The 4α-Demethylation of Lanostenone[1]

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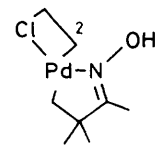
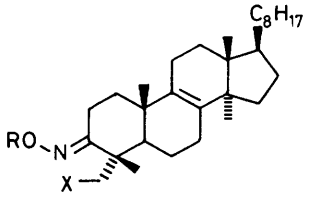
Cyclopalladiation of lanostenone oxime occurs at the equatorial 4α-methyl group. Oxidation of the acetate of this complex with $Pb(OAc)_4$ forms the 4α-acetoxymethyl compound which on reduction and hydrolysis yields 4β-demethyl-lanostenone.

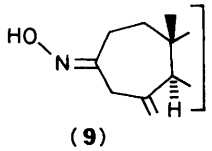
The biochemical conversion of lanosterol into cholesterol involves the oxidation of the 4α-methyl group to hydroxymethyl and then to carboxyl which in combination with oxidation of the 3β-hydroxyl produces a β-oxo acid which decarboxylates to the 4β-demethyl-lanostenone.[2] Chemical mimics of this process have been lacking in contrast to the elegant functionalisation of axial methyl groups by the Barton[3] reaction and related processes. A route to the activation of tertiary equatorial methyl groups was suggested by Shaw's observation[4] that pinacolone oxime underwent cyclopalladiation to form the complex (**1**) with Na_2PdCl_4–AcOH–AcONa. Reaction of the oxime (**2**) of lanost-8(9)-en-3-one under the same conditions gave an intractable solid (*ca.* 80%) which we were unable to crystallise. However



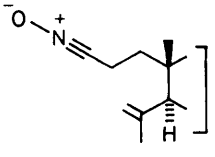
(**1**)



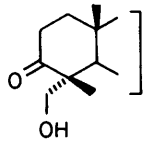
(**2**) R = X = H
(**3**) R = H, X = $PdCl]_2$
(**4**) R = H, X = $PdCl.PPh_3$
(**5**) R = H, X = I
(**6**) R = Ac, X = $PdCl]_2$
(**7**) R = Ac, X = OAc
(**8**) R = H, X = OH



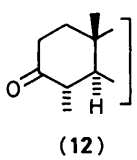
(**9**)



(**10**)



(**11**)



(**12**)

reduction with NaB^2H_4–MeOH established the presence of palladacycle (**3**) since the oxime was regenerated containing *ca.* 60% of a mono-deuteriated species; ^2H n.m.r. spectroscopy showed a triplet at δ 1.12 p.p.m. demonstrating that the ^2H was present in a methyl group. Control experiments using $NaBH_4$–MeO^2H showed that 10—20% of ^2H was also incorporated under these conditions suggesting that the preparations contained a substantial amount of palladacycle (**3**). The incorporations in the latter experiments may be due to Pd^0–$^1H^2H$ reduction. Reaction of compound (**3**) with Ph_3P–PhH gave the crystalline monomeric complex (**4**) (70%) which was fully characterised and reacted with I_2–CH_2Cl_2 to give the iodomethyl compound (**5**) (40%), δ_H 3.32 (1 H, d, *J* 10 Hz) and 3.66 (1 H, d, *J* 10 Hz). On treatment with NaOH–H_2O–THF, the iodide (**5**) was converted into the ring expanded oxime (**9**) (50%); although this is a simple 1,2-migration product the mechanism is not obvious since base is required. If it is a 1,2 migration then the migratory aptitude of the σ bond must be enhanced by oxyanion formation from the hydroximino group (by σ N–O donation to the C–C σ*?). Alternative formulations are possible such as intermediate nitrosocyclopropane formation or cleavage to nitrile oxide followed by an 'ene' reaction (**10**). In the former, the equatorial disposition of the iodomethyl group renders the reaction stereoelectronically unlikely, while in the latter the 'ene' reaction would have to be favoured over the more normal 1,3-dipolar addition.

