Syntheses of Steroidal π-Allyl Palladium Chloride Complexes†

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The reaction of the following steroidal olefins with palladium(II) chloride in the presence of potassium acetate in acetic acid afforded the corresponding steroidal π-allyl palladium chloride complexes: 5α-cholest-1-, -2-, and -3-ene; cholest-4- and -5-ene; 3-methyl- and 3-phenyl-5α-cholest-2-ene; 3β-chloro- and 3β-acetoxycholest-5-ene; and 5β-cholest-1-, -2-, and -3-ene.

There has been a considerable amount of work done on the syntheses of π-allyl palladium complexes in the area of the chain compound.[1] Also, in the case of monocyclic π-allyl palladium complexes, their syntheses have been reported for 1-*p*-menthen-3-ol,[2] 3-halocycloalkene,[3] β-pinene,[4] cycloalkene,[5] and alkylidenecycloalkanes.[5] On the other hand, with respect to steroids there have been no reports of syntheses except for the case of π-allyl palladium complexes of Δ^4-3-oxo steroids,[6] and of 5α-cholest-3-ene,[7] cholest-4-ene,[7] cholest-5-ene,[7] 5α-cholest-6-ene,[7] ergosterol,[8] and 3-methoxy-*cis*-19-norpregna-1,3,5(10),17(20)-tetraene.[10] These syntheses have mainly depended on methods using sodium tetrachloropalladate(II) or bis(benzonitrile)dichloropalladium(II). In addition, the preparations of π-allyl palladium complexes of chain compounds[11] using palladium(II) chloride and sodium acetate have also been described.

There is one report which does make some reference to a π-allyl palladium complex: F. J. McQuillin and D. G. Parker[12] reported that the reaction of (+)-3,7-dimethyl-1,6-octadiene with palladium(II) chloride and potassium acetate in acetic acid gave α-terpinyl acetate as the main product and π-allyl palladium complex as a minor product. However, there has been no report concerning the synthesis of cycloalkenyl π-allyl palladium complexes using palladium(II) chloride and potassium acetate. Hence, we attempted the syntheses of some steroidal π-allyl palladium complexes according to the procedures described by McQuillin and Parker. Not only did we want to demonstrate such syntheses, but we are planning a research project to investigate the stereospecificity of nucleophilic substitutions for the steroidal π-allyl palladium complexes.

In the present paper, we would like to report that the reaction of the following steroidal olefins readily yielded the corresponding steroidal π-allyl palladium chloride complexes: 5α-cholest-1- (**1**), -2- (**2**), and -3-ene (**3**); cholest-4- (**4**) and -5-ene (**5**); 3-methyl- (**6**) and 3-phenyl-5α-cholest-2-ene (**7**); 3β-chloro- (**8**) and 3β-acetoxycholest-5-ene (**9**), with a functional group at the C_3-position; and 5β-cholest-1- (**10**), -2- (**11**), and -3-ene (**12**).

Results and Discussion

The reactions of 5α-cholest-1- (**1**) and -2-ene (**2**) with palladium(II) chloride both yielded yellowish crystals (**19**); mp 154—159 °C. When **1** was used as the starting material, **2** was given in a 25% yield. It is considered that **1** was isomerized to the more stable 2-ene compound (**2**) by a 1:3 shift of a hydrogen from the allylic position to a double-bond carbon in the presence of palladium(II) chloride in acetic acid.[13] The NMR spectrum of **19** showed a multiplet at δ 4.9—5.6 ppm due to three protons. From this spectrum, however, it could not be determined whether the structure of **19** was of the 1-3η- or 2-4η-type; and so the following procedure was carried out: the 2α-bromo-5α-cholestan-3-one (**13**) was reduced with sodium borodeuteride to give the 3-deuteriobromohydrin (**14**). This bromohydrin was then converted to 3-deuterio-5α-cholest-2-ene (**15**). By treating **15** with palladium(II) chloride according to the method mentioned above, yellowish crystals (**19'**) were obtained. The NMR spectrum of **19'** showed AB-type signals, doublets (J=6.8 Hz) at δ 5.45 and 5.05 ppm. From this fact, complex **19** was confirmed to be a 1-3η-type complex, namely, di-μ-chloro-bis[(1-3η-5α-cholesten-2α-yl)palladium(II)], in which the palladium is coordinated at the α-face of the steroid, not showing the C-19 methyl signal in the low field.[7-9]

