The Crystal and Molecular Structure of (±)-3-Methoxy-B-nor-9β-estra-1,3,5(10)-trien-17-one

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The compound (±)-3-methoxy-B-nor-9β-estra-1,3,5(10)-trien-17-one, a synthetic, modified estrogen, crystallizes in space group $P2_1/c$ with $a=8\cdot792$ (3), $b=5\cdot760$ (3), $c=28\cdot84$ (4) Å, $\beta=94\cdot31$ (7)°, and $Z=4$. Data were obtained about two different axes on a two-circle diffractometer. The structure was solved by direct methods and refined by block-diagonal least-squares calculations to an R value of 0·060 for 1783 observed reflections. As a result of the unnatural *cis* B–C ring junction the molecular skeleton is bent, with the C–D part approximately 60° out of the plane of the A and B rings.

Introduction

Experiments with halogenated or otherwise chemically modified estrogens have led to the conclusion that the feminizing and the anti-arteriosclerotic effects of these compounds are not necessarily tied to one another, and that anti-arteriosclerotic drugs without feminizing side-effects might be found among chemically modified estrogens (Applezweig, 1962).

As part of a program of introducing chemical modifications into the steroid skeletons of estrogens Burckhalter & Sciavolino (1967) synthesized the compound 9β-B-norestrone methyl ether, or 3-methoxy-B-nor-9β-estra-1,3,5(10)-trien-17-one (I), hereinafter referred to as BNE. The modifications were twofold: a five-instead of six-membered B-ring, and a *cis* instead of a *trans* junction between the B and C rings.

(I)
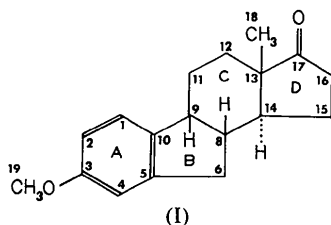
The X-ray crystallographic structure determination was undertaken in order to verify the stereochemical structure assignment (I), especially the B/C ring junction, and to determine the geometry of the modified steroid skeleton.

Experimental

A sample of BNE was kindly supplied by Dr J. H. Burckhalter of the University of Michigan. Single crystals suitable for X-ray work were obtained from methanol solution by slow evaporation at room temperature.

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The cell parameters a, c and β were calculated by a least-squares procedure (Burnham, 1964) from diffractometer measurements of the 2θ values of 12 equatorial layer $h0l$ reflections obtained with Cu $K\alpha$ ($\lambda=1\cdot5418$ Å) radiation. The value of b was obtained from Weissenberg and precession photographs.

Crystal data

$C_{18}H_{22}O_2$, M.W. 270·4. Monoclinic, space group $P2_1/c$; $a=8\cdot792$ (3), $b=5\cdot760$ (3), $c=28\cdot84$ (4) Å, $\beta=94\cdot31$ (7)°, $V=1456\cdot4$ Å^3, $Z=4$; $D_x=1\cdot233$ g cm^{-3}, $F(000)=584$, μ for Cu $K\alpha$ ($\lambda=1\cdot5418$ Å)$=7\cdot4$ cm^{-1}.

Intensity data were collected with a Supper–Datex automatic diffractometer of Weissenberg geometry using Cu $K\alpha$ radiation, balanced-filter monochromatization, and pulse-height analysis. Two crystals of nearly equal size were used. Both were between 0·4 and 0·5 mm in all three dimensions. The first crystal was mounted on the b axis and yielded data for the nets hKl ($K=0$–6); the second was mounted on a and was used to collect data for $0kl$, $1kl$, and $6kl$.

The diffractometer was operated in the moving-crystal stationary-counter mode with two distinct procedures for accumulating the counts.

