Stereochemistry of Formation of α-(4—6η)-PdCl Complexes from Steroidal αβ-Unsaturated Ketones; *X*-Ray Crystal Structure of the α-(4—6η) Progesterone Complex of Pentane-2,4-dionatopalladium

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Summary [6β-^{2}H]- and [6α-^{2}H]-Cholest-4-en-3-one react with palladium(II) chloride in dry tetrahydrofuran to give the α-(4—6η)-PdCl compound with highly stereoselective loss of the 6β-deuteron or proton; the α-stereochemistry has been firmly established by a full *X*-ray structural analysis of the α-(4—6η)Pd(acac) derivative of progesterone (Hacac = pentane-2,4-dione).

RECENT communications[1,2] have reported that whereas the loss of a proton during formation of both α-(4—6η)- and β-(4—6η)-PdCl derivatives from reaction of [6β-^{2}H]-cholest-4-ene with $[(PhCN)_2PdCl_2]$ is stereospecific in the *syn*-sense, the stereochemistry of proton loss during formation of α-(4—6η)-PdCl derivatives from 3-oxo-4-ene steroids was more ambiguous. [6β-^{2}H]Cholest-4-en-3-one was reported to react with 'substantial retention of ^{2}H,[1]' and subsequently, preferential loss of 6β-^{2}H was reported.[2] Reaction of [6β-^{2}H]-2,2-dimethylcholest-4-en-3-one with $[(PhCN)_2PdCl_2]$ was reported to proceed with almost equal loss of 6β-^{2}H and 6α-^{1}H.[1]

In view of our interest in preparative applications of palladium–allyl complexes of αβ-unsaturated carbonyl compounds[3,4] we report our observations on the stereochemistry and mechanism of allyl formation from steroidal 4-en-3-ones. We first felt that although the stereochemistry of the single isomer produced in these reactions could be assigned as α-(4—6η)† with some confidence on the basis of n.m.r. evidence, confirmation was desirable. Accordingly a single-crystal *X*-ray analysis of α-(4—6η)-(3,20-dioxopregn-4-enyl)pentane-2,4-dionatopalladium(II) was carried out.

Crystal data: $C_{24}H_{36}O_4Pd$, $M = 518{\cdot}95$, orthorhombic, $a = 16{\cdot}002(8)$, $b = 15{\cdot}284(8)$, $c = 10{\cdot}155(5)$ Å, $U = 2483{\cdot}7$ Å^3, $D_m = 1{\cdot}39(1)$, $D_c = 1{\cdot}39$ g cm^{-3}, $Z = 4$, space-group $P2_12_12_1$, $F(000) = 1080$. Single crystal *X*-ray data between the limits $6 < 2\theta < 50°$ were measured with a Philips PW1100 diffractometer, and using the ω-scan technique with graphite monochromated Mo-K_α radiation, 1717 unique data $[I > 3\sigma(I)]$ were recorded. The structure was solved by Patterson and Fourier techniques and refined using full-matrix least-squares methods. Hydrogen atom co-ordinates were calculated and the model was refined, using anisotropic thermal parameters for palladium, isotropic for all other species, to a current *R*-factor of 0·062 using unit weights for each observation. The absolute configuration was determined by comparing the *R*-factors for the model and its mirror image. The structure clearly shows that the palladium atom is α relative to the steroid skeleton, and carbon–palladium bond distances compare favourably with those found in other π-allyl palladium(II) complexes (Figure).[5]†

