# Conformational Studies. Part 14.[1] An *X*-Ray Analysis of 6α-Hydroxy-4,4-dimethylandrostan-3-one

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Crystals of the title compound are monoclinic, space group $P2_1$, with two molecules in a cell of dimensions $a$ = 14.555(2), $b$ = 7.899(1), $c$ = 8.084(1) Å, β = 105.71(1)°. The structure was solved by direct methods and refined by full-matrix least-squares calculations; $R$ = 0.036 for 2 603 observed reflections. Ring A has a fully staggered twist-boat conformation intermediate between the C(2) ··· C(5) and C(3) ··· C(10) boat conformations, in which all potential non-bonded interactions are simultaneously minimised. This structure is in accordance with previous conclusions [2] using $^1$H n.m.r. spectroscopy.

IN another investigation,[2] we prepared 6α-hydroxy-4,4-dimethylandrostan-3-one (1) and concluded, on the basis of $^1$H n.m.r. spectroscopy that ring A had a boat conformation, with C-3 and C-10 at the stem/stern positions, in contrast to 4,4-dimethylandrostan-3-one (2) which clearly [2] exists with ring A in the anticipated chair conformation. It was thus of interest to investigate the conformation of (1) in the solid state. This we have done, by *X*-ray crystallography which shows that ring A in (1) has a fully staggered boat conformation, intermediate between the C(2) ··· C(5) and C(3) ··· C(10) boats, in which all potential non-bonded interactions are simultaneously minimized. The effect of the introduction of a 6α-hydroxy-substituent (a group of ' small ' size) upon the conformation of ring A is very striking and provides a most convincing demonstration of the reality of the 4,4-dimethyl effect [3] and of our general thesis [4] that appropriate 1,3-hydrogen/methyl interaction between C(4) and C(6) are responsible for numerous subtle conformational effects,[5] as deduced from o.r.d. and/or c.d. evidence in 4,4-dimethyl (and analogous) steroids and terpenoids.

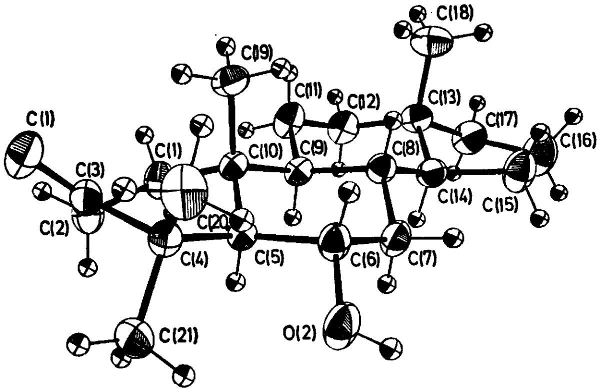


FIGURE 1 Molecular conformation and numbering scheme for (2)

## DISCUSSION

The molecular conformation is shown in Figure 1, together with the numbering scheme. Details of molecular geometry are in Table 1. In contrast to the closely associated derivative (3), in which ring A is found to be in a slightly deformed chair conformation,[6] ring A in (1) exists in a fully staggered twist-boat conformation. Thus, the Newman projection along the C(4) ··· C(1) vector (Figure 2) and the torsion angle data (Table 1) clearly show that the ring A conformation is intermediate between those of C(3) ··· C(10) and C(2) ··· C(5) boats. This essentially strain-free conformation minimises all relevant methyl ··· methyl, methyl ··· hydrogen, methyl ··· hydroxy, and hydrogen ··· hydrogen interaction. All hydrogens were located from difference syntheses and the methyl groups adopt conformations about the appropriate C–C bonds which are within 2 to 5° of being fully staggered. The hydroxy-hydrogen is oriented away from the bulky methyl groups at C(4), with a C(5)–C(6)–O(2)–H torsion angle of 169°, and takes part in an intermolecular O–H ··· O hydrogen bond (2.887 Å, Table 1) to the carbonyl oxygen O(1) of a neighbouring molecule; in