Initially hKl ($K=0$–5) data were collected by the conventional background-scan-background procedure. Each background count was made for 50 s. Scans were made over a 2·0° range at a crystal speed of 1° min^{-1}. These scans were carried out with each of the two filters α(Co) and β(Ni). If the accumulated counts for the two scans are $S(\alpha)$ and $S(\beta)$, and the four 50 s background counts $B1(\alpha)$, $B2(\alpha)$, $B1(\beta)$, and $B2(\beta)$, the peak intensity can be taken as

$$I=S(\beta)-S(\alpha)-(1\cdot2)\,[B1(\beta)+B2(\beta)-B1(\alpha)$$
$$-B2(\alpha)]\,.$$

In order to overcome certain drawbacks in the above procedure a variable step scan technique was subsequently devised. In this technique each reflection is assigned an individual scan range depending on the expected width of the peak. Furthermore, each scan range is broken up into ten equal parts, whose ac-

cumulated counts are individually recorded on the punched output tape. With crystal angle scans ranging from 2·5 to 6° several of the ten partial scans will represent readings of the background on each side of the peak. The recognition of the presence of a statistically significant peak, the assignment of 'peak' and 'background' steps, and the evaluation of the integral under the peak are done by means of an appropriate data reduction program (Hanson, 1969).

Data for the nets hKl ($K=2$–6), $0kl$, and $6kl$ were collected with this variable step scan technique, repeating some of the nets previously recorded. A comparison of the two counting procedures showed, as expected, that the variable step scan method gave better results at very low 2θ values. The variable step scan technique was also found to give more reliable results for very weak reflections. Consequently, in combining the data gathered by the two methods, the intensities of strong or moderately strong, medium-angle reflections were averaged, after being placed on a common scale, while for weak or low-angle reflections only the variable step scan intensities were used.

The raw intensities from the different nets were placed on a common scale by means of a least-squares procedure which minimizes the departure from zero of the logarithms of all ratios of values for equivalent reflections from different nets. A description of the scaling procedure has been given by Schilling (1968). The scale factors within each series of zero and upper level nets measured with the same crystal and scan technique were essentially constant, i.e., no trend was observed in going from low to high levels. Of the 2306 unique reflections scanned, 1801 (78%) were judged to be of measurable intensity. Lorentz–polarization and counting-loss corrections were applied, but absorption corrections were not.

The structure was solved by direct methods (Karle &

Karle, 1966) using the *PHASE* program in the X-RAY 67 system of programs (Stewart, 1967, 1970). Atom coordinates obtained from the E map were verified and refined by means of a difference Fourier synthesis. The coordinates from this synthesis were used as the starting model for the least-squares refinement.

Following block-diagonal refinement of C and O parameters to $R=\sum||F_o|-|F_c||/\sum|F_o|=0\cdot13$ all hydrogen atoms were found in a difference synthesis. The refinement was continued with 9×9 blocks for the C and O parameters and 4×4 blocks for the H parameters. Since evidence of secondary extinction was found, 18 strong, low-angle reflections were excluded from the final refinement. The excluded reflections were those for which the expected effect of secondary extinction was the greatest (Zachariasen, 1967). For the remaining 1783 observed reflections the final R value was 0·060.

The refinement minimized the quantity $\sum w(|F_o|-k|F_c|)^2$, where w is the weight of an observed structure factor, taken as $(8/F_o)^2$ if $F_o>8$, and as unity otherwise. The atomic scattering factors of Berghuis, Haanappel, Potters, Loopstra, MacGillavry & Veenendaal (1955) were used for carbon and oxygen, those of Stewart, Davidson & Simpson (1965) for hydrogen. The least-squares calculations were done with the *CLS* program of Schilling (1970). Fourier calculations were carried out with the X-RAY system (Stewart, 1967).

Tables 1 and 2 give the final atomic parameters and their standard deviations, the latter obtained from the diagonal elements of the inverse least-squares matrix.*

Table 1. *Fractional atomic coordinates and anisotropic thermal parameters* ($\times10^3$) *of the nonhydrogen atoms*

The estimated standard deviation, given in parentheses, refers to the last significant place. The thermal parameters U_{ij} (Å²) are those of the temperature factor $\exp[-2\pi^2(U_{11}a^{*2}h^2+\ldots2U_{12}a^*b^*hk+\ldots)]$.

