SHORT PAPER

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The preparation and crystal structure of 16-acetylandrosta-4,16-dien-3-one†

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Dehydroisoandrosterone was formylated at C-16 by a Vilsmeier reaction and by condensation with methyl formate. The product of the latter reaction was converted to 16-acetylandrosta-4,16-dien-3-one and its X-ray crystal structure was determined.

Keywords: 16-acetylandrosta-4,16-dien-3-one, X-ray crystal structure.

There has recently been a resurgence of interest in the pregnanes in the light of their possible role in brain chemistry. The binding of progesterone to the steroid receptor has been described in terms of a ring A binding : ring D acting model. Consequently changes in the relative position of the ring D side chain and the ring A unsaturated ketone are of interest. In this paper we describe the preparation of a ring D isomer of 16-dehydroprogesterone, 16-acetylandrosta-4,16-dien-3-one **7**, and its 17-chloro analogue **4**. 16-Acetylandrosta-4,16-dien-3-one itself, the 16-isomer of dehydroprogesterone, has been synthesised previously[1] by a Grignard reaction on 3β-acetoxy-16-cyanoandrosta-5,16-diene followed by an Oppenauer oxidation. It has also been obtained via the cleavage products of some D-homosteroids which were obtained as by-products from the iododecarboxylation of a dinorcholanic acid.[2]

The Vilsmeier reagent based on phosphorus oxychloride and dimethylformamide has been used for introducing the formyl group onto the steroid framework.[3–5] The development[6] of a modified reagent based on *N*-formylmorpholine has enhanced the value of this procedure. This permitted the preparation of 16-acetyl-17-chloroandrosta-4,16-dien-3-one **4** as a progesterone analogue via the 16-formyl derivative.

Acetylation of dehydroisoandrosterone **1** and treatment of the 3-acetate with the modified Vilsmeier reagent gave the 16-formyl derivative [**2**, R = Ac; δ_H 9.99,singlet, CHO].[4] Reaction of this aldehyde with methyl magnesium iodide gave the C-16 epimeric methyl carbinols. The reaction was accompanied by loss of the 3-acetate to give the 3-alcohol. The alcohols were oxidised by the Oppenauer method to give the 17-chloro compound **4**. Attempts to hydrogenlyse the 17-chlorine with tri-*n*-butyltin hydride were unsuccessful, presumably because the 17-position is sterically hindered both by the C-13 methyl group and the C-16 substituent.

Reduction of the 16-formyl group in **2** (R = Ac) with sodium borohydride gave the 16-hydroxymethyl derivative (**6**, R^1 = Ac, R^2 = H). This was hydrolysed to the diol (**6**, R^1 = R^2 = H) with potassium carbonate and it was acetylated with acetic anhydride to give the diacetate (**6**, R^1 = R^2 = Ac). However, again the chlorine remained unreactive towards hydrogenolysis.

16-Acetylandrosta-4,16-dien-3-one (**7**), was obtained from dehydroisoandrosterone **1** by conversion to the 16-hydroxymethylene derivative with sodium hydride and methyl formate.[7] Methylation of this with caesium fluoride and methyl iodide gave the methyl enol ether **3**[7] which was reduced with sodium borohydride to the 17β-alcohol.

Hydrolysis of the methyl ether with hydrochloric acid was accompanied by dehydration to give the known 16-formyl-3β-hydroxyandrosta-5,16-diene **5**.[7] Reaction of this aldehyde with methyl magnesium bromide in ether and Oppenauer oxidation of the mixture of alcohols gave 16-acetylandrosta-4,16-dien-3-one **7** in a more direct route than those described previously.[1,2] The X-ray crystal structure of 16-acetylandrosta-4,16-dien-3-one **7** is shown in Fig. 1. The 01–02 distance is 11.55Å compared to 11.81Å in progesterone. **8** Hence the distances between the two carbonyl groups are comparable but their relative positions on the carbon skeleton are different.

Experimental

Silica for chromatography was Merck 9385. Light petroleum refers to the fraction b.p. 60–80°C. Extracts were dried over sodium sulfate. ^{1}H NMR spectra were determined at 300 MHz for solutions in deuteriochloroform. IR spectra were determined as nujol mulls.

