THE CRYSTAL AND MOLECULAR STRUCTURE OF 17-THIA-3-METHOXY-ESTRA-1,3,5(10) TRIENE-17 DIOXIDE

SURENDRA SINH AND V. M. PADMANABHAN
Neutron Physics Division, Bhabha Atomic Research Centre, Trombay, Bombay 400 085, India.

ABSTRACT

The title compound $C_{18}H_{24}O_3S$ (estra-sulfone), a heterocyclic thia-steroid crystallises in the monoclinic system, space group $P2_1/a$, and with cell dimensions $a = 13.480(2)$, $b = 10.563(2)$, $c = 11.205(1)$Å and $\beta = 93.97(2)°$ with $z = 4$. The structure was solved using counter data and Multan programme and the R factor (hydrogen atoms included) was 0.058. Ring A shows complete aromaticity while B and C rings have distorted chair conformation. The pseudo rotation parameters for the ring D show 13β envelope conformation. The B/C and C/D rings junctions are cis (which are unusual) and the molecule has 8α, 9α, 13β and 14β configuration. An inter-experimental comparison was done for the results obtained from CAD-4 and Trombay-computer controlled diffractometer data.

INTRODUCTION

THE chemistry as well as pharmacology of heterocyclic steroids has attracted a great deal of attention as some of these modified steroids possess significant anticancer and antiovulation activity. The activity depends on the conformation of the steroidal skeleton as well as on the groups attached to it. Since oxygen, nitrogen and sulfur can be introduced in the various available positions of the steroidal skeleton, a large number of heterocyclic steroids can be synthesised. The compound 17-thia-3-methoxy-estra-1,3,5(10)triene-17 dioxide (Molecular formula $C_{18}H_{24}O_3S$ and called estra-sulfone) a heterocyclic analogue of estrone was synthesised[1] in the Bio-organic Division. As the conformation and stereo chemistry of the molecule could not be ascertained by other methods, structure determination by x-ray diffraction was undertaken.

EXPERIMENTAL

Crystals of estra-sulfone were grown by slow evaporation of its methanol solution. The unit cell constants were determined initially by photographic method and were subsequently refined from diffractometer measurement. The crystal data are: Monoclinic, $a = 13.480(2)$, $b = 10.563(2)$; $c = 11.205(1)$Å, $\beta = 93.97(2)°$, $\rho_{obs} = 1.345(2)$, $\rho_{cal} = 1.337$ gm cm^{-3} space group $P2_1$ a, $\mu(CuK_\alpha) = 18.55$ cm^{-1} $\mu(MoK_\alpha) = 2.16$ cm^{-1}. Three dimensional x-ray intensity data with CuK_α radiation for 1870 reflections were collected on an indigenously fabricated four circle diffractometer (controlled by Electronics Corporation of India Ltd., Computer TDC-312 system), employing ω-2θ step scan technique. The structure was solved by direct methods using the programme MULTAN. Full matrix refinement of positional and anisotropic thermal parameters of non-hydrogen atoms gave an R index of 0.081. On further refinement with hydrogen atoms included (with isotropic thermal parameters) the R factor converged to 0.058. (The coordinates of atomic positions are not listed and will be available from the authors.)

RESULTS AND DISCUSSION

The bond lengths and torsion angles are given in figure 2 and the bond-anlges in figure 3. The e.s.d. in bond distance is 0.006 Å and angles 0 4°. Figure 4 is an ORTEP drawing with the molecule viewed down the b-axis. The four molecules are held together by simple van der Waal's forces (figure 1) and there are no unusually short intermolecular contacts. The conformation of the molecule can be described by considering the individual rings.

Ring A: Ring A shows typical aromaticity and delocalization of π electrons to produce a mean bond length of 1.387 Å. This is in close agreement to values for some other estra-triene derivatives[2]. The bond angles as expected are close to 120°. There is no special effect of methoxy substitution at position 3 on the bond lengths and bond angles in the ring. The planarity of the ring is also shown by the fact the intra-ring torsional angles are all near zero.