	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	−0·0628 (4)	0·2756 (7)	0·5434 (1)	45 (2)	60 (2)	34 (2)	16 (2)	7 (1)	8 (2)
C(2)	−0·1754 (4)	0·1050 (7)	0·5360 (1)	54 (2)	56 (2)	34 (2)	17 (2)	2 (1)	−2 (2)
C(3)	−0·2822 (4)	0·0716 (6)	0·5688 (1)	38 (2)	52 (2)	40 (2)	8 (2)	−4 (1)	1 (2)
C(4)	−0·2778 (4)	0·2106 (7)	0·6085 (1)	34 (2)	64 (2)	38 (2)	9 (2)	3 (1)	−3 (2)
C(5)	−0·1674 (4)	0·3798 (6)	0·6149 (1)	32 (2)	58 (2)	36 (2)	13 (2)	−3 (1)	−2 (2)
C(6)	−0·1475 (4)	0·5576 (7)	0·6532 (1)	38 (2)	69 (2)	45 (2)	10 (2)	1 (1)	−13 (2)
C(8)	0·0178 (4)	0·6471 (6)	0·6488 (1)	41 (2)	47 (2)	43 (2)	11 (2)	−1 (1)	−1 (2)
C(9)	0·0419 (4)	0·6189 (6)	0·5959 (1)	43 (2)	54 (2)	40 (2)	7 (2)	−2 (1)	8 (2)
C(10)	−0·0591 (4)	0·4133 (6)	0·5822 (1)	37 (2)	55 (2)	33 (2)	14 (2)	−2 (1)	8 (2)
C(11)	0·2088 (4)	0·6074 (7)	0·5824 (1)	45 (2)	68 (2)	39 (2)	1 (2)	2 (1)	18 (2)
C(12)	0·3153 (4)	0·4634 (7)	0·6154 (1)	44 (2)	60 (2)	36 (2)	3 (2)	8 (1)	6 (2)
C(13)	0·2989 (4)	0·5405 (6)	0·6652 (1)	35 (2)	41 (2)	36 (2)	−3 (1)	0 (1)	4 (2)
C(14)	0·1335 (3)	0·5009 (6)	0·6774 (1)	32 (2)	42 (2)	34 (2)	0 (1)	−1 (1)	−2 (2)
C(15)	0·1440 (4)	0·5168 (7)	0·7307 (1)	47 (2)	63 (2)	34 (2)	−3 (2)	6 (1)	−7 (2)
C(16)	0·2915 (4)	0·3886 (7)	0·7449 (1)	50 (2)	58 (2)	35 (2)	0 (2)	2 (1)	7 (2)
C(17)	0·3873 (4)	0·4067 (6)	0·7032 (1)	40 (2)	45 (2)	36 (2)	2 (1)	−1 (1)	6 (2)
C(18)	0·3528 (4)	0·7960 (7)	0·6729 (1)	75 (2)	62 (2)	56 (2)	7 (2)	−4 (1)	−10 (2)
C(19)	−0·3978 (5)	−0·2535 (8)	0·5281 (1)	54 (3)	52 (3)	61 (2)	−12 (2)	−4 (1)	8 (2)
O(3)	−0·3968 (3)	−0·0904 (5)	0·5650 (1)	59 (2)	70 (2)	53 (2)	−6 (1)	4 (1)	−13 (2)
O(17)	0·5153 (3)	0·3304 (5)	0·7014 (1)	47 (2)	79 (2)	52 (1)	17 (1)	−0 (1)	10 (2)

Discussion of the structure

The results of the determination as illustrated in Fig. 1 confirm the predicted structure (I). The main differences from the natural estrogens are the sharp bend at the cis B/C ring junction, and the five-membered B ring.
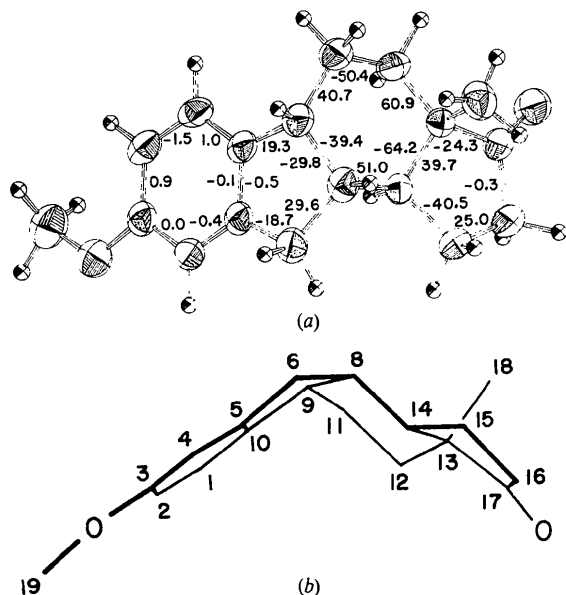

