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SYNTHESIS, X-RAY STRUCTURE AND MOLECULAR MECHANICS STUDIES OF THE BOAR TAINT STEROID (5α-ANDROST-16-EN-3-ONE)[1]

PHILIP J. COX
School of Pharmacy, Robert Gordon's Institute of Technology, Schoolhill, Aberdeen AB9 1FR, Scotland

and

ALAN B. TURNER
Chemistry Department, University of Aberdeen, Old Aberdeen AB9 2UE, Scotland

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Abstract—5α-Androst-16-en-3-one has been prepared from 5α-androstan-3β-ol-17-one in an overall yield of 34% by the vinyl iodide route. Accurate molecular dimensions have been determined by X-ray crystal structure analysis and by molecular mechanics calculations. There is significant twisting of the angular methyl groups in the molecule.

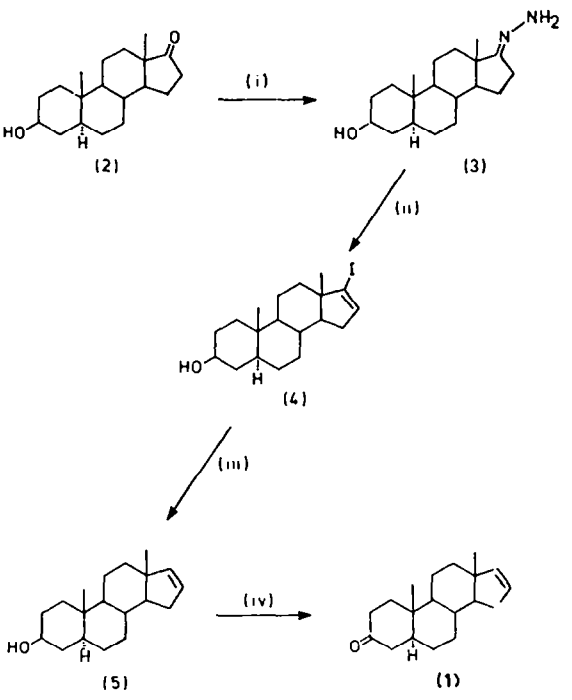
Androstenone (1) has an intense musky and urinous odour[2a] and is thought to have played a significant role as a sex attractant in the evolution of mammals.[2b] The steroid (1) is present in the saliva of male pigs, and has been shown to induce the immobilization reflex (mating stance) in the oestrous sow.[3a] It accumulates in the fat of male pigs and is considered to be responsible for the off-flavour of boar meat known as "boar taint".[3b] The odour and taste of androstenone are assumed to be mediated by interaction of the steroid with receptor membranes in the appropriate sensory apparatus, as evidenced for example by the isolation of androstenone receptors from the olfactory epithelium of the sow[4] and the demonstration that certain neurons in the olfactory bulbs of sows produce excitatory responses to androstenone.[5] In this paper we report X-ray diffraction studies of the molecule, and we compare the data obtained by this method with molecular parameters derived by molecular mechanics calculations, with the object of evaluating the latter method for use in studies of steroid structure-odour relationships. Recently Bernardinelli and Gerdil[6] have reported X-ray studies on the macrocyclic musks, *cis*- and *trans*-civetone and muscone, and their dinitrophenylhydrazone derivatives.

Synthesis of androstenone. Androst-16-enes can be obtained from both 17-hydroxy- and 17-oxo-steroids by a variety of methods.[7] Older methods[8] include pyrolysis of esters such as 17-benzoates and acetates, which give only moderate yields, and methyl carbonates, which give excellent yields.[9] 17-Ketones can be transformed by the sequence involving cyanohydrin formation, dehydration, hydrolysis and decarboxylation, or *via* reaction of their tosylhydrazone derivatives with lithium aluminium hydride or alkyllithium compounds. Conversion of 17-hydrazones to vinyl iodides, followed by reductive removal of the I atom from the 17-position is another convenient route,[10] which we have recently used for the synthesis of 14β-androstenone.[1] Denitroamination of 17-nitroamines by elimination of nitrous oxide has recently been shown to yield androst-16-enes under mild conditions, although rearranged products are also formed.[11]