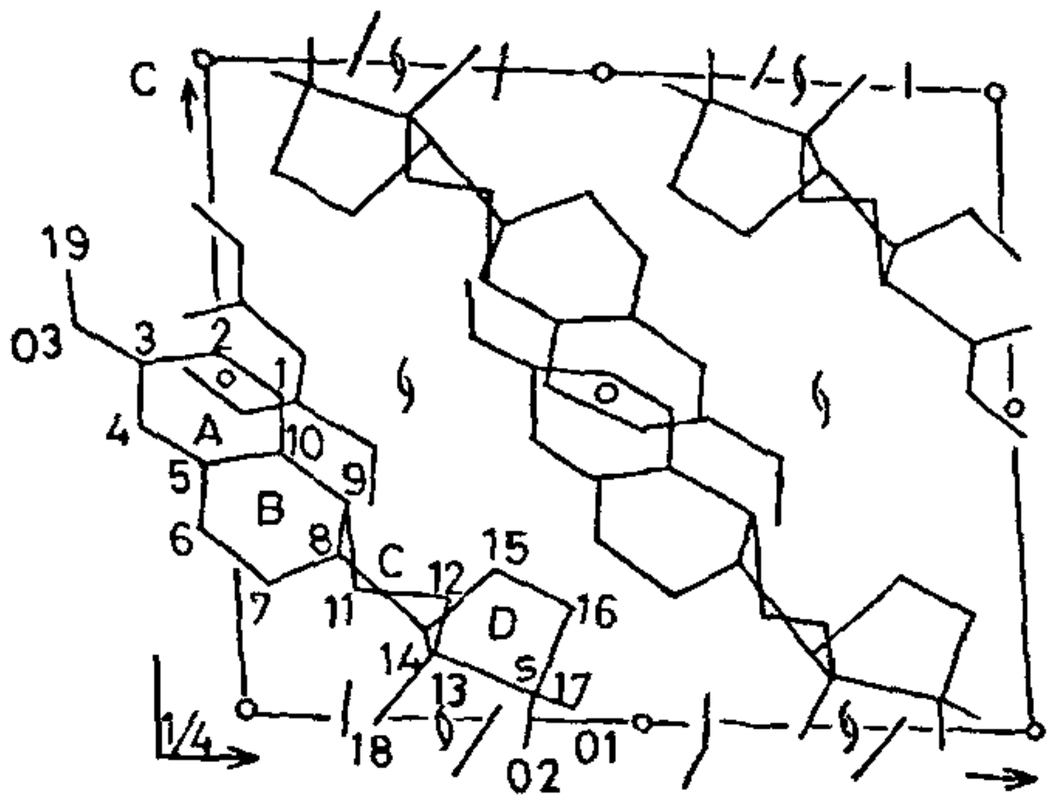

Figure 1. Projection of the unit cell of estra-sulfone down b-axis.

