Substitution at the 4-Methyl of Lanost-8-en-3-one

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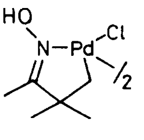
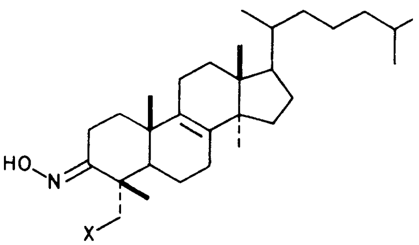
Reaction of the oxime of lanost-8-en-3-one with Na_2PdCl_4 carbopalladates a 4-methyl group which can be converted into monodeuteriomethyl and iodomethyl compounds.

In 1978 Shaw and co-workers[1] showed that pinacolone oxime reacted with Na_2PdCl_4 to give the dimer (**1**). If this reaction was applicable to 2,2-dimethylcyclohexanone derivatives it might allow the preparation of substitution products at the equatorial 'unactivated' methyl group. This approach has the added attraction that it would parallel the order of bond-making and -breaking found in the biosynthetic conversion of lanosterol into cholesterol.[2]

We have found that the oxime of lanost-8-en-3-one (**2**) reacts with Na_2PdCl_4–NaOAc–AcOH to give a compound (81%) formulated as the dimer (**3**). As it is a rather intractable material we have been unable to characterise it fully. However, on reaction with Ph_3P, it is converted into the crystalline monomer (**4**) which has been characterised† (combustion analyses, 300 MHz ^1H n.m.r. spectroscopy, m/z 844 for $^{106}Pd^{35}Cl$). Reduction of the dimer with NaB^2H_4 gave a monodeuterio oxime (**5**) (78%) which in its ^2H n.m.r. spectrum showed a triplet at δ 1.12 p.p.m. establishing that the ^2H had become bonded in a methyl group. Reaction of the monomer (**4**) with I_2–$CHCl_3$ gave the iodomethyl compound



(**1**)



(**2**) X = H

(**3**) X = PdCl/2

(**4**) X = Pd.Cl.PPh_3

(**5**) X = ^2H

(**6**) X = I

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† The palladium stereochemistry has not yet been determined.

(**6**) (40%) [^{1}H n.m.r. δ 3.32 (1H, d, *J* 10 Hz), 3.66 (1H, d, *J* 10 Hz)]. Palladation of the oxime of 2,2,6-trimethylcyclohexanone gave the expected dimer which was fully characterised and which on oxidation with *m*-chloroperbenzoic acid gave 2-chloromethyl-2,6-dimethylcyclohexanone oxime.‡ We believe these results establish the potential of the Shaw reaction for selective functionalisation of the *gem*-dimethyl group and we are pursuing this chemistry with the particular objective of introducing oxygen functionality.

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‡ The introduction of chlorine at the site of the C–Pd bond was unexpected and we are unable to offer a rationale at present.