Reaction of 3β-acetoxyandrost-5-en-17-one with the Vilsmeier reagent: Phosphorus oxychloride (4.3 cm^3) was added to a stirred mixture of *N*-formylmorpholine (5.8 cm^3) in dichloromethane (15 cm^3) over a period of 10 min at 50°C. The mixture was then stirred at 20° for 20 min. 3β-Acetoxyandrost-5-en-17-one (4.98 g) in dichloromethane (100 cm^3) was added in portions over 20 min at room temperature. The mixture was then heated at 45 – 50°C for 4 days (TLC control). The solution was diluted with dichloromethane and washed with aqueous sodium hydrogen carbonate, water and dried. The solvent was evaporated and the residue was chromatographed on silica. Eluation with 5% ethyl acetatet: light petroleum gave 3β-acetoxy-17-chloroandrosta-5,16-diene (1.08 g), m.p. 168–169°C (lit.,[9] 175–175°C), ν_{max}/cm^{-1} 1734; δ_H 0.89 (3H, s, H-18), 0.96 (3H, s, H-19), 1.99 (3H, s, OAc), 0.95–2.30 (17H, overlapping multiplets), 4.60 (lH, tt, *J* 4.2 and 12.2 Hz, H-3), 5.39 (lH, d, *J* 5.2 Hz, H-6), 5.60 (lH, dd, *J* 1.6 and 1.7 Hz, H-16). This was followed by 3β-acetoxy-17-chloro-16-formylandrosta-5,16-diene (**2**, R = AC), (3.4 g), m.p. 180–182°C (lit.,[4] 180–181°C), ν_{max}/cm^{-1} 1734, 1673; δ_H 0.88 (3H, s, H-18), 1.02 (3H, s, H-19), 2.06 (3H, s,OAc), 0.90–2.30 (17H overlapping multiplets), 4.59 (lH, tt, *J* 4.4 and 12.4 Hz,H-3), 5.41 (lH, d, *J* 4.9 Hz, H-6), 9.99 (lH,s, 16-CHO).

Preparation of 16-acetyl-17-chloroandrosta-4,16-dien-3-one (**4**): 3β-Acetoxy-17-chloro-16-formylandrosta-5,16-diene (960 mg) in dry ether (150 cm^3) was treated with methyl magnesium iodide in ether (3M, 16.7 cm^3) at room temperature overnight. Saturated aqueous ammonium chloride (100 cm^3) was added. The organic layer was separated, washed with water and dried. The solvent was evaporated and the inseparable mixture of 16-methyl carbinols (800 mg) crystallised from ethyl acetate:light petroleum as needles, m.p. 189–192°C (Found: C, 71.5; H, 8.6. $C_{21}H_{31}Cl0_2$ requires C, 71.9; H, 8.9%),ν_{max}/cm^{-1} 3582; δ_H 0.65 (3H, s, H-18), 0.90 (3H, s, H-19), 1.23 and 1.29 (total 3H, each d, *J* 6.5 Hz, 16-CH(OH)CH_3), 0.95–2.00

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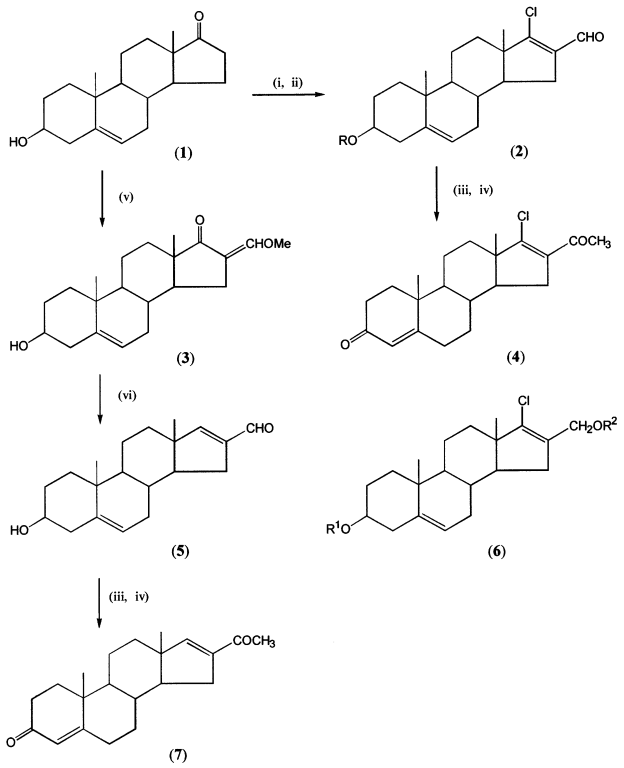
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M)*.



Scheme 1 (i) Ac_2O/pyridine; (ii) $POCl_3$/N-formylmorpholine; (iii) CH_3MgI; (iv) $Al(OiPr)_3$/cyclohexanone; (v) NaH/HCO_2Me, then CsF/MeI; (vi) $NaBH_4$/MeOH, then HCl

(17H, overlapping multiplets), 3.51 (lH, tt, *J* 5.2 and 12.3 Hz, H-3), 4.00 (lH, m, 16-C*H*(OH)CH_3), 5.38 (1H, d, *J* 4.7 Hz, H-6).

