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# THE MOLECULAR STRUCTURE OF A 6-THIAESTROGEN[1]

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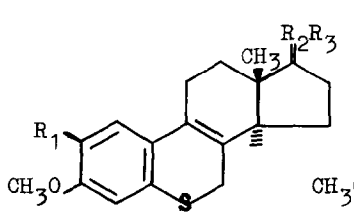
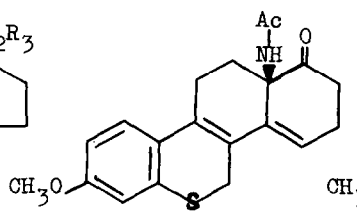
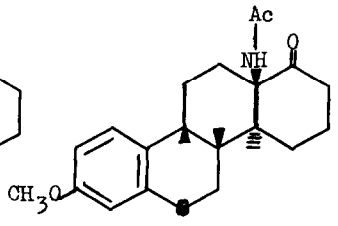
The remarkable result of the Pd-hydrogenation of Δ8.9-6-thiaestrogen 1[3] as compared with the analogous reaction[4] of the corresponding carbocyclic steroids is of prime importance in the total synthesis of all-trans-6-thiaestrone. Formation of both 8α, 9α-H as well as 8β-9β-H products was shown to occur, the latter isomer not being observed generally in this type of reduction.







1. $R_1$ = H $R_2R_3$ = O
2.
3.
4. $R_1$ = $OCH_3$ $R_2$ = H $R_3$ = β-OH
5. $R_1$ = H $R_2$ = H $R_3$ = β-OH

In order to investigate this anomalous reaction further, ketone 2[5], and alcohols 4 and 5 were hydrogenated. On hydrogenation of ketone 2 the reaction proceeded extremely slow and was stopped when no vinylproton ($H_{15}$) was visible in the NMR. One stereoisomer of D-homo-6-thiaestrone 3 was obtained in good yield, mp 308-310°C, IR $\overset{KBr}{max}$ 3400 $cm^{-1}$ (NH) 1710 $cm^{-1}$ ( C = O ) NMR ($D_6$-DMSO) δ 1,96 (s, $\underline{CH_3}$ - C = O ). Due to lack of proper references the configuration of the new compound could not be established from NMR, but the C/D junction was supposed to be trans in analogy with other catalytic reductions of the 14,15 double bonds of D-homosteroids[6]. Reduction of the 8.9 double bond could yield α- and β-cis products as stated above, although α-cis

seemed to be favoured here, for sterical reasons. An x-ray investigation showed that the first supposition was correct i.e. the C/D junction is trans, however, the reduction of the 8.9 unsaturation occured exclusively from the β-side.

Monoclinic crystals were grown by recrystallization from nitromethane The cell dimensions, measured from calibrated zero layer Weissenberg films are a=13.847(1), b=6.154(1), c=26.141(2)Å, β=106,31(1)°. Z=4.Space group $P2_1/c$. With a Nonius automatic single crystal diffractometer 1500 independent intensities were collected at room temperature with CuKα radiation. Because of the small size of the crystal the absorption correction could be ignored.

The sulphur position was found from its Harker peaks in an $E^2$-Patterson synthesis. A fourfold minimum function with the Patterson centred at the 4 sulphur positions revealed all other 24 steroid atoms. The refinement was carried out by means of a block diagonal least squares program. At the stage R=25% a difference synthesis showed a molecule of nitromethane, which was included in the further refinement cycles. The refinement was terminated at R= 11%.

The results of the structure determination are summarized in fig.1 and fig.2. The standard deviations of bond lengths and angles are 0.02 Å and 1° respectively. A list of atomic parameters and a list of structure factors can be obtained from the laboratory of the first author.