The sample of androstenone (1) used in this study was prepared from epiandrosterone by the four-step sequence outlined in the Scheme. This route to androst-16-enes was developed by Barton *et al.*[10] following work in the triterpene field aimed at the conversion of a ketone function into a methylene group *via* reduction of a di-iodo-derivative. In the steroid series, a 17,17-di-iodo-intermediate, if formed, would readily undergo elimination of hydrogen iodide (16β-H and 17α-I) to give the vinyl iodide. Epiandrosterone (2) gave the hydrazone derivative (3) with hydrazine hydrate in ethanol, and the hydrazone (3) was converted into the iodoalkene (4) by base-catalysed oxidation with iodine in anhydrous dioxan. Absence of water has recently been identified as a factor in optimizing the yields of vinyl iodides in this reaction,[12] although useful yields are usually obtained with hindered ketone hydrazones as geminal diiodide formation is not favoured. The removal of the I atom by reduction with Na in boiling ethanol was the only difficult step in the sequence, the androst-16-en-3β-ol (5) being occasionally contaminated with starting iodoalkene (4), particularly when the reduction was run on a small scale. The final oxidation of the 3-alcohol (5) to the ketone (1) was conveniently carried out with chromium trioxide in pyridine[13] in order to avoid any possibility of migration of the angular Me group.[14] The overall yield obtained in the sequence (2)→(3)→(4)→(5)→(1) was 34%.

X-Ray crystal structure determination. The X-ray co-ordinates and temperature factors were used to generate a general view of the molecule (Fig. 1) and a stereoscopic crystal packing diagram (Fig. 2).

Crystal data. $C_{19}H_{28}O$, $M = 272.4$, orthohombic, $a = 8.495(3)$, $b = 10.057(8)$, $c = 18.490(7)$ Å, $U = 1579.7$ Å, $Z = 4$, $D_c = 1.15$ gm cm^{-3}, $F(000) = 600$, Mo $-K_\alpha$ radiation, $\lambda = 0.7107$ Å, $\mu = 0.35$ cm^{-1}, Space group $P2_12_12_1$



(i) NH_2NH_2 . Et_3N . EtOH (93%)
(ii) I_2, dioxan, Et_3N (64%)
(iii) N_2, EtOH (70%)
(iv) CrO_3-py CH_2Cl_2 (81%)

Crystallographic measurements. Final values of the cell dimensions were determined from angular measurements on a Nicolet P3 automatic diffractometer. Reflexions in the range $\theta < 25°$ were surveyed and the intensities of 1367 independent reflexions with $I > 3\sigma(I)$ were obtained.

Structure analysis. The crystal structure was elucidated by direct methods using the MULTAN program.[15] The H atoms were located in difference electron density distributions calculated at intermediate stages of structure refinement utilising program SHELX.[16] The co-ordinates for all atoms and anisotropic thermal parameters for the C and O atoms were varied in least-squares calculations. The non-Me and Me hydrogens were each given common isotropic temperature factors and refined with bond length constrictions of 1.00 Å. Convergence was reached at R 4.4% and the weighting scheme used in the final cycles of least-squares refinement was

$$w = 0.3559/(\sigma^2|F_0|).$$

Final positional parameters are listed in Table 1 and torsion angles are given in Table 2. Structure amplitudes and thermal parameters are listed in a Supplementary Publication.

Molecular mechanics calculations. The molecular force-field calculations were performed with the program PECALC[17] utilizing WBFF2[18] modified for use by the inclusion of parameters for ketones.[19] Calculations for the steroid were terminated when $\nabla E_s(x)$† was less than 10^{-7} K cal mol^{-1} $Å^{-1}$.

Molecular structure. Bond lengths and valency angles for the X-ray and molecular mechanics calculations are compared in Figs. 3 and 4. For the X-ray study the e.s.d.'s for bond lengths and valency angles are 0.003–0.005 Å and 0.2–0.3° respectively. The torsion angles are listed in Table 2.

The differences in geometry between the X-ray and molecular mechanics models, although small, are most pronounced when atoms of the cyclopentene ring are involved. All except three of the bond lengths agree to within 3σ and where there are larger discrepancies the X-ray bond lengths appear short. This, to some extent, is due to the anisotropic thermal motion of the atoms and when the effects of libration are taken into consideration it is general to observe a small increase in bond length.[20] The largest difference involves the C(16)–C(17) double bond where the X-ray study gives 1.302(5) Å and the molecular mechanics calculations 1.336 Å. For comparison a simple C_{sp^2}–C_{sp^2} double bond[21] is generally accepted to be 1.337 Å and strain-free values of 1.337 and 1.335 Å are quoted by Allinger[22] and White[23] respectively. Other accurate X-ray structures of 16-enesteroids are substituted at position 17, often with a 20-carbonyl function such that the endocyclic double bond forms part of a chromophore. In these molecules[24,25] the double bond length range is 1.327(4)–1.354(4) Å.