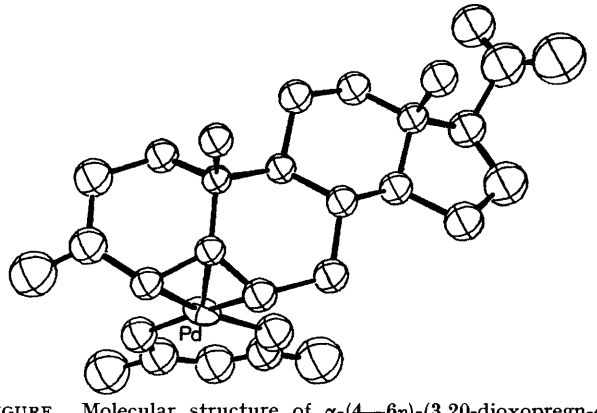
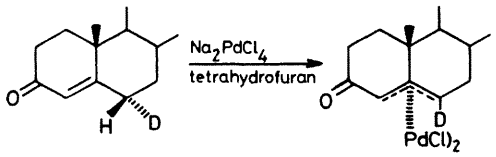


FIGURE. Molecular structure of α-(4—6η)-(3,20-dioxopregn-4-enyl)pentane-2,4-dionatopalladium(II).

† The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

[6α-^{2}H]Cholest-4-en-3-one (**1**) (93% ^{2}H) was prepared by an improved literature procedure.[6] Reaction with palladium chloride in dry tetrahydrofuran under reflux for 40 h gave the α-(4—6η)-PdCl complex (**2**) (38%). Careful integration of the signal at δ 3·4 (H-4) compared with that at δ 4·4 (H-6) showed a ratio of 100 (4-H) to 12·3 (6-H). Assuming that no exchange of H-4 for deuterium had occurred, the ^{2}H content of the allylpalladium compound was 87% showing that almost exclusive loss of 6β-H had occurred. Recovered cholestenone had 72·9% $^2H_1$ and 6·7% $^2H_2$ by mass spectrometry, showing that a small but significant amount of scrambling had occurred. ^{2}H N.m.r. spectroscopy was used in an attempt to estimate quantitatively how much deuterium had been scrambled into the 6β-position. Unfortunately the chemical shifts of the 6α- and 6β-deuterons, measured in pure 6β- and 6α-monodeuteriated cholest-4-en-3-one, were very close (2·33 and 2·27 p.p.m., respectively) and quantitative estimation was not possible. However, the recovered material was qualitatively shown to be mainly the [6α-^{2}H]steroid.



(1) 93% D (2) 87% D

Under similar conditions a sample of [6β-^{2}H]cholest-4-en-3-one (98% ^{2}H) gave the allylpalladium complex whose ^{1}H n.m.r. spectrum showed an average integral ratio of 100 (4H) to 85 (6H), again suggesting substantial loss of the 6β-^{2}H. However, recovered cholestenone now showed considerable deuterium loss ($^2H_0$, 43; $^2H_1$ 41; and $^2H_2$, 16%) suggesting that the ^{2}H which was retained in the allylpalladium compound could have arisen because of scrambling of deuterium into the unreactive 6α-position of cholestenone prior to reaction with Na_2PdCl_4. When calcium carbonate (4 mol. equiv.) was added to the reaction mixture, the recovered starting material showed far less scrambling ($^2H_0$, 19; $^2H_1$, 80; and $^2H_2$ 1%) but the allyl complex still showed an integral ratio of 100 (4H) to 80 (6H), similar to the previous reactions. Comparison of the results for reactions of the [6α-^{2}H]- and [6β-^{2}H]-cholestenones suggests that there is a significant primary kinetic isotope effect in the complex formation reaction, compatible with a rate-controlling step involving loss of 6β-hydrogen.

The results reported above clearly indicate highly stereoselective loss of 6β-^{1}H or ^{2}H during formation of α-(4-6η)-PdCl compounds. This could either be associated with the much greater reactivity of the pseudo-axial 6β-hydrogen (a reactivity ratio of 53:1 for 6β:6α hydrogens in base-catalysed enolisation has been quoted[7]) or a more general requirement for loss of hydrogen on the face *trans* to the incoming metal atom. In view of reported results for [6β-^{2}H]dimethylcholest-4-en-2-one[2] the latter explanation appears to be unlikely. Further investigations in a more flexible ring system support the former proposal.[8]

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