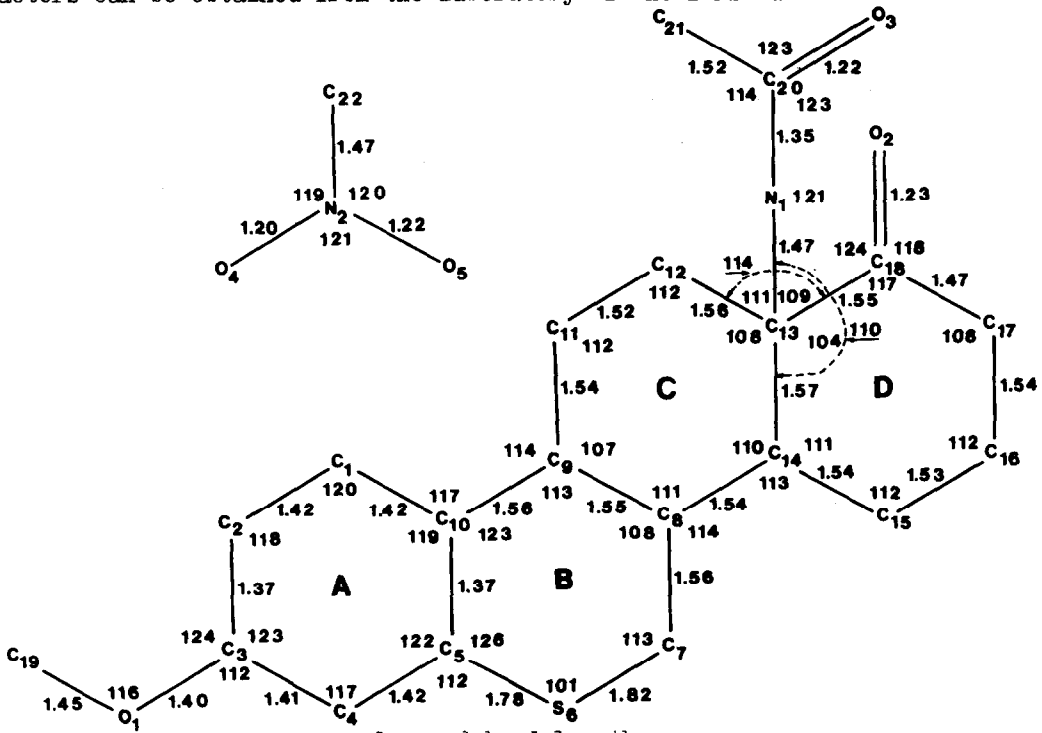



Fig.1. Bond angles and bond lengths.

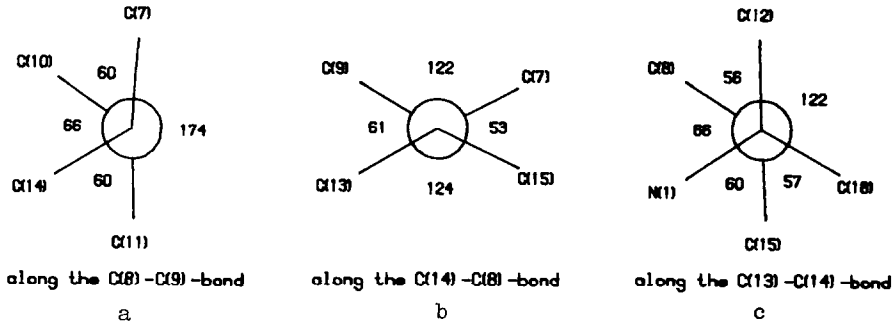



Fig.2 Newman projections along some bonds.

The configuration of the molecule is such that the B/C junction is cis (see fig. 2a), the C/D junction is trans (see fig. 2c) and the protons of C(8) and C(14) (see fig.2b) are in the trans-configuration. In comparison with estrone itself, the proton at C(9) is the only with an alternative position. The acetyl-amino group is planar and the bond C(14) - C(13) is lying approximately in the plane. The aromatic ring A is also planar within the limits of accuracy. The methyl-group of the ether-function eclipses the bond C(2)- C(3). The ring B is in a deformed half chair conformation; clockwise going and starting with C(5) - C(10) the torsion angles along the bonds of this ring are -2, +28, -60, +68, -41 and +9°. The rings C and D are approximately ideal chairs according to their torsion angles: -60, +58, -58, +55, -56, +61, and +57, -62, +60,-53, +55, -50° respectively.

A tentative explanation for this anomalous reduction process is the following: assuming the hydrogenation being a cis addition process where the two hydrogens are not transferred at the same moment, one of the carbon atoms will have a (partial) radical character. This radical is more stabilized on $C_9$ than $C_8$, because of the possible maximum overlap with the aromatic nucleus. As can be seen from models this is the case when the first hydrogen is $C_8$-β-H. Steric factors, however, oppose the β-hydrogenation process. When additional S participation -eventually combined with the formation of a β-Pd-C $\overset{\uparrow}{=}$ C complex[7] - of this radical becomes important, the sterically favoured process might be counterbalanced and even overruled by this electronically determined reaction pathway.

As far as our results indicate the β-hydrogenation is a common pathway of all S-steroids, which is again evidenced from compound 4, yielding the β-cis isomer as the sole product (mp 149,5 - 152,5° C).
IR $\overset{KBr}{max}$ 3250 $cm^{-1}$ (OH) NMR ($CDCl_3$) 0,80 (s, $\underline{CH_3}$), ~ 3.0 (m, $C_9$-$\underline{H}$), centered round 2,63 and 3,23 (two quartets, $C_7$-$\underline{CH_2}$), 3,60 (t,$C_{17}$-α-H).
Furthermore, Pd-hydrogenation of 5 yielded a single alcohol which was

oxidized ($Ag_2CO_3$) to the known 9-H-iso-6-thia-estrone[4].

REFERENCES:

*Satisfactory elemental analyses and spectral data have been obtained for all compounds mentioned here.

1. Part XIX in the series "Heterocyclic steroids". For part XVIII see ref.5.
2. Part of the forthcoming thesis of W.M.B. Könst, University of Amsterdam.
3. W.N. Speckamp, J.G. Westra, H.O. Huisman, Tetrahedron, 26, 2353 (1970).
4. C. Rufer, E. Schröder, H. Gibian, Liebigs Ann.Chem., 705, 211 (1967).
5. W.M.B. Könst, Mrs. J.L. van Bruynsvoort, W.N. Speckamp, H.O. Huisman, Tetrahedron Letters, 2527 (1970).
6. S.N. Anachenko, V.Ye. Limanov, V.N. Leonov, V.N. Rzheznikov, I.V. Torgov, Tetrahedron, 18, 1355 (1962).
7. S-participation in the stabilization of the Pd/C ⇌ C complex could also contribute to the preferred β-hydrogenation[8].
8. K. Hanaya, Bull.Chem. Soc. Japan 43, 442 (1970).

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