The presence of the double bond in ring D has the overall effect of making the α-face of the molecule less concave than usual. This can be shown by comparison with a similar steroid that possesses a cyclopentane ring. For example, it can be calculated

†Where x are the Cartesian co-ordinates and E_s is the steric energy of the molecule.

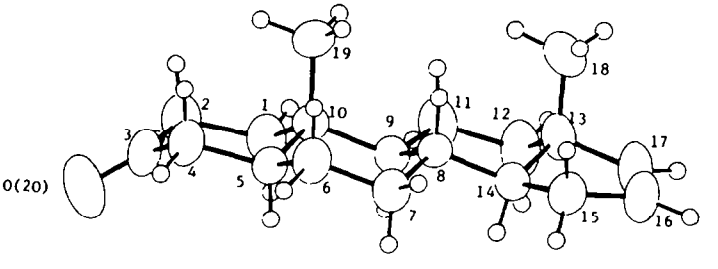


Fig. 1. The atomic arrangement in the molecule.

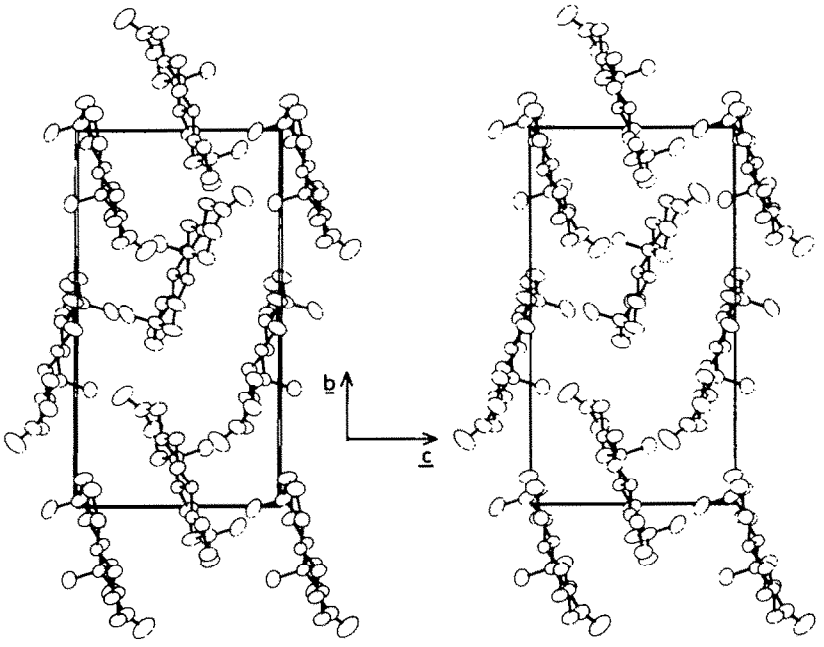


Fig. 2. A stereoscopic view of the crystal packing.

Table 1. Fractional atomic co-ordinates ($\times 10^4$) with e.s.d.'s and equivalent values of the anisotropic temperature factor coefficients ($\times 10^3$) $U_{eq} = \frac{1}{3}(U_{11} + U_{22} + U_{33})$