The oxidation of the C–Pd bond in (**3**), (**4**). and their *O*-acetates was investigated using a variety of oxidising agents, the most satisfactory being $Pb(OAc)_4$. Acetylation of compound (**4**) gave an unstable acetate (**6**) which was immediately oxidised with $Pb(OAc)_4$–PyrH–THF[5,6] followed by reductive work-up with $NaBH_4$ to give the diacetate (**7**) (50%).† Reaction of the diacetate (**7**) with Na_2CO_3–MeOH gave the oxime (**8**) (91%) which was reduced with $TiCl_3$ forming the ketol (**11**) (70%). Oxidation of the ketol (**11**) with Jones' reagent and CrO_3–AcOH did produce C_{29} decarboxylation products but they were additionally oxidised and it became clear that the rate of oxidation of the 1^{γ}-OH was slow compared to nuclear oxidation. In the event the demethyl compound (**12**) (67%) was most readily prepared by treatment of the ketol (**11**) with Na_2CO_3–MeOH which induced a retro-aldol condensation.

From our work and that of others,[6] the Shaw reaction appears to work well with α,α-dimethylcyclohexanone oximes but not with the corresponding cyclopentanone derivatives. In addition, the C–Pd bond of the products appears to be relatively unreactive compared to that of Ar–Pd derivatives. However this reaction may provide a prototype for the activation of remote unactivated C–H bonds.

Experimental

Cyclopalladiation of Lanost-8(9)-en-3-one Oxime (**2**).—A mixture of lanost-8(9)-en-3-one oxime (**2**) (1.7 g), Na_2PdCl_4 (1.25 g), and NaOAc (0.34 g) in AcOH (120 ml) was stirred at room temperature for 3 days.

† Similar oxidation of the complex (**3**) gave a low yield of chloromethyl oxime.

The precipitated yellow organopalladium complex (**3**) was removed by filtration and washed well with water. In order to render it less intractable it was taken up in $CHCl_3$, an equal quantity of EtOH was added to promote precipitation, and the solvents were evaporated under reduced pressure to give *di-μ-chloro-bis(lanost-*8(9)*-en-*3*-one oxime-*C^{30},N*)dipalladium*(II) (**3**) as a pale yellow powdery solid (1.81 g), m.p. 208—214 °C.

A solution of the complex (**3**) (261 mg) and Ph_3P (244 mg) in PhH (8 ml) was stirred at room temperature for 12 h. The solvent was then evaporated off under reduced pressure, leaving a pale brown solid, which was purified by dry column chromatography, eluting initially with hexane and later with hexane–Et_2O (3:2). Recrystallisation from hexane–Et_2O (3:2) afforded the pale yellow, highly crystalline *derivative* (**4**) (260 mg), m.p. 134—135 °C, $[\alpha]_D$ +43° ($CHCl_3$); δ_H 0.60 (s, 3 H) and 7.31 (br s, 1 H); *m/z* 844 (Found: C, 68.45; H, 7.9; Cl, 4.3; N, 1.5; P, 3.9; $C_{48}H_{65}ClNOPPd$ requires C, 68.24; H, 7.75; N, 1.66; Cl, 4.20; P, 3.67%).

A stirred suspension of the complex (**3**) (18 mg) in dry MeOH (6 ml) was treated with Na B^2H_4 (4 mg), a black precipitate of Pd being formed immediately. The mixture was quenched after 1 h by the addition of water (5 ml) and extracted with Et_2O (3 × 10 ml); the extract was filtered through a plug of Celite, dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to leave a white solid. Purification by t.l.c., eluting with hexane–Et_2O (3:2), gave the oxime (**2**) as a white solid (11 mg), m.p. 160—162 °C; $\delta_{2_{\alpha}}$ 1.12 (t) (Found: M^+, 442.4022. $C_{30}H_{50}DNO$ requires *M*, 442.4022).