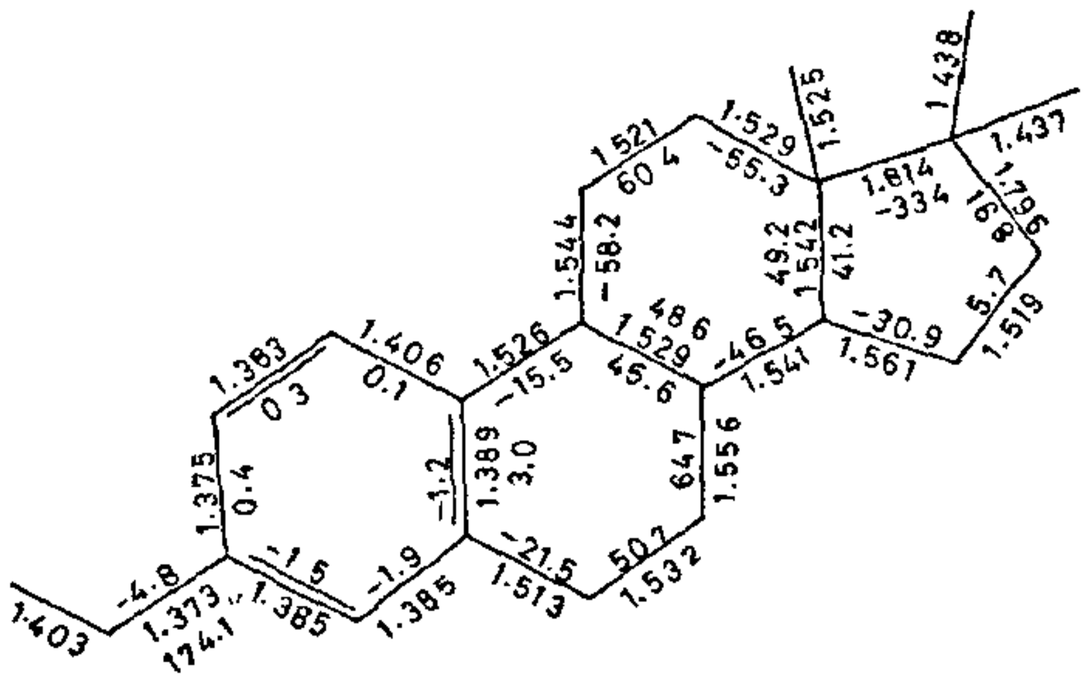

Figure 2. Bond lengths and torsion angles.

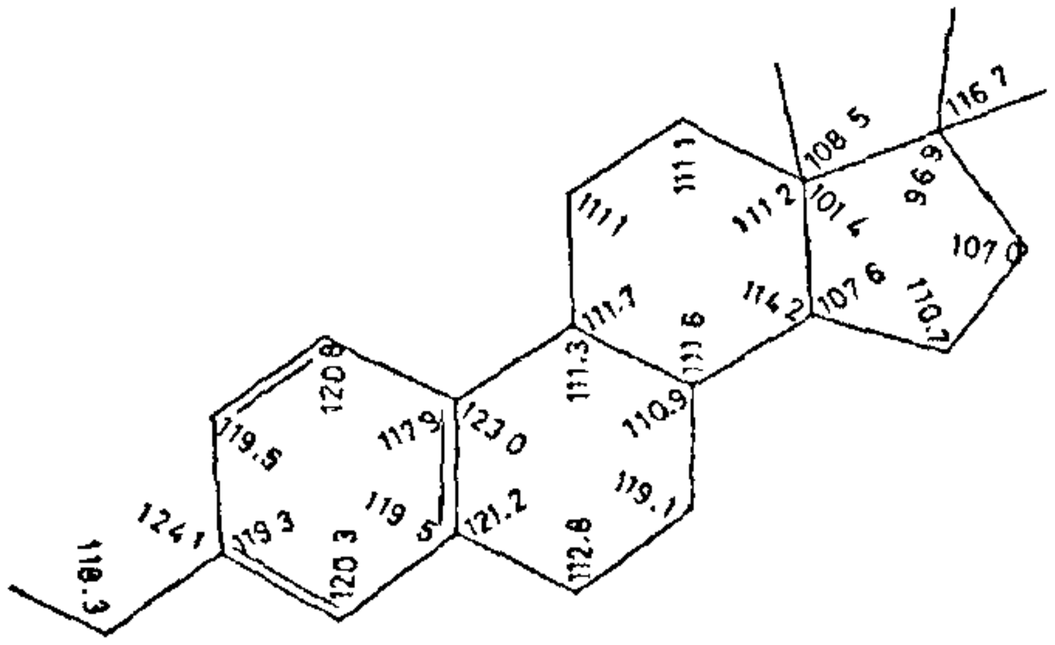

Figure 3. Bond angles.