C(1)	8499(3)	6583(4)	6525(2)	58(1)
C(2)	9353(4)	6777(4)	7251(2)	67(2)
C(3)	8324(4)	7404(4)	7806(2)	60(2)
C(4)	6703(4)	6833(4)	7877(2)	59(2)
C(5)	5890(3)	6728(3)	7134(1)	42(1)
C(6)	4195(3)	6233(3)	7202(2)	53(1)
C(7)	3368(3)	6257(3)	6474(1)	49(2)
C(8)	4279(3)	5460(3)	5912(1)	40(1)
C(9)	6000(3)	5960(3)	5849(1)	41(1)
C(10)	6880(3)	5902(3)	6590(2)	42(1)
C(11)	6913(3)	5300(4)	5222(2)	61(2)
C(12)	6008(4)	5217(4)	4499(2)	70(2)
C(13)	4378(4)	4619(3)	4619(2)	56(2)
C(14)	3533(3)	5521(3)	5166(1)	44(2)
C(15)	1778(4)	5242(3)	5045(2)	56(2)
C(16)	1768(4)	4934(4)	4250(2)	68(2)
C(17)	3176(5)	4668(4)	4013(2)	72(2)
C(18)	4474(5)	3172(3)	4861(2)	76(2)
C(19)	7096(4)	4461(3)	6841(2)	65(2)
O(20)	8772(3)	8340(3)	8168(2)	97(2)
H(1A)	8340(3)	7478(4)	6301(2)	
H(1B)	9179(3)	6028(4)	6202(2)	
H(2A)	10293(4)	7357(4)	7171(2)	
H(2B)	9703(4)	5887(4)	7431(2)	
H(4A)	6776(4)	5926(4)	8095(2)	
H(4B)	6061(4)	7421(4)	8198(2)	
H(5)	5825(3)	7646(3)	6928(1)	
H(6A)	3611(3)	6817(3)	7548(2)	
H(6B)	4206(3)	5301(3)	7389(2)	
H(7A)	2291(3)	5868(3)	6528(1)	
H(7B)	3279(3)	7199(3)	6305(1)	
H(8)	4256(3)	4518(3)	6086(1)	
H(9)	5947(3)	6921(3)	5713(1)	
H(11A)	7191(3)	4376(4)	5375(2)	
H(11B)	7899(3)	5820(4)	5137(2)	
H(12A)	6606(4)	4645(4)	4152(2)	
H(12B)	5895(4)	6132(4)	4293(2)	
H(14)	3656(3)	6500(3)	5089(1)	
H(15A)	1116(4)	6036(3)	5162(2)	
H(15B)	1414(4)	4465(3)	5338(2)	
H(16)	0802(4)	4936(4)	3941(2)	
H(17)	3438(5)	4515(4)	3493(2)	
H(18A)	5252(5)	3085(3)	5263(2)	
H(18B)	4815(5)	2609(3)	4443(2)	
H(18C)	3415(5)	2871(3)	5032(2)	
H(19A)	6044(4)	4023(3)	6884(2)	
H(19B)	7636(4)	4447(3)	7322(2)	
H(19C)	7750(4)	3972(3)	6479(2)	

Table 2. Torsion Angles (°) for the X-ray study (with e.s.d.'s) followed by corresponding values from molecular mechanics calculations