Preparation of the Iodomethyl Oxime (**5**).—A solution of I_2 (95 mg) in $CHCl_3$ (3 ml) was added to a stirred solution of the complex (**3**) (211 mg) in $CHCl_3$ (10 ml). After 24 h at room temperature, the mixture was filtered through a plug of Celite to remove the black precipitate of Pd that had formed and the solvent was evaporated off under reduced pressure, leaving a brown solid. Purification by t.l.c., eluting with hexane–Et_2O (3:2) afforded the iodide (**5**) as a white solid (61 mg), m.p. 179—181 °C, $[\alpha]_D$ +14° ($CHCl_3$); δ_H 0.69 (s, 3 H), 1.04 (s, 3 H), 1.24 (s, 3 H), 3.32 (d, 1 H, *J* 10 Hz), 3.68 (d, 1 H, *J* 10 Hz), and 7.37 (br s, 1 H, exchangeable with D_2O) (Found: C, 63.4; H, 9.1; I, 22.1; N, 2.45%; M^+, 567.2940; $C_{30}H_{50}INO$ requires C, 63.48; H, 8.88; I, 22.37; N, 2.47%; *M*, 567.2940).

Reaction of the Iodomethyl Oxime (**5**) *with Sodium Hydroxide*.—0.22M Sodium hydroxide in EtOH (40 μl) was added to a solution of the iodomethyl oxime (**5**) (49 mg) in tetrahydrofuran (20 ml) and the mixture was stirred at room temperature for 30 min, during which time a slight yellow colouration was produced. Water (40 ml) and 2M HCl (0.5 ml) were added, the mixture was extracted with Et_2O (2 × 15 ml), and the extract, after being washed with water (1 × 10 ml), was dried ($MgSO_4$). After t.l.c., eluting with hexane–Et_2O (3:2), a white solid (**9**) (19 mg) was isolated, m.p. 116—118 °C, $[\alpha]_D$ +24° ($CHCl_3$); δ_H 0.67 (s, 3 H), 0.99 (s, 3 H), 3.00 (d, 1 H, *J* 18 Hz), 3.49 (d, 1 H, *J* 18 Hz), 4.85 (s, 1 H), and 5.07 (s, 1 H) (Found: C, 79.1; H, 10.9; N, 2.8%; M^+, 439.3811. $C_{30}H_{49}NO$ requires *M*, 439.3814. $C_{30}H_{49}NO{\cdot}H_2O$ requires C, 78.8; H, 11.2; N, 3.1%).

30-*Acetoxylanost-*8(9)*-en-*3*-one Oxime O-Acetate* (**7**).—The dimeric organopalladium complex (**3**) (150.6 mg) was stirred for 45 min at room temperature with Ac_2O (39.6 mg), *N,N*-dimethylaminopyridine (5 mg), and Et_3N (39.2 mg) in dry CH_2Cl_2 under N_2. The mixture was washed twice with water, dried quickly ($MgSO_4$), and evaporated under reduced pressure to give a brown oil. The oil was immediately dissolved in dry THF (10 ml), pyridine (20.4 mg) was added, and the mixture was stirred at room temperature for a further 15 min. The mixture was cooled to −30 °C, $Pb(OAc)_4$ (114.6 mg) in CH_3CO_2H (4 ml) was added and the mixture was stirred for 24 h, allowing it to warm to room temperature. Sodium borohydride (11 mg) in 1M NaOH (4 ml) was added, whereupon a fine black precipitate formed. The mixture was stirred for 15 min, the precipitated Pd was removed by filtration through Celite, and the solution was extracted with Et_2O; the extracts were washed with water and then with saturated aqueous $NaHCO_3$ until all the acetic acid had been removed. The solution was dried ($MgSO_4$) and evaporated under reduced pressure to give a pale yellow oil containing some crystals (120 mg). Flash column chromatography, eluting with light petroleum (b.p. 60—80 °C)–Et_2O (4:1) gave 30-*acetoxylanost-*8(9)*-en-*3*-one oxime O-acetate* (**7**) (70.3 mg) as white needles, m.p. 141—142 °C (Found: C, 75.1; H, 10.3; N, 2.6%; M^+, 541.4142. $C_{34}H_{55}NO_4$ requires C, 75.4; H, 10.2; N, 2.6%; *M*, 541.4131); $\nu_{max.}$ 1 760 and 1 730 cm^{-1}; δ_H 0.68 (3 H, s), 1.03 (3 H, s), 1.17 (3 H, s), 2.03 (3 H, s), 2.16 (3 H, s), and 4.20 (2 H, q, *J* 11 Hz).