Fig. 1. (a) Thermal ellipsoid plot of the BNE molecule with ring torsion angles (°). 50% probability ellipsoids are used for C and O atoms; hydrogens are represented as spheres of 0·1 Å radius. (b) Schematic view of the molecule at approximately right angles to that of (a). The hydrogen atoms have been omitted for clarity.
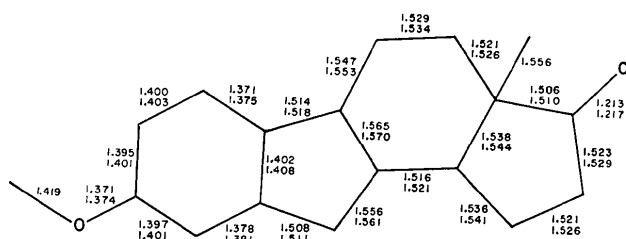

Fig. 2. Bond distances (Å) in the BNE molecule. Where two values are given, the lower one is corrected for rigid-body thermal motion. Estimated standard deviations are 0·005 Å.
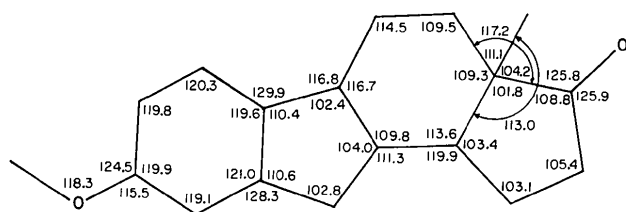

Fig. 3. Bond angles (°) in the BNE molecule. Estimated standard deviations are 0·3°.

Table 2. *Fractional coordinates and isotropic thermal parameters of the hydrogen atoms*

The numbering follows that of the carbon atoms to which the hydrogens are attached.

	x	y	z	B (Å²)
H(1)	0·007 (4)	0·293 (7)	0·520 (1)	4·6 (9)
H(2)	−0·180 (4)	0·013 (7)	0·508 (1)	3·8 (7)
H(4)	−0·348 (4)	0·170 (7)	0·633 (1)	4·8 (9)
H(6)	−0·231 (6)	0·690 (9)	0·645 (2)	7·5 (13)
H'(6)	−0·157 (5)	0·486 (8)	0·685 (2)	6·1 (10)
H(8)	0·035 (4)	0·823 (6)	0·661 (1)	4·1 (8)
H(9)	−0·001 (4)	0·765 (7)	0·581 (1)	4·7 (9)
H(11)	0·216 (4)	0·543 (7)	0·550 (1)	4·8 (9)
H'(11)	0·252 (4)	0·771 (7)	0·581 (1)	4·7 (9)
H(12)	0·295 (4)	0·307 (6)	0·614 (1)	3·0 (7)
H'(12)	0·428 (4)	0·479 (7)	0·606 (1)	4·4 (9)
H(14)	0·104 (5)	0·332 (7)	0·667 (2)	5·1 (10)
H(15)	0·052 (4)	0·436 (6)	0·742 (1)	3·7 (8)
H'(15)	0·144 (4)	0·676 (6)	0·742 (1)	3·3 (7)
H(16)	0·287 (5)	0·226 (9)	0·750 (2)	6·4 (11)
H'(16)	0·351 (4)	0·457 (7)	0·775 (1)	4·4 (8)
H(18)	0·359 (5)	0·847 (7)	0·709 (2)	6·0 (11)
H'(18)	0·446 (5)	0·810 (8)	0·660 (2)	5·8 (10)
H"(18)	0·281 (5)	0·903 (7)	0·656 (1)	5·0 (9)
H(19)	−0·299 (5)	−0·355 (7)	0·531 (2)	5·3 (9)
H'(19)	−0·410 (4)	−0·167 (7)	0·497 (1)	4·8 (9)
H"(19)	−0·491 (7)	−0·384 (12)	0·538 (2)	11·3 (19)