C(10)	C(1)	C(2)	C(3)	−49.9(4)	−50.7	C(2)	C(1)	C(10)	C(5)	55.1(3)	55.0
C(2)	C(1)	C(10)	C(9)	170.9(2)	171.8	C(2)	C(1)	C(10)	C(19)	−66.8(3)	−66.8
C(1)	C(2)	C(3)	C(4)	46.6(4)	48.1	C(1)	C(2)	C(3)	O(20)	−132.0(3)	−130.8
C(2)	C(3)	C(4)	C(5)	−50.1(4)	−49.7	O(20)	C(3)	C(4)	C(5)	128.6(3)	129.1
C(3)	C(4)	C(5)	C(6)	−176.2(2)	−177.2	C(3)	C(4)	C(5)	C(10)	56.1(3)	54.2
C(4)	C(5)	C(6)	C(7)	174.8(2)	173.3	C(10)	C(5)	C(6)	C(7)	−58.1(3)	−57.8
C(4)	C(5)	C(10)	C(1)	−57.9(3)	−57.0	C(4)	C(5)	C(10)	C(9)	−175.8(2)	−175.4
C(4)	C(5)	C(10)	C(19)	62.5(3)	62.6	C(6)	C(5)	C(10)	C(1)	175.0(2)	175.3
C(6)	C(5)	C(10)	C(9)	57.1(3)	57.0	C(6)	C(5)	C(10)	C(19)	−64.6(3)	−65.0
C(5)	C(6)	C(7)	C(8)	55.6(3)	55.2	C(6)	C(7)	C(8)	C(9)	−55.4(3)	−54.5
C(6)	C(7)	C(8)	C(14)	−177.0(2)	−175.1	C(7)	C(8)	C(9)	C(10)	57.1(3)	56.0
C(7)	C(8)	C(9)	C(11)	−173.0(2)	−172.7	C(14)	C(8)	C(9)	C(10)	−178.7(2)	178.6
C(14)	C(8)	C(9)	C(11)	−48.8(3)	−50.1	C(7)	C(8)	C(14)	C(13)	−175.1(2)	−176.3
C(7)	C(8)	C(14)	C(15)	−50.0(3)	−49.9	C(9)	C(8)	C(14)	C(13)	61.7(3)	61.5
C(9)	C(8)	C(14)	C(15)	−173.2(2)	−172.0	C(8)	C(9)	C(10)	C(1)	−172.3(2)	−172.8
C(8)	C(9)	C(10)	C(5)	−56.2(3)	−55.7	C(8)	C(9)	C(10)	C(19)	66.1(3)	67.1
C(11)	C(9)	C(10)	C(1)	58.2(3)	56.9	C(11)	C(9)	C(10)	C(5)	174.3(2)	173.9
C(11)	C(9)	C(10)	C(19)	−63.4(3)	−63.3	C(8)	C(9)	C(11)	C(12)	45.3(3)	47.4
C(10)	C(9)	C(11)	C(12)	174.3(3)	177.7	C(9)	C(11)	C(12)	C(13)	−50.4(4)	−51.7
C(11)	C(12)	C(13)	C(14)	58.5(3)	58.8	C(11)	C(12)	C(13)	C(17)	169.1(3)	167.1
C(11)	C(12)	C(13)	C(18)	−65.8(4)	−68.1	C(12)	C(13)	C(14)	C(8)	−67.5(3)	−66.3
C(12)	C(13)	C(14)	C(15)	158.2(2)	160.4	C(17)	C(13)	C(14)	C(8)	168.1(2)	171.1
C(17)	C(13)	C(14)	C(15)	33.9(3)	37.9	C(18)	C(13)	C(14)	C(8)	55.9(3)	58.4
C(18)	C(13)	C(14)	C(15)	−78.4(3)	−74.9	C(12)	C(13)	C(17)	C(16)	−139.9(3)	−138.4
C(14)	C(13)	C(17)	C(16)	−25.0(4)	−24.8	C(18)	C(13)	C(17)	C(16)	92.6(4)	94.5
C(8)	C(14)	C(15)	C(16)	−160.2(3)	−165.1	C(13)	C(14)	C(15)	C(16)	−31.7(3)	−36.2
C(14)	C(15)	C(16)	C(17)	16.9(4)	20.7	C(15)	C(16)	C(17)	C(13)	5.4(4)	2.8

from the X-ray atom co-ordinates of 3-methylene-5α-androstane[26] that the Me carbon separation is 4.704(7) Å and the methyl twist (given by the pseudo torsion angle C(19)–C(10)—C(13)–C(18) is −0.4(3)°. The current X-ray study of the boar taint steroid yields a smaller Me carbon separation of 4.477(5) Å and a significant Me twist of 8.6(3)°.

No short intermolecular contacts were observed in the crystal structure but crystal packing forces are known to influence angle size more than bond length. For example when two steroid molecules crystallise in one asymmetric unit geometrical deviations between them are most pronounced in the torsion angles and least pronounced in the bond lengths. As Allinger[27] concludes, this is an expected trend as the force constants are large for bond deformation, intermediate for angle bonding and very small for torsional variation. The present study employing a force field not specifically designed for steroids is in agreement with this observation. Indeed 3β-hydroxy-16-methyl-5, 16-pregnadien-20-one[24] crystallises with two molecules in the asymmetric unit and differences in endocyclic torsion angles between the independent molecules range from 0.1° to 4.6°. These differences compare favourably to those shown in Table 2, for the present X-ray and molecular mechanics study, which range from 0.1° to 4.9°.

It may be concluded that the force field used should be suitable for obtaining detailed geometry of similar molecules although minor parameter adjustments may be required. In these instances care is required to ensure that the force field has taken into consideration preferred conformations of any side chain.[28] Finally, there are limitations to obtaining geometrical agreement, the X-ray model being subject to experimental errors and the molecular mechanics model being dependent on the initial model, the force field and the energy minimization method.