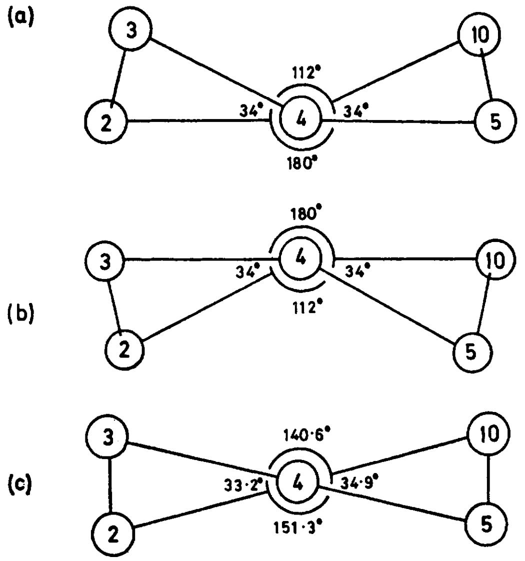


FIGURE 2 Newman projections along the C(4) ··· C(1) vector of (a) a C(10) ··· C(3) boat, (b) a C(2) ··· C(5) boat, and (c) the conformation found in (1) which is intermediate between (a) and (b)

TABLE 1

Interatomic distances (Å) and angles (°) for 6α-hydroxy-4,4-dimethylandrostan-3-one

(a) Intramolecular distances

| | | | |
|---|---|---|---|
| C(1)–C(2) | 1.529(2) | C(11)–C(12) | 1.533(2) |
| C(1)–C(10) | 1.547(2) | C(12)–C(13) | 1.525(2) |
| C(2)–C(3) | 1.507(2) | C(13)–C(17) | 1.534(2) |
| C(3)–C(4) | 1.518(2) | C(13)–C(18) | 1.530(2) |
| C(4)–C(5) | 1.574(2) | C(13)–C(14) | 1.536(2) |
| C(5)–C(6) | 1.538(2) | C(14)–C(15) | 1.536(2) |
| C(5)–C(10) | 1.560(2) | C(15)–C(16) | 1.543(3) |
| C(6)–C(7) | 1.526(2) | C(16)–C(17) | 1.552(3) |
| C(7)–C(8) | 1.532(2) | C(20)–C(4) | 1.539(2) |
| C(8)–C(9) | 1.543(2) | C(21)–C(4) | 1.547(3) |
| C(8)–C(14) | 1.525(2) | O(1)–C(3) | 1.214(2) |
| C(9)–C(10) | 1.559(2) | O(2)–C(6) | 1.425(2) |
| C(9)–C(11) | 1.535(2) | O(2)–H(1) | 0.79 |
| C(10)–C(19) | 1.537(2) | | |

(b) Angles

| | | | |
|---|---|---|---|
| C(2)–C(1)–C(10) | 115.1(1) | C(1)·C(10)–C(19) | 109.7(1) |
| C(1)–C(2)–C(3) | 110.8(1) | C(5)–C(10)–C(19) | 111.3(1) |
| C(2)–C(3)–C(4) | 114.7(1) | C(9)–C(10)–C(19) | 111.0(1) |
| C(2)–C(3)–O(1) | 122.1(1) | C(1)–C(10)–C(5) | 107.4(1) |
| C(4)–C(3)–O(1) | 123.1(1) | C(1)–C(10)–C(9) | 107.8(1) |
| C(3)–C(4)–C(5) | 109.2(1) | C(5)–C(10)–C(9) | 109.6(1) |
| C(3)–C(4)–C(20) | 110.1(1) | C(9)–C(11)–C(12) | 113.6(1) |
| C(3)–C(4)–C(21) | 103.6(1) | C(11)–C(12)–C(13) | 110.9(1) |
| C(5)–C(4)–C(20) | 115.1(1) | C(12)–C(13)–C(14) | 107.8(1) |
| C(5)–C(4)–C(21) | 110.2(1) | C(12)–C(13)–C(17) | 116.1(1) |
| C(4)–C(5)–C(6) | 112.4(1) | C(12)–C(13)–C(18) | 110.3(1) |
| C(4)–C(5)–C(10) | 113.2(1) | C(14)–C(13)–C(17) | 100.5(1) |
| C(6)–C(5)–C(10) | 113.1(1) | C(14)–C(13)–C(18) | 113.0(1) |
| C(5)–C(6)–C(7) | 112.3(1) | C(17)–C(13)–C(18) | 108.9(1) |
| C(5)–C(6)–O(2) | 106.3(1) | C(13)–C(14)–C(15) | 103.6(1) |
| C(7)–C(6)–O(2) | 110.9(1) | C(13)–C(14)–C(8) | 114.7(1) |
| C(6)–C(7)–C(8) | 112.9(1) | C(8)–C(14)–C(15) | 119.6(1) |
| C(7)–C(8)–C(9) | 108.4(1) | C(14)–C(15)–C(16) | 104.1(1) |
| C(7)–C(8)–C(14) | 111.5(1) | C(15)–C(16)–C(17) | 106.1(1) |
| C(9)–C(8)–C(14) | 109.4(1) | C(16)–C(17)–C(13) | 104.5(1) |
| C(8)–C(9)–C(10) | 112.5(1) | C(6)–O(2)–H(1) | 122 |
| C(8)–C(9)–C(11) | 112.4(1) | O(2)–H(1) · · · O(1)$^{I}$ | 176 |
| C(10)–C(9)–C(11) | 113.7(1) | | |

(c) Intermolecular constants

O(2) · · · O(1$^{I}$) 2.887

The superscript (I) refers to equivalent position $x, y, -1 + z$.