Similarly, 5α-cholest-3-ene (**3**) gave the α-3-5η-complex (**20**).[7] In the case of cholest-4-ene (**4**), a yellowish crystalline material was also obtained, and on chromatography two π-allyl complexes were yielded, which were confirmed to be α-3-5η- (**20**)[7] and β-3-5η-type complexes (**21**);[7] on the other hand, with cholest-5-ene (**5**) the two complexes which were obtained were crystals (**22**, mp 105—109 °C and **23**, mp 151—155 °C) which had α-5-7η- (**22**)[7] and α-4-6η-type (**23**)[7] structures.

The reaction of 3-methyl-5α-cholest-2-ene (**6**) gave complex (**24**); mp 161—165 °C. This product was presumed to be an α-1-3η-type complex from the AB-type signals due to the C_1–H and the C_2–H in its NMR spectrum. In the case of 3-phenyl-5α-cholest-2-ene (**7**), two compounds, **25** and **26**, were given. Compound **25** showed doublets due to the C_1- and C_2-protons at δ 4.80 and 5.30 ppm respectively in the NMR spectrum, while compound **26** showed two multiplets due to the C_2- and C_4-protons at δ 4.6—5.2 and 5.5—5.8 ppm respectively in the NMR spectrum. From these data, the two complexes were confirmed to be α-1-3η- (**25**) and α-2-4η-type complexes (**26**). These results suggest that the reaction of a 2-ene derivative possessing a methyl group at the C_3 position gives a product which has a greater regioselectivity than in the case of the phenyl group.

Similarly, the reaction of 3β-chloro- (**8**) and of 3β-acetoxycholest-5-ene (**9**) with palladium(II) chlo-

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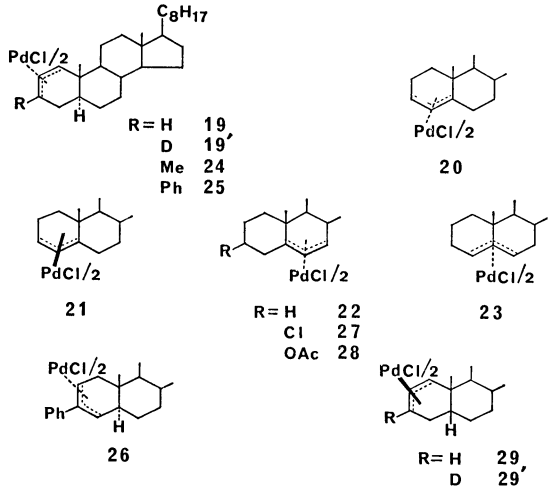
TABLE 1. YIELDS AND PHYSICAL DATA OF STEROIDAL π-ALLYL PALLADIUM CHLORIDE COMPLEXES (**19**—**29′**)