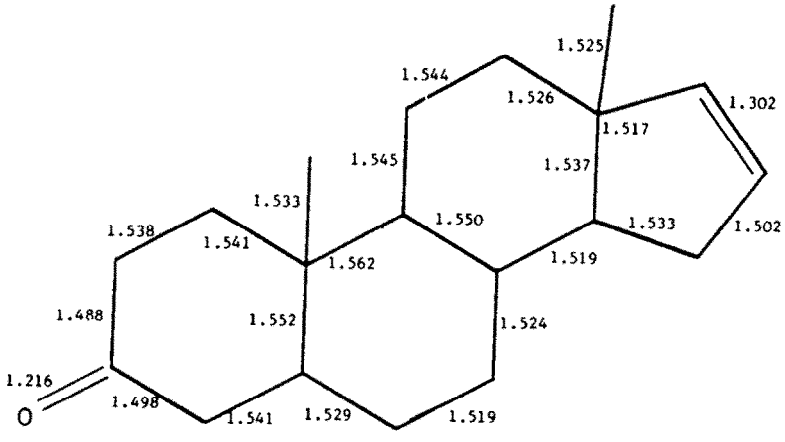
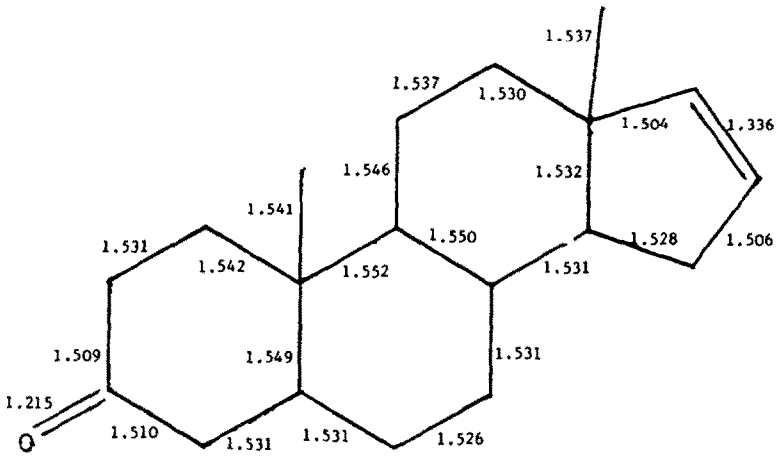
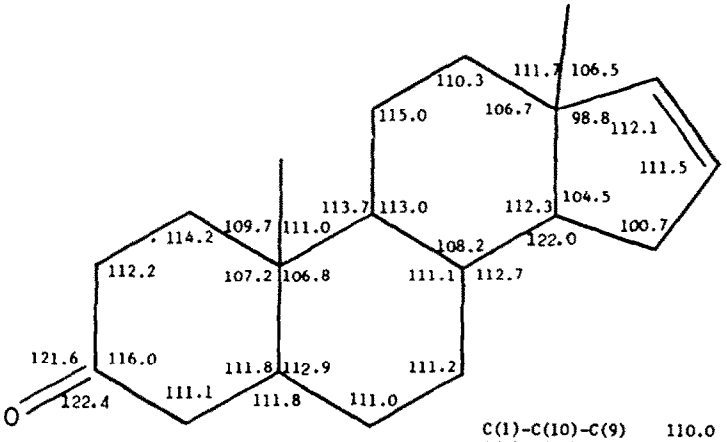


Fig. 3(a).

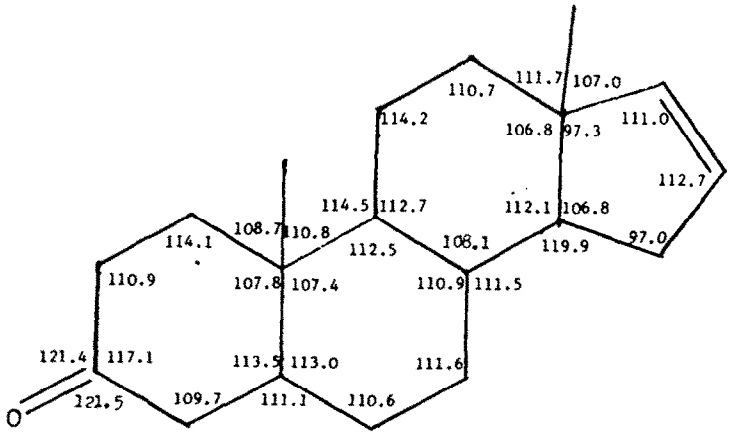


(b)

Fig. 3. Bond lengths (Å), (a) X-ray study, (b) Molecular mechanics calculations.