Toluene (70 cm^3) was placed in a 100 ml three-necked flask fitted with a dropping funnel and condenser. A portion (15 cm^3) of the toluene was distilled from the flask. The above mixture of alcohols (720 mg) and cyclohexanone (15 cm^3) were then added. A further portion of toluene (10 cm^3) was distilled and then aluminium isopropoxide (2 g) in dry toluene (20 cm^3) was added over a period of 20 min whilst toluene (20 cm^3) was distilled from the mixture. The reaction was heated under reflux for a further hour and then a saturated solution of potassium tartrate (30 cm^3) was added. The solution was steam distilled with the regular addition of water until about 250 cm^3 distillate had been collected. The residue was cooled and extracted with dichloromethane. The extract was washed with water, brine and dried. The solvent was evaporated and residue was chromatographed on silica. Elution with 10% ethyl acetate:light petroleum gave 16-acetyl-17-chloro-androsta-4, 16-dien-3-one (**4**), (400 mg) which crystallised as needles, m.p. 160–162°C (Found: C, 72.3; H, 7.6. $C_{21}H_{27}C10_2$ requires C, 72.7; H, 7.8%), ν_{max}/cm^{-1} 1680; δ_H 0.79 (3H, s, H-18), 1.22 (3H, s, H-19), 0.80–2.30 (17H overlapping multiplets), 2.30 (3H, s, $COCH_3$), 5.67 (1H, s, H-4).

Reduction of 3β-acetoxy-17-chloro-16-formylandrosta-5, 16-diene: The steroid (500 mg) in tetrahydrofuran (100 cm^3) and methanal (2 cm^3) was treated with sodium borohydride (800 mg) at room temperature for 2h. Acetic acid (2 cm^3) was added and the mixture was concentrated in vacuo. Water was added and the product was recovered with ethyl acetate. The extract was washed with aqueous sodium hydrogen carbonate, water and dried. The solvent was evaporated and the residue chromatographed on silica. Elution with 10% ethyl acetate:light petroleum gave 3β-acetoxy-17-chloro-16-hydroxymethylandrosta-5, 16-diene (6, R^1 = Ac, R^2 = H) (400 mg) as needles, m.p. 150–151°C (Found: C, 69.5; H, 8.3. $C_{22}H_{31}C10_3$ requires C, 69.7; H, 8.2%), ν_{max}/cm^{-1} 3500, 1727; δ_H 0.85 (3H, s, H-18), 0.99 (3H, s, H-19), 0.95–2.10 (17H, overlapping multiplets), 2.04 (3H, s, OAc), 4.20 and 4.31 (each 1H, d, *J* 12.8 Hz, 16-CH_2OH), 4.59 (1H, tt, *J* 5.1 and 12.5 Hz, H-3), 5.40 (1H, d, *J* 4.7 Hz, H-6).

17-Chloro-3β-hydroxy-16-hydroxymethylandrosta-5, 16-diene, (6, R^1 = R^2 = H), prepared by hydrolysis with aqueous methanolic potassium carbonate, had m.p. 217–218°C (Found: C, 70.8; H, 8.7. $C_{20}H_{29}C10_2$ requires C, 70.3; H, 8.7%), ν_{max}/cm^{-1} 3300 (br), δ_H 0.78

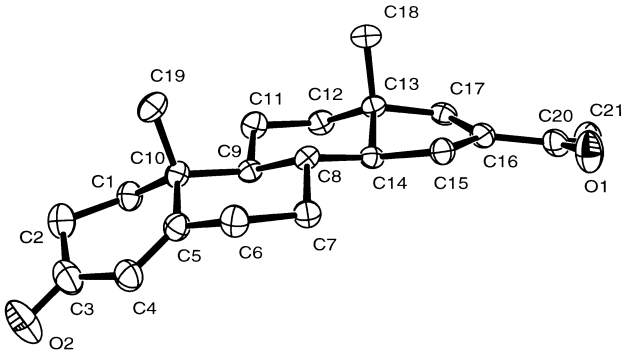


Figure 1 X-ray crystal structure of compound 7

(3H, s, H-18), 0.91 (3H, s, H-19), 0.80–2.10 (17H, overlapping multiplets), 3.50 (1H, tt, *J* 4.7 and 12.6 Hz, H-3), 4.19 and 4.31 (each lH, d, *J* 12.8 Hz, l6-CH_2OH), 5.30 (IH, d, *J* 5.1 Hz, H-6). The diacetate, (**6**, R^1 = R^2 = Ac) prepared with acetic anhydride in pyridine, had m.p. 78–79°C (Found: C, 68.6; H, 7.6. $C_{24}H_{33}C10_4$ requires C, 68.5: H, 7.9%), ν_{max}/cm^{-1} 1749; δ_H 0.87 and 0.90 (each 3H, s, H-18 and H-19), 0.80–2.10 (178, overlapping multiplets), 2.02 and 2.10 (each 3H, s, OAc), 4.59 (IH, tt, *J* 4.7 and 12.8, H-3), 4.65 and 4.73 (each lH, d, *J* 12.7 Hz, l6-CH_2OAc), 5.40 (lH, d, *J* 4.8 Hz, H-6).