Materials	Products	Isolated yield/%	Mp(dec) °C	NMR ($CDCl_3$, δ/ppm)	Elemental analysis(%)
1	**19**	51	154—159	0.92 (s, 3H) 4.9—5.6 (m, 3H)	Found (Calcd for $C_{54}H_{90}Pd_2Cl_2$) C H 64.61 8.77 (63.40) (8.86)
2	**19**	61			
15	**19′**		157—160	0.92 (s, 3H) 5.05 (d, J=6.8 Hz, 1H) 5.45 (d, J=6.8 Hz, 1H)	
3	**20**[7]	48	165—168	0.90 (s, 3H) 4.81 (m, 1H) 5.12 (d, J=6.5 Hz, 1H)	63.42 8.90 (63.40) (8.86)
4	**20**[7]	30			
	21[7]	4	165—170	1.42 (s, 3H) 4.85 (m, 1H) 5.28 (d, J=6.5 Hz, 1H)	63.81 8.80 (63.40) (8.86)
5	**22**[7]	18	105—109	0.98 (s, 3H) 4.55 (dd, J=7.0 and 1.0 Hz, 1H) 5.14 (d, J=7.0 Hz, 1H)	63.86 8.95 (63.40) (8.86)
	23[7]	2	151—155	1.12 (s, 3H) 3.76 (m, 2H)	63.91 8.96 (63.40) (8.86)
6	**24**	65	161—165	0.92 (s, 3H) 4.79 (d, J=6.8 Hz, 1H) 5.27 (d, J=6.8 Hz, 1H)	Found (Calcd for $C_{56}H_{94}Pd_2Cl_2$) C H 63.90 8.86 (63.99) (9.01)
7	**25**	34	178—181	0.94 (s, 3H) 4.97 (d, J=7.1 Hz, 1H) 5.75 (d, J=7.1 Hz, 1H)	Found (Calcd for $C_{66}H_{98}Pd_2Cl_2$) C H 68.59 8.43 (67.45) (8.41)
	26	20	173—178	0.93 (s, 3H) 5.50—5.80 (m, 2H)	68.18 8.51 (67.45) (8.41)
8	**27**	60	123—126	1.03 (s, 3H) 4.45—5.00 (m, 1H) 4.71 (d, J=7.5 Hz, 1H) 5.21 (d, J=7.5 Hz, 1H)	Found (Calcd for $C_{54}H_{88}Pd_2Cl_4$) C H 59.96 8.24 (59.40) (8.12)
9	**28**	54	122—126	1.04 (s, 3H) 2.11 (s, 3H) 4.25 (d, J=7.5 Hz, 1H) 4.73 (d, J=7.5 Hz, 1H) 5.05—5.70 (m, 1H)	Found (Calcd for $C_{58}H_{94}O_4Pd_2Cl_2$) C H 61.06 8.39 (61.16) (8.32)
10	**29**	63	170—173	1.27 (s, 3H) 4.70—5.18 (m, 2H) 5.18—5.55 (m, 1H)	Found (Calcd for $C_{54}H_{90}Pd_2Cl_2$) C H 63.14 8.95 (63.40) (8.86)
11	**29**	76			
18	**29′**		157—160	1.28 (s, 3H) 5.05 (d, J=6.8 Hz, 1H) 5.45 (d, J=6.8 Hz, 1H)	
12	**21**[7]	58	165—170		



ride yielded 3β-chloro-α-5-7η- (**27**) and 3β-acetoxy-α-5-7η-type complexes (**28**) respectively. These structures were determined from the NMR spectra, which showed the doublets due to the C_6- and C_7-positions.

5β-Cholest-1- (**10**) and -2-ene (**11**) gave the same product (**29**). The NMR spectrum showed two multiplets at δ 5.18—5.55 ppm (1H) and at δ 4.70—5.18 ppm (2H). From the NMR spectrum, however, it could not be determined whether the structure of **29** was of the 1-3η- or 2-4η-type; therefore, the following procedure was carried out: the deuteride derivative, namely, 3-deuterio-5β-cholest-2-ene (**18**), was prepared from 2β-bromo-5β-cholestan-2-one (**16**) according to the procedure described for **15**. This structure was determined from the fact that no signal due to the C_3–H appeared in the NMR spectrum. The reaction of **18** with palladium(II) chloride gave a yellowish compound (**29'**). The NMR spectrum of **29'** showed doublets at δ 4.96 and 5.40 ppm and showed the C-19 methyl signal at δ 1.27 ppm.[7-9] From these data, compound **29'** was determined to be di-μ-chloro-bis[(1-3η-5β-cholesten-2β-yl)palladium(II)]. The reaction of 5β-cholest-3-ene (**12**) with palladium(II) chloride yielded a compound which was identical with the compound, **21**, obtained in the case of cholest-4-ene.