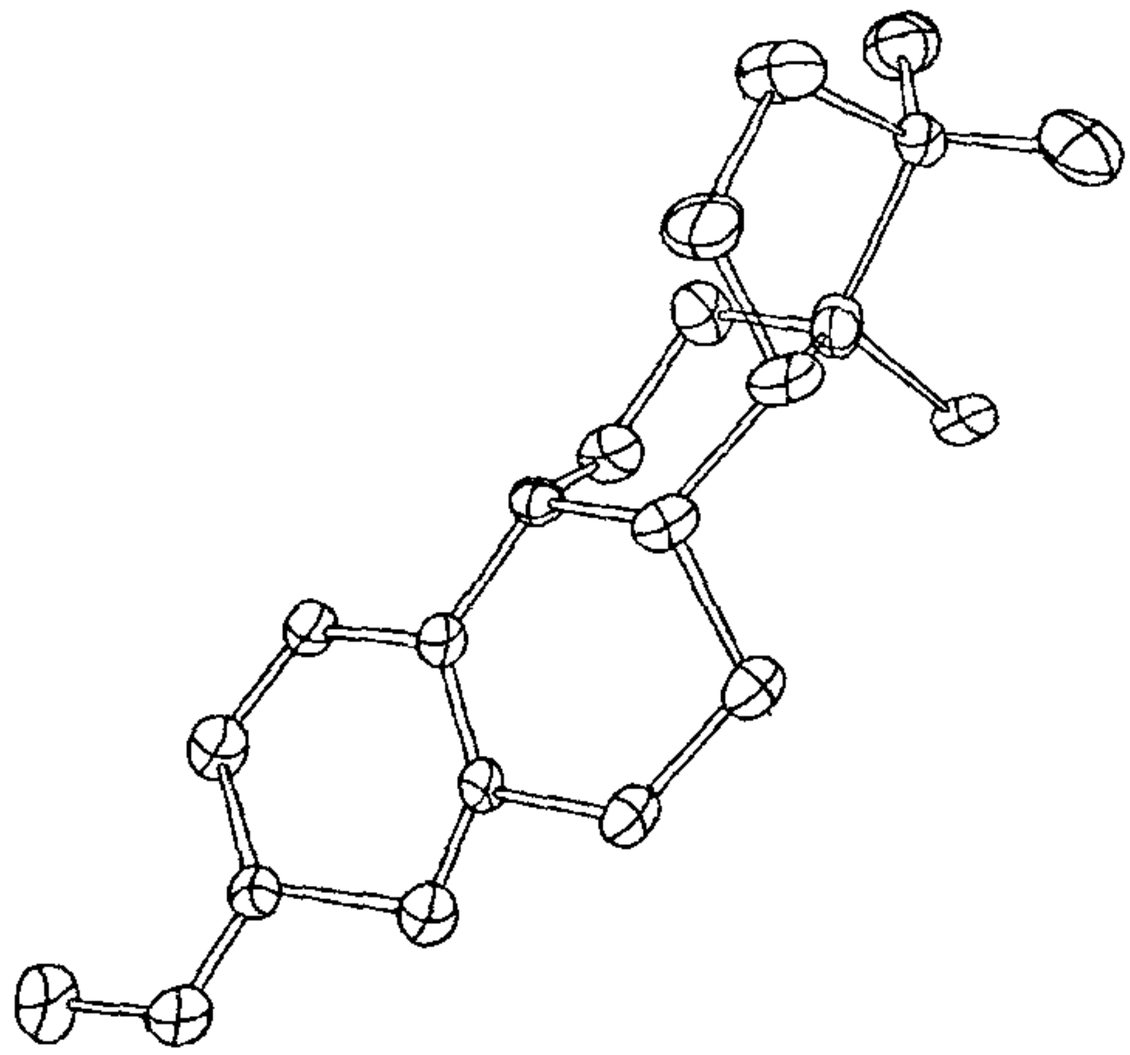

Figure 4. ORTEP drawing of the molecule down b-axis.

Ring B: The bond lengths in the ring are close to the expected value 1.540 A except for the bond C(5)—C(6) which 1.517 A. As observed by Cooper *et al.* in the case of 1,3,5(10) estra-triene[3], this shortening and the nonzero value for the torsion angle C(9)—C(10)—C(5)—(3.0) may be due to repulsion between hydrogens attached to C(6) and to C(15) and C(16) of the equivalent molecule at ($\frac{1}{2} + x$, $\frac{1}{2} - y$, z). The values of symmetry parameters $\Delta C_s(5)$ and $\Delta C_2(5\text{–}10)$ are 42.77 and 6.0 respectively thereby showing that the geometry of the ring is closer to C_2 symmetry *i.e.* it is in a distorted half chair conformation. The least squares plane for the ring B shows that the atoms C(5), C(6), C(9) and C(10) are in one plane and atoms C(8) and C(7) to be above and below the plane by 0.33 Å and 0.36 Å respectively. This 7α—8β conformation of B ring is favoured in almost all the 1,3,5(10) estra-triene derivatives[3].

Ring C: Ring C exhibits bond lengths and angles close to 1.541 Å and 109.2° except for the bond angles C(8)—C(14)—C(13) (113.97°) and C(12)—C(13)—C(14) (112.79°). These large values may be attributed to the presence of a five membered heterocyclic ring attached to C ring. The torsion angles suggest a chair conformation for the ring and this is also verified by the fact that the least squares plane of the ring shows the atoms to be alternately above and below the plane. The chair is slightly distorted due to the presence of sulfur at position 17 in the D ring, resulting in strain in that ring which is transmitted through the junction C/D.