Preparation of 16-acetylandrosta-4,16-dien-3-one (**7**): 16-Formyl-3β-hydroxyandrosta-5,16-diene (5) (300 mg)[7] in ether (150 cm^3) was treated with methyl magnesium bromide in ether (lM, 10 cm^3) overnight. The solution was cooled and treated with excess saturated ammonium chloride. The organic phase was separated and the aqueous layer was re-extracted with chloroform. The organic extracts were dried and the solvent evaporated to give a residue (230 mg) which was used immediately. Toluene (20 cm^3) was added and a portion (8 cm^3) was distilled from the flask. Cyclohexanone (8 cm^3) was added and a further portion of toluene (4 cm^3) was distilled. Aluminium isopropoxide (800 mg) in dry toluene (10 cm^3) was added dropwise over a period of 10 min. The solution was heated under reflux whilst a further portion of toluene (17 cm^3) was distilled. The mixture was cooled and aqueous potassium tartrate (10 cm^3) was added. The mixture was steam distilled with the regular addition of water, until 125 cm^3 of distillate had been collected. The residue was extracted with chloroform. The extract was washed with aqueous sodium hydrogen carbonate, water and dried. The solvent was evaporated and the residue was chromatographed on silica. Elution with 25% ethyl acetate: light petroleum gave 16-acetylandrosta-4,16-dien-3-one (7) (180 mg) as needles, m.p. 198–200°C (lit.,[1] 199–200°C) ν_{max}/cm^{-1} 1708, 1677, 1663; δ_H 0.91 (3H, s, H-18), 1.22 (3H, s, H-19), 0.80–2.30 (17H, overlapping multiplets), 2.30 (3H, s, 16-$COCH_3$), 5.74 (lH, s, H-4), 6.78 (lH, d, *J* 1.7 Hz, H-17).

Crystal data and structure determination Compound: **7** $C_{21}H_{28}O_2$, M_r = 312.43, orthorhombic, space group $P2_12_12_1$ (No.19), *a* = 7.3923(2), *b* = 9.8194(3), *c* = 23.7794(7)Å; α = β = γ = 90°C, *V* = 1726.10(9)$Å^3$, *Z* = 4, D_C = 1.20 g/cm^{-3}, F(000) 680, μ = 0.08 mm^{-1}, λ = 0.71073Å. Data were collected using a crystal of 0.3 × 0.3 × 0.2 mm on a Kappa CCD diffractometer. A total of 7377 reflections were collected for 3.77 < θ < 24.71 and -8≤ *h* ≥ 8, -11 ≤ *k* ≥ 7, -27 ≤ 1 ≤ 19. There were 2670 independent reflections and 2105 reflections with $I > 2\sigma(I)$. No absorption correction was applied. The structure was solved by direct methods and refined using SHELXL-97. The final R indices were [$I > 2\sigma(I)$] R_1 0.044, wR_2 = 0.097 and R indices (all data) R_1 = 0.067 and wR_2 = 0.097. The goodness-of-fit on F^2 was 0.870 and the largest difference peak and hole was 0.14 and –0.17 $eÅ^{-3}$. The data will be deposited at the Cambridge Crystallographic Data Centre.

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References

1 J. Fajkos and F. Šorm, *Chem, Listy*, 1957, **51**, 579 *(Chem,,Abs*, 1957, **51**, 10554).
2 B. Kreiger and E. Kaspar, *Chem, Ber.*, 1967, **100**, 1169.

3 D. Burn, G. Cooley, M.T. Davies, J.W. Ducker, B. Ellis, P. Feather, A.K. Hiscock, D.N. Kirk, A.P. Leftwick, V. Petrow, and D.M. Williamson, *Tetrahedron*, 1964, **20**, 597.
4 R. Sciaky and U. Pallini, *Gazz. Chim. Ital.*, 1966, **96**, 1241.
5 H. Laurent and R. Wiechert, *Chem. Ber.*, 1968, **101**, 2393.
6 A.R. Katritzky, I.V. Shcherbakova, R.D. Tack and P.J. Steel, *Can, J. Chem.*, 1992, **70**, 2040.
7 J. Fajkos and F. Šorm, *Chem. Listy*, 1953, **47**, 712 *(Chem. Abs.*, 1955, **49**, 357).
8 C. Romets, C. Altona, H.J.C. Jacobs and R.A.G. De Graaff, *Terpenoids and Steroids, Specialist Periodical Report*, 1974, **4**, 531.
9 G.W. Moench and W.A. Neuklis, *J. Chem, Soc.*, 1965, 788.