Catalytic Oxygenation of Cholesterol with a Platinum Catalyst under Moderate Pressure of Oxygen

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Synopsis. The catalytic oxygenation of cholesterol **1** with a platinum black catalyst under moderate pressure (20—25 atm) of oxygen yielded eleven oxidation products, **3**—**13a**. The reaction pathway of the catalytic oxygenation is discussed on the basis of the results for several reaction conditions.

Although the autoxidation of cholesterol (**1**) has been well-known for a long time, its mechanism has recently been clarified by Smith et al.[1a,b] On the other hand, Sneeden and Turner[2] performed the catalytic oxygenation of various steroidal alcohols with a platinum black catalyst (platinum catalyst) at ordinary pressures of oxygen and reported that the reaction proceeded easily, though their attempts concerning the catalytic oxygenation of **1** failed. However, in our previous paper[3] we reported success with the catalytic oxygenation of **1** with a platinum catalyst at room temperature under ordinary pressure of oxygen.

In this paper, we describe the structure of new products obtained by performing the catalytic oxygenation of **1** with a platinum catalyst at 80 °C under ordinary pressure and at 90 °C under moderate pressure (20—25 atm) of oxygen.

In the catalytic oxygenation of cholestanol with a platinum catalyst, the yield of cholestanone varied according to the method of preparing the platinum catalyst. Therefore, in order to investigate the catalyst activity, we performed the catalytic oxygenation of cholestanol using a platinum catalysts prepared under various conditions in ethyl acetate at room temperature for 24 h under ordinary pressures of oxygen, and obtained the results shown in Fig. 1. From the experimental results, it was found that the maximum yield (78%) of cholestanone was obtained when the platinum catalyst prepared by reducing platinum oxide (100 mg; 4.4×10^{-4} mol) with hydrogen (45 ml; 2.0×10^{-3} mol) was used.

For the catalytic oxygenation of **1** at moderate pressures of oxygen, we used the method of Sneeden and Turner.[2] The results of the catalytic oxygenation of **1** at ordinary pressure and at moderate pressure of oxygen performed using platinum catalyst under various conditions are given in Table 1. These oxidation products (**3**—**13a**) were directly identified by comparing them with the authentic samples by a known preparation method.[4-6]

The catalytic oxygenation of **1** with a platinum catalyst at 80 °C under ordinary pressure of oxygen gave oxidation products **3**—**9** with a good yield. In addition to the above products **3**—**9**, the reaction products **10**, **11**, and acidic substances **12a**, **13a** were newly isolated by the catalytic oxygenation of **1** using a catalytic amount of platinum catalyst under a moderate oxygen pressure. This was considered attributable to the effect of applying the moderate oxygen pressure, with the oxidation products