The A ring and all atoms attached to it are nearly planar, as expected. The methoxy carbon, C(19), is within 0·14 Å of this plane. The B ring is an α envelope with C(8) 0·50 Å below the plane of C(5), C(6), C(9) and C(10). [The designation α implies displacement from the molecule away from angular methyl C(18); β implies displacement in the same direction as angular methyl C(18)]. The C ring is an unsymmetrical chair with C(8), C(11), C(12) and C(14) very nearly coplanar. C(9) is 0·49 Å below, and C(13) 0·73 Å above the plane. The D ring is an envelope with C(14) 0·63 Å below the plane of C(13), C(15), C(16) and C(17).

The non-hydrogen valence distances are given in Fig. 2 and the corresponding angles in Fig. 3. The estimated standard deviations of the angles and distances were calculated (Busing, Martin & Levy, 1964) from the variances of the fractional coordinates and the estimated standard deviations of the lattice parameters.

The thermal motion of the steroid nucleus can be reasonably described in terms of rigid-body thermal motion treatment of Schomaker & Trueblood (1968). The root mean square difference between the observed U_{ij} and those calculated from the **T**, **L**, and **S** tensors is 0·004 Å². This compares well with the average e.s.d. of the input U_{ij}'s, which is 0·002 Å². The eigenvalues of the libration tensor, 4·4, 1·9 and 1·7°, correspond to anisotropic libration with the axis of the largest libration amplitude nearly parallel to the long axis of the molecule. The bond distances corrected for this motion are given below the uncorrected distances in Fig. 2. The corrections are seen to be small, amounting to approximately one standard deviation.

There are no unusual carbon–carbon or carbon–oxygen bond distances or angles in the molecule. The mean C–H distance is 1·02 Å, which is as expected in X-ray measurements.

More detailed analyses of the geometry of the BNE molecule are given by Hanson (1969) and by Duax & Norton (1975).

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The Crystal and Molecular Structure of
(±)-2,3-Dimethoxy-18-nor-8,13-diaza-1,3,5(10)-estratrien-17-one

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The synthetic steroid, (±)-2,3-dimethoxy-18-nor-8,13-diaza-1,3,5(10)-estratrien-17-one, crystallizes in space group $P2_1/n$ with $a = 7·531$ (4), $b = 29·82$ (1), $c = 7·637$ (4) Å, $β = 116·92$ (3)° and $Z = 4$. The structure was solved by the Patterson search procedure and was refined by block-diagonal least-squares calculations to a final R value of 0·06. The molecular conformation is very similar to that found in the natural estrogens with the largest deviation in the D ring, which contains a nearly planar amide group. The thermal motion is best described in terms of two rigid groups, one composed mainly of rings A and B, the other of ring D. The largest amplitude of libration is in the latter group.

Introduction

Modification of estrogens to their aza analogs has been suggested as a way to enhance their desirable medicinal properties while reducing unwanted side effects (Martin-Smith & Sugrue, 1964). As described in a preliminary report (Burckhalter, Abramson, MacConnell,

Thill, Olson, Hanson & Nordman, 1968), the azaestrogen (±)-2,3-dimethoxy-18-nor-8,13-diaza-1,3,5(10)-estratrien-17-one (I) has a structure which is very similar to that of 4-bromoestrone (Norton, Kartha & Lu, 1963). The lack of pharmacological evaluation precludes any discussion of these properties in relation to the structure at the present time. However, there are two related azaestrogens whose crystal structures are known; both show low estrogenic activity. The compounds 8-azaestrone hydrobromide (Majeste & Trefonas, 1969) and 8-azaestradiol (Brown & Trefonas, 1972) also have structures which are similar to the cor-

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