Thus, on the basis of all of the foregoing results, it can be concluded that the reagent used in this work [palladium(II) chloride containing potassium acetate in acetic acid] is applicable to the steroidal olefins. In the reaction of 5α- and 5β-steroidal olefins with this reagent, the former products were α-π-allyl palladium complexes, in which palladium coordinated at the α-face, while the latter products were β-π-allyl palladium complexes in which palladium coordinated at the β-face. These results are also in agreement with the facts that the α-face of 5α-steroidal olefins is less hindered than the β-face, and that the β-face of 5β-steroidal olefins is less hindered than the α-face.[14] This method showed more regioselectivity than the method using bis(benzonitrile)palladium chloride reported by Knox *et al.*[7]

Experimental

All the melting points are uncorrected. The IR and NMR spectra were measured using a Hitachi model 215 grating infrared spectrometer and a nuclear magnetic resonance spectrometer, Hitachi-Perkin Elmer R-20A, in carbon tetrachloride and deuteriochloroform, with TMS as the internal standard.

General Procedure. A mixture of steroidal olefin (1.30×10^{-3} mol), palladium(II) chloride (2.60×10^{-3} mol), potassium acetate (2.60×10^{-3} mol), and acetic acid (15 ml) was stirred at 55—60 °C. After 20—25 h, the reaction mixture turned to brownish yellow; and then it was filtered to remove the unchanged palladium(II) chloride. The filtrate was taken up in ether, and the ether extracts were washed with a sodium hydrogen carbonate solution and with water, and then dried and evaporated. The resultant oil was chromatographed on neutral aluminum oxide. Elution with benzene gave yellowish or greenish crystals from acetone.

Materials. The following compounds were synthesized by the methods described in literature: 5α-cholest-1-[15] (**1**), -2-[15] (**2**), and -3-ene[16] (**3**); cholest-4-[17] (**4**) and -5-ene[18] (**5**); 3-methyl-[19] (**6**) and 3-phenyl-5α-cholest-2-ene[20] (**7**); 3β-chloro-[18] (**8**) and 3β-acetoxycholest-5-ene[21] (**9**); and 5β-cholest-1-[22] (**10**), -2-[22] (**11**), and -3-ene[23] (**12**).

*Synthesis of 3-Deuterio-5α- (**15**) and 3-Deuterio-5β-cholest-2-ene (**18**).* A mixture of 2α-bromo-5α-cholestan-3-one (**13**) (100 mg) and methanol-d_1 was treated with sodium borodeuteride (80 mg) with at room temperature. After 1 h, water was added and the mixture was extracted with ether. The ethereal solution was washed with water, dried, and evaporated under reduced pressure. The resultant oil, on crystallization from methanol, gave needles of 3-deuteriobromohydrin (**14**) (53 mg); mp 103—105 °C, IR (KBr): 3400 cm^{-1}, NMR (CCl_4): δ=4.05 (1H, q, J=12 and 4.5 Hz). A mixture of **14** (50 mg) and zinc powder in acetic acid was stirred under refluxing conditions. After the usual work-up, the resultant oil, on crystallization from acetone, gave needles of **15** (33 mg); mp 73—74 °C, IR (KBr): 1640 cm^{-1}; NMR (CCl_4): δ=5.50 (1H, m, $W/2$=7.5 Hz). The reduction of 2β-bromo-5β-cholestan-3-one (**16**) (233 mg) was done in accordance with the procedure described for **14**. Attempts to crystallize the resultant oil (**17**) were unsuccessful, and so the products were used in the next step without purification [IR (NaCl): 3384 cm^{-1}]. A mixture of the 3-deuteriobromohydrin (**17**) (200 mg), zinc powder, and acetic acid was stirred under refluxing conditions. After the usual work-up, the resultant oil, on crystallization from acetone, gave needles of **18** (108 mg); mp 46.5—47.5 °C, IR (KBr): 3025, 2250, and 1647 cm^{-1}; NMR (CCl_4): δ=5.45 (1H, m, $W/2$=10.5 Hz).

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