(a)



(b)

Fig. 4. Valency angles (°), (a) X-ray study, (b) Molecular mechanics calculations.

EXPERIMENTAL

Gas chromatography was performed on a Perkin–Elmer F-11 instrument using 1 m × 3 mm (i.d.) glass columns packed with 3% silicone SE-30 on Chromosorb-W HP (100–200 mesh) at 250° with a N_2 flow rate of 33 ml min^{-1}. Et_3N was freshly redistilled and dioxan was pre-dried over solid KOH before being decanted and distilled over Na. It was stored under N_2 over molecular sieve type 4A. For other general directions see Ref. 29.

3β-Hydroxy-5α-androstan-17-one hydrazone. A soln of 3β-hydroxy-5α-androstan-17-one (3.5 g) in EtOH (25 ml) was treated with Et_3N (6 ml) and hydrazine hydrate (17 ml). The mixture was heated under reflux for 2 hr, cooled, and then poured onto water. The crude product was collected, washed with water, and crystallised from aqueous EtOH to give the hydrazone (33 g, 93%), m.p. 269–271° [Lit.[30] 183–187° (aq. acetone) for material prepared from 3β-acetoxy-5α-androstan-17-one], δ 0.81 (s, 18- and 19-Me), 3.58 (m, 3α-H), *m/z* 304 (M^+, 33%), 289 (33), 288 (100), 107 (13), 96 (11), 93 (11), 81 (10), 79 (12), 72 (25).

17β-Iodo-5α-androst-16-en-3β-ol. A soln of the hydrazine (1.3 g) in dry dioxan (27 ml) and Et_3N (6 ml) was treated with excess of I_2 (2.3 g) in small portions during 30 min at room temp, and, after N_2 evolution had ceased, the mixture was poured onto dilute Na_2SO_3aq. The ppt was collected, washed with water, and crystallised from MeOH to give the iodoalkene as colourless needles (1.1 g, 64%), m.p. 147.5–149° (Lit.[31] 148–150°), R_T 9.0 min, δ 0.72 (s, 18-Me), 0.83 (s, 19-Me), 3.60 (m, 3α-H), 6.13 (m, 16-olefinic H), *m/z* 400 (M^+, 43%), 386 (20), 385 (100), 367 (34), 276 (42), 273 (66), 257 (35), 240 (35), 239 (26), 219 (22), 161 (58), 147 (37), 145 (26), 133 (29), 131 (24), 121 (24), 119 (24), 117 (22), 107 (82), 105 (48), 93 (93), 91 (83).

5α-Androst-16-en-3β-ol. The iodoalkene (0.88 g) was reduced by the method of Barton *et al.*[10] to give the alkene (0.44 g, 70%), m.p. 125–126° (from acetone) (Lit.[32] 125–127°), R_T 3.3 min.

5α-Androst-16-en-3-one. To a stirred soln of the 3β-alcohol (115 mg) in CH_2Cl_2 (4 ml) was added a soln of CrO_3 (330 mg) in anhyd pyridine (0.5 ml) and CH_2Cl_2 (7 ml). The mixture was stirred for 30 min at 22°. The supernatant liquid was decanted from the black ppt, which was washed with ether. The crude product obtained on evaporation of the organic solvents was dissolved in ether, washed successively with sat $NaHCO_3$aq, sat NaClaq, and dried ($MgSO_4$). Evaporation of the ether and crystallisation from ether–hexane gave the pure ketone (93 mg, 81%), m.p. 139–140° (Lit.[2a] 140–141°), undepressed by admixture with an authentic sample, m.p. 139–140°, R_T 3.5 min, δ 0.77 (s, 18-Me), 61.03 (s, 19-Me), 5.69 (m, 16-olefinic H), 5.83 (m, J ~ 55 Hz, 17-olefinic H), *m/z* 272 (M^+, 44%), 257 (72), 149 (43), 148 (20), 147 (52), 135 (22), 133 (20), 124 (25), 107 (55), 105 (32), 95 (67), 94 (85), 93 (72), 91 (61), 81 (52), 80 (23), 79 (100), 77 (44).

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