 (6)
H117'	0.089 (7)	0.376 (8)	0.557 (6)
H117''	0.099 (7)	0.251 (8)	0.528 (6)
Isotropic Temperatures Factors fixed at 5.0			
H13'	0.229 (7)	0.527 (10)	0.495 (6)
H13''	0.264 (8)	0.500 (9)	0.586 (6)
H13'''	0.354 (7)	0.466 (10)	0.557 (6)
H3'	0.977 (8)	-0.007 (9)	0.366 (6)
H3''	0.849 (7)	-0.044 (10)	0.317 (6)
H3'''	0.888 (8)	0.094 (9)	0.319 (7)

hydrogen atoms had fixed isotropic temperature factors of 5.0 \AA^2 . The refinement converged to a final value of $R = 0.03_6$ with all shifts being less than one-tenth the estimated standard deviations in the last cycle.

The entire refinement procedure was repeated using $\frac{1}{\sigma_2}$ weights. The coordinates refined to the same values within one standard deviation. However, the refinement converged only to a value of $R = 0.05_6$ and the estimated standard deviations were $1\frac{1}{2}$ times as large. Hence, the results reported herein are for the refinement using unit weights.

Results.

Table I lists the final coordinates and anisotropic temperature factors for the non-hydrogen atoms. Table II lists the final coordinates of the hydrogen atoms and the fixed isotropic temperature factors. The bond distances have an estimated standard deviation of 0.01_5 \AA and the bond angles have an E.S.D. slightly less than 1.0° . These values are summarized in Figure 1 which is a schematic drawing of the molecule. Finally, Figure II is an ORTEP (7) stereo drawing of the molecule.

The phenyl ring with its methoxy group affords a check on the internal consistency of the results. Within the phenyl ring, the C-C distances average to $1.38_6 \pm 0.01_8 \text{ \AA}$ and the internal angles to $120.0 \pm 1.5^\circ$, all in good agreement with the accepted literature values (8). Furthermore, least-squares calculation of the best plane containing the six phenyl atoms leads to a plane with an E.S.D. value of 0.007 \AA . The methoxy substituent at the 3-position bears out a similar level of consistency. Thus, the phenyl-oxygen distance of 1.34_8 \AA ; the oxygen-methyl distance of 1.40_6 \AA ; and the methoxy angle of 119.2° agree quite closely with their respective values (1.35_1 \AA , 1.43_1 \AA , 118.7°) in *p*-azoxyanisole (9).

TABLE III

Least-Squares Planes and Dihedral Angles

Atoms Involved	Equation of Plane	E.S.D. of Plane
C1, C2, C3, C4, C5, C10	$.3371p + .9382q - .0779r = 3.173$	0.007 \AA
C2, C3, C4, O3	$.3446p + .9358q - .0743r = 3.245$	0.004 \AA
C11, C12, C13, O12	$.4988p + .7928q + .3505r = 5.738$	0.007 \AA
C14, C15, C16, C17	$.3762p + .8913q + .2530r = 4.532$	0.014 \AA

Dihedral Angles

Planes Involved	Dihedral Angle
(C5, C9, C10) and (C6, C7, N8)	123.9°
(C14, C15, C16, C7) and C13, C14, C17)	135.8°

For the three remaining rings, one can compare the molecular parameters within the rings to those found for the other "estrogenic" compounds whose structures have already been determined, namely: 8-azaestrone hydrobromide (5), 4-bromoestrone (10), 4-bromoestradiol (11), and estriol (12). The internal angles agree within one E.S.D. in all cases except at \angle (C9, C8, C11). Here, the angle in the present study (112.2°) differs by at least four E.S.D. from that found in the other studies cited above (108 , 106 , 105 , 107.7° , respectively). Within this same C-ring, the distances C11-C12 and C12-C13 in this study differ by at least two E.S.D. values from those found in the other four studies. These results are anticipated, since this is the only one of the five compounds to have a keto oxygen in this ring (at the C-12 position). The bond distance (1.18_5 Å) and angles (121.6 , 126.0°) for this keto oxygen agree with those found in the 8-azaestrone (5) and the bromoestrone (10) studies. Analogously, since this compound does not have an oxygen at the 17-position in the D-ring as do the other four, it is not unexpected that two of the four distances in the D-ring (namely C14-C15 and C16-C17) differ by four E.S.D. values from those given in the other study. Overall, the distances and angles obtained here, compared to all of those in the other studies, indicate that the molecular parameters in the estrogen ring system remain relatively constant regardless of:

- (a) the insertion of a nitrogen at the 8-position
- (b) whether any of the rings has a hydroxy, keto or methoxy substituent.

The largest perturbation would appear to be the location of the keto-group with its maximum effect being that of changing the adjacent bond lengths by an average of 0.04 Å.

Although a certain rigidity of ring structure, and consequently of distances and angles is maintained, there are a number of ways in which these rings can be fused to each other leading to a variety of possible conformations. The structure of estrone (10) with hydrogens at the C-9 and C-14 positions in the α -configuration and the hydrogen at the C-8 position in the β -configuration is the "natural" conformation. The previously reported structure of 8-azaestrone hydrobromide also was found to have the natural conformation. The conformations and means of identifying the conformations for the possible 8-azasteroid isomers are discussed elsewhere (13). Significantly, this compound does not have the natural conformation. The hydrogen at the C-9 position has an "unnatural" β -configuration whereas the hydrogens attached to C-8 and to C-14 have their natural configuration, namely β and α , respectively. This results in an unusual *cis*-junction between the B and C rings. A second unusual feature of this ring system is that both the B and C rings lie in a boat

rather than a chair conformation. The B-ring, for example, has a dihedral angle across the C5-N bond of 133.9° . With the keto group removed from the D-ring, the four atoms (C14, C15, C16, C17) not involved with a bridging atom are essentially planar (E.S.D. = 0.014 Å) and form a dihedral angle of 95.7° with the plane defined by atoms C13, C14, C17. The planes data are summarized in Table III.

No abnormal crystal effects are anticipated since the crystal shows no close-contacts between molecules. Except for the single instance discussed subsequently, no bromine-ring distances less than 4.0 Å are found. Similarly, all light atom distances between molecules are greater than 3.6 Å. The one rather unusual feature is the $N^+ \dots Br^-$ distance of 3.18 Å. The hydrogen atom involved in the hydrobromide (H8), lies on the line connecting the N^+ and Br^- (\angle (N-H...Br) = 180°) at a distance of 0.90 Å from the N^+ and 2.28 Å from the Br^- . Thus there is strong evidence of hydrogen bonding through the bromide ion linking the molecules.

Acknowledgments.

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