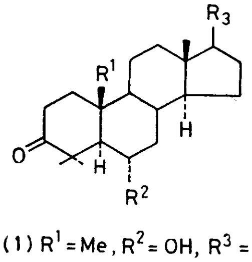
(d) Torsion angles within the rings

| | | | |
|---|---|---|---|
| C(10)C(1)–C(2)C(3) | 22.9 | C(14)C(8)–C(9)C(11) | −49.4 |
| C(1)C(2)–C(3)C(4) | −62.4 | C(8)C(9)–C(11)C(12) | 50.9 |
| C(2)C(3)–C(4)C(5) | 34.6 | C(9)C(11)–C(12)C(13) | −55.0 |
| C(3)C(4)–C(5)C(10) | 28.0 | C(12)C(13)–C(14)C(8) | 56.7 |
| C(4)C(5)–C(10)C(1) | −63.3 | C(11)C(12)–C(13)C(14) | −59.8 |
| C(5)C(10)–C(1)C(2) | 35.3 | C(13)C(14)–C(8)C(9) | 55.9 |
| C(9)C(10)–C(5)C(6) | 50.6 | C(17)C(13)–C(14)C(15) | 46.2 |
| C(10)C(5)–C(6)C(7) | −50.4 | C(13)C(14)–C(15)C(16) | −34.5 |
| C(5)C(6)–C(7)C(8) | 54.3 | C(14)C(15)–C(16)C(17) | 9.3 |
| C(6)C(7)–C(8)C(9) | −57.8 | C(15)C(16)–C(17)C(13) | 19.2 |
| C(7)C(8)–C(9)C(10) | 59.0 | C(14)C(13)–C(17)C(16) | −39.9 |
| C(8)C(9)–C(10)C(5) | −55.9 | | |

this way chains of molecules are produced in the *c*-direction (Figure 3).

Rings B and C adopt slightly deformed chair conformations (internal ring torsion angles are in the range 50—59° in ring B and 49—60° in ring C); ring D (with $\Delta = 12.3°$ and $\phi m = 46.5°$ [7]) has close to the same half-chair conformation distorted towards a C(13) envelope as was found [6] in ring D of (3) ($\Delta = 7.0°$ $\phi m = 46.6°$). These data provide additional collateral evidence in addition to those already reported [6] for the reality of conformational transmission.

The bond lengths and angles are in accord with expected values; some bond lengths, averaged where appropriate are C($sp^3$)–C($sp^3$) 1.540, C($sp^3$)–C($sp^2$) 1.512, C($sp^2$)=O 1.214, C($sp^3$)–O 1.425 Å. The two longest C–C bonds in the molecule C(4)–C(5) 1.574(2) and C(5)–C(10) 1.560(2) Å are in the overcrowded region of the molecule and in each case involve a fully substituted tertiary carbon atom and a secondary carbon atom; bond length extension has also been observed in other molecules with similar geometries.[8]



(1) R$^1$ = Me, R$^2$ = OH, R$^3$ = H

(2) R$^1$ = Me, R$^2$ = R$^3$ = H

(3) R$^1$ = Me, R$^2$ = H, R$^3$ = ICH$_2$CO$_2$

EXPERIMENTAL

Crystals of (1) are colourless needles elongated along *c*. Preliminary cell parameters and space-group data were obtained from precession and Weissenberg photographs; accurate cell parameters were obtained by a least-squares procedure applied to 12 general reflections ($10° < \theta < 20°$) measured on a computer-controlled Hilger and Watts Y290 diffractometer.