Ring D: The values of C—S bond lengths of 1.824 Å and 1.796 Å are indicative of bonds involving 3d orbitals of sulfur and are quite close to the values reported in literature[4]. The pseudo-rotation parameters as described by Romers *et al.*[5] are $\Delta = 10.8°$ and $\varnothing_m = 42.4°$ showing the ring to be in conformation between that of half-chair and 13 envelope. The least squares plane of the ring shows that the atoms 15, 16 and 17 are in one plane with atoms 14 and 13 above and below by 0.134 Å and 0.521 Å respectively and hence the conformation of the ring is close to 13β envelope. The two oxygens are symmetrically disposed to the ring.

In the methoxy side group O(3)—C(19) bond is trans to C(3)—C(14) and belong to A conformer of Duax *et al.*[2] The B, C and C/D junctions are both cis (which is unusual), indicating flexibility in the form[6] and as is to be expected the values of the two torsion angles at the cis junctions are nearly equal. The overall shape of the molecule suggests that it is in 8α—9α—13β—14β conformation.

Inter experimental comparison: Three dimensional intensity data was collected with CAD-4 diffractometer (at Indian Institute of Science, Bangalore) with Mo K_α radiation, with another crystal of the same compound estra-sulfone. This data gave an R factor of 7.2% for non-hydrogen atoms and 4.8% for hydrogen atoms included. Inter experimental comparison has been done in the basis of half normal probability plots[7] on positional and thermal parameters (of non-hydorgen atoms only), from the CAD-4 and TXD (Trombay x-ray diffractometer) data sets. The positional and thermal parameters have been compared separately and the half normal probability plot for both are straight lines passing through the origin showing that the errors are normally distributed. The positional parameters give a half normal probability plot with slope 1.21 thereby showing that the standard deviations of Trombay data have been underestimated by 21%. The half normal probability plot for thermal parameter gave a slope of 1.32 indicating that the standard deviations for thermal parameters are also underestimated to a greater extent.

Authors thank Dr. P. S. Jogdeo for giving the crystals.

1. Jogdeo, P. S. and Bhide, G. V., *Steroids*, 1979, **33**, 601.
2. Duax, W. L., Weeks, C. M. and Rohrer, D. C., *Topics in stereochemistry*, Vol. 9, p. 271, John Wiley & Sons.
3. Cooper, A., Norton, D. A. and Hauptman, H., *Acta Crystallogr.*, 1969, **B25**, 814.
4. Romers, C., Altona, C., Buys, H. R. and Havinga, E., *Topics in stereochemistry*, Vol. 4, p. 38, John Wiley & Sons.
5. Romers, C., Altona, C., Jacobs, J. C. and DeGraaff, R. A. G., *Terpenoids and steroids*, Vol. 4, p. 531, (The Chemical Society, London).
6. Rucourt, R., *Topics in stereochemistry*, Vol. 8, p. 159, John Wiley & Sons.
7. Abrahams, S. C. and Keve, E. T., *Acta Cryst.*, 1971 **A27**, 157.

FOSSIL MAMMAL FOOTPRINTS FROM THE SIWALIKS OF SOUTH-CENTRAL NEPAL

ROBERT M. WEST, T. R. PANT*, J. H. HUTCHISON† AND GLENN C. CONROY‡
Geology Section, Milwaukee Public Museum, Milwaukee, Wisconsin 53233, USA.
*Department of Mines and Geology, Lainchur, Kathmandu, Nepal.
†Museum of Palaeontology, University of California, Berkeley, California 94720, USA.
‡Division of Biology and Medicine, Brown University, Providence, Rhode Island 02912, USA.

ABSTRACT

Footprint impressions made by two different mammals were found in fluvial sedimentary rocks of the Siwalik Group in south-central Nepal in 1982. These are the first ichnofossils reported from the Siwaliks through all of South Asia. The rocks are of late early middle Siwalik age. One animal was probably a bovid and the other an anthracothere.

INTRODUCTION

THE Siwalik Group, a thick fluvial sedimentary sequence deposited from Miocene to Pleistocene along the southern flank of the Himalayas, has been studied extensively in India and Pakistan for over 150 years. However, only recently[1,2] has paleontologic investigation extended into the Siwaliks of Nepal. The