30-*Hydroxylanost-*8(9)*-en-*3*-one Oxime* (**8**).—A mixture of 30-acetoxylanost-8(9)-en-3-one oxime *O*-acetate (**7**) (34.6 mg) and Na_2CO_3 was stirred overnight in MeOH. The solvent was evaporated under reduced pressure, Et_2O was added to the residue, and the mixture was washed with 2M HCl and with water, dried ($MgSO_4$), and evaporated under reduced pressure to give 30-*hydroxylanost-*8(9)*-en-*3*-one oxime* (**8**) as a white solid (26.7 mg). This was generally sufficiently pure to proceed without further purification, but for characterisation it was purified by flash column chromatography, eluting with light petroleum (b.p. 60—80 °C)–Et_2O (1.1), to give (**8**) (20.5 mg), m.p. 182—184 °C (Found: C, 78.1; H, 11.4; N, 3.2%; M^+, 457.3916. $C_{30}H_{51}NO_2$ requires C, 78.7; H, 11.2; N, 3.1%; *M*, 453.3920).

30-*Hydroxylanost-*8(9)*-en-*3*-one* (**11**).—A buffered $TiCl_3$ solution was prepared by adding NH_4OAc (422 mg) in water (16 ml) to 30% $TiCl_3$–water (470 μl) under N_2. A solution of the oxime (**8**) (92.6 mg) in THF (15 ml) was added to the deep blue solution, and the mixture was stirred overnight under N_2. The resulting light grey suspension was poured into Et_2O and the aqueous phase was extracted with ether. The combined extracts were washed with saturated aqueous $NaHCO_2$ and brine, dried (Na_2SO_4), and evaporated under reduced pressure to give a pale yellow solid. Dry column chromatography eluting with light petroleum (b.p. 68—80 °C)–Et_2O (gradient elution) gave 30-*hydroxylanost-*8(9)*-en-*3*-one* (**11**) (62.9 mg), m.p. 138—141 °C (Found: C, 80.3; H, 11.4%; M^+, 442.3802. $C_{30}H_{50}O_2$ requires C, 81.4; H, 11.4%; *M*, 442.3811); $\nu_{max.}$ 3 700 and 1 690 cm^{-1}; δ_H 0.70 (3 H, s), 1.04 (3 H, s), and 3.56 (2 H, dd, *J* 12 Hz).

4β-*Demethyl-lanost-*8(9)*-en-*3*-one* (**12**).—A mixture of the ketol (**11**) (46.3 mg) and Na_2CO_3 in MeOH was stirred at room temperature for 24 h. The methanol was evaporated under reduced pressure and Et_2O and water were added to the residue. The organic phase was washed with 2M HCl, dried ($MgSO_4$), and evaporated under reduced pressure, leaving a translucent white solid. Dry column chromatography, eluting with light petroleum (b.p. 60—80 °C)–Et_2O (gradient elution) gave the ketone (**12**) (28.8 mg), m.p. 105—108 °C; $\nu_{max.}$ 1 710 cm^{-1}; δ_H 0.74 (3 H, s) and 1.03 (3 H, d, *J* 6 Hz) (Found: M^+, 412.3705. $C_{29}H_{48}O$ requires *M*, 412.3705).

Acknowledgements

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