*Crystal Data.*—$C_{21}H_{34}O_2$, $M_r = 318.5$. Monoclinic, $a = 14.555(2)$, $b = 7.899(1)$, $c = 8.084(1)$ Å, $\beta = 105.71(1)°$,

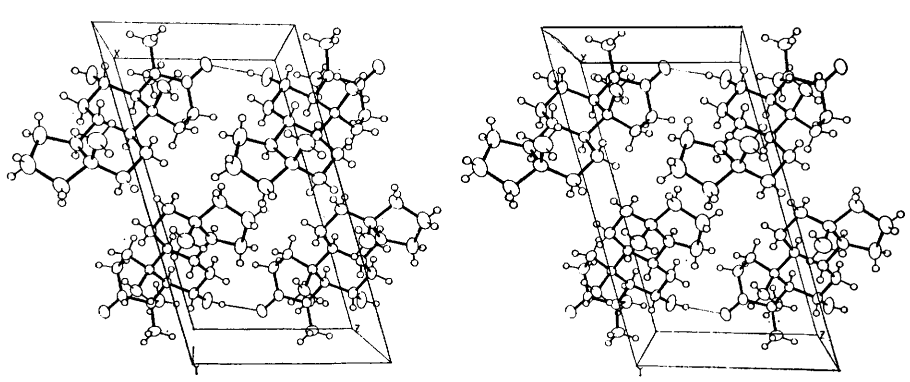


FIGURE 3 Stereoview of the crystal structure of (2) showing the hydrogen bonding

$U = 894.7$ Å$^3$, $Z = 2$, $D_c = 1.18$ g cm$^{-3}$, $F(000) = 352$, (20 °C; Mo-$K_\alpha$; $\lambda = 0.710\,69$ Å, $\mu = 0.83$ cm$^{-1}$). Space group $P2_1/m$ ($C^2_{2h}$) or $P2_1$ ($C^2_2$) from absent reflections: $0k0$, $k = 2n + 1$; $P2_1$ from structure analysis.

TABLE 2

Final positional parameters (C and O × $10^4$, H × $10^3$) for 6α-hydroxy-4,4-dimethylandrostan-3-one with estimated standard deviations in parentheses

| Atom | *x*/*a* | *y*/*b* | *z*/*c* |
|---|---|---|---|
| C(1) | 7 227(1) | 5 018(3) | 2 789(2) |
| C(2) | 7 793(1) | 3 550(3) | 3 812(2) |
| C(3) | 8 845(1) | 3 756(3) | 3 987(2) |
| C(4) | 9 115(1) | 3 737(3) | 2 299(2) |
| C(5) | 8 297(1) | 4 600(3) | 866(2) |
| C(6) | 8 652(1) | 5 261(3) | −642(2) |
| C(7) | 7 856(1) | 6 095(3) | −2 030(2) |
| C(8) | 7 342(1) | 7 500(3) | −1 326(2) |
| C(9) | 6 936(1) | 6 737(3) | 86(2) |
| C(10) | 7 726(1) | 5 950(3) | 1 590(2) |
| C(11) | 6 276(1) | 7 972(3) | 679(2) |
| C(12) | 5 497(1) | 8 741(3) | −802(2) |
| C(13) | 5 932(1) | 9 592(3) | −2 106(2) |
| C(14) | 6 531(1) | 8 263(3) | −2 734(2) |
| C(15) | 6 751(1) | 9 114(3) | −4 292(2) |
| C(16) | 5 848(2) | 10 164(4) | −5 109(3) |
| C(17) | 5 231(1) | 10 105(3) | −3 816(2) |
| C(18) | 6 510(1) | 11 148(3) | −1 309(3) |
| C(19) | 8 390(1) | 7 329(3) | 2 604(2) |
| C(20) | 10 114(1) | 4 509(3) | 2 549(2) |
| C(21) | 9 175(1) | 1 829(3) | 1 910(2) |
| O(1) | 9 427(1) | 3 876(3) | 5 377(1) |
| O(2) | 9 031(1) | 3 836(3) | −1 312(2) |
| H(1) | 917 | 388 | −219 |
| H(11) | 664 | 458 | 210 |
| H(12) | 710 | 582 | 358 |
| H(21) | 758 | 252 | 324 |
| H(22) | 769 | 353 | 492 |
| H(51) | 785 | 373 | 41 |
| H(61) | 912 | 612 | −25 |
| H(71) | 813 | 657 | −287 |
| H(72) | 740 | 525 | −255 |
| H(81) | 779 | 838 | −87 |
| H(91) | 654 | 581 | −42 |
| H(111) | 598 | 738 | 141 |
| H(112) | 665 | 887 | 130 |
| H(121) | 515 | 956 | −35 |
| H(122) | 508 | 787 | −136 |
| H(141) | 621 | 722 | −309 |
| H(151) | 730 | 982 | −394 |
| H(152) | 685 | 829 | −508 |
| H(161) | 602 | 1 130 | −528 |
| H(162) | 551 | 969 | −618 |
| H(171) | 473 | 929 | −416 |
| H(172) | 496 | 1 119 | −372 |
| H(181) | 704 | 1 076 | −41 |
| H(182) | 613 | 1 188 | −85 |
| H(183) | 674 | 1 173 | −215 |
| H(191) | 884 | 683 | 355 |
| H(192) | 801 | 812 | 300 |
| H(193) | 872 | 787 | 188 |
| H(201) | 1 033 | 450 | 153 |
| H(202) | 1 059 | 401 | 347 |
| H(203) | 1 009 | 568 | 283 |
| H(211) | 966 | 130 | 280 |
| H(212) | 933 | 168 | 85 |
| H(213) | 858 | 131 | 184 |

The intensities of all reflections ($2° < \theta < 30°$ Mo-$K_\alpha$) were measured on a computer-controlled Hilger and Watts Y290 four-cicle diffractometer in our usual way.[9] During the data collection no significant decrease in the intensities of three standard reflections was observed. The data were corrected for the Lorentz and polarisation factors but no absorption correction was applied as it was negligible. Of the 2 778 unique intensities measured, 175 reflections had a net count of less than $3\sigma$ above background and were excluded from the refinement.

*Structure Analysis.*—The structure was solved by using the multiple-solution program MULTAN78.[10] The first *E*-map revealed almost the entire molecule except for the methyl carbon atoms which were subsequently located from a difference Fourier synthesis.[11] Initial full-matrix anisotropic least-squares refinement lowered $R$ to 0.099 and at this stage a difference map showed electron-density maxima in most of the plausible positions for the hydrogen atoms. The positions of these atoms were then idealised with C–H = 0.95 Å and included as fixed contributions in the least-squares refinement; overall isotropic thermal parameters were refined for the different types of hydrogen ($CH$, $CH_2$, $CH_3$, and $OH$). Four additional cycles of full-matrix least-squares refinement gave the final $R$ value of 0.036 and $R' = [\Sigma w\Delta^2/\Sigma wF_o^2]^{\frac{1}{2}} = 0.039$. In the early stages of refinement, unit weights were used, and in the final stages weights were derived from the counting statistics. In the final cycle of refinement, the largest shift/error ratio was 0.20 in the $z/c$ co-ordinate of the O(2) atom and the final difference map was featureless.

The scattering factors for the non-hydrogen atoms were taken from ref. 12 and for the hydrogen atoms from ref. 13. Although the absolute configuration was not determined, it was known from chemical grounds, and in all calculations the correct absolute stereochemistry was used. Anomalous dispersion corrections were applied for all the non-hydrogen atoms. Final positional parameters are given in Table 2. The observed and final calculated structure amplitudes and the thermal parameters are listed in Supplementary Publication No. SUP 22767 (20 pp.).*

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* For details of the Supplementary Publication scheme, see Notice to Authors No. 7, in *J.C.S. Perkin II*, 1979, Index issue.

REFERENCES

[1] Part 13, J. M. Midgley, W. B. Whalley, B. E. Ayres, G. H. Phillipps, G. Ferguson, and M. Parvez, preceding paper.

[2] J. M. Midgley, J. E. Parkin, and W. B. Whalley, *J.C.S. Perkin I*, 1977, 834.

[3] C. Djerassi, 'Optical Rotatory Dispersion,' McGraw-Hill, New York, 1960, p. 90 *et seq.*

[4] *E.g.* M. J. T. Robinson and W. B. Whalley, *Tetrahedron*, 1963, **19**, 2123; and in numerous public lectures.

[5] C. Djerassi, O. Halpern, V. Halpern, and B. Riniker, *J. Amer. Chem. Soc.*, 1958, **80**, 4001.

[6] G. Ferguson, E. W. Macauley, J. M. Midgley, J. M. Robertson, W. B. Whalley, and B. A. Lodge, *J.C.S. Perkin II*, 1979, 1170.

[7] C. Altona, H. J. Geise, and C. Romers, *Tetrahedron*, 1968, **24**, 13.

[8] R. Hoge and C. E. Nordmann, *Acta Cryst.*, 1974, **B30**, 1435.

[9] G. Ferguson, D. F. Rendle, J. M. Midgley, and W. B. Whalley, *J.C.S. Perkin II*, 1978, 267.

[10] P. Main, S. Hull, L. Lessinger, G. Germain, J.-P. Declercq, and M. M. Woolfson, (1978) MULTAN78—a system of computer programs for the automatic solution of crystal structures from *X*-ray diffraction data: University of York and Louvain.

[11] SHELX, G. M. Sheldrick, University Chemical Laboratory, Cambridge CB2 1EW.

[12] D. T. Cromer and B. J. Mann, *Acta Cryst.*, 1968, **A24**, 321.

[13] R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, 1965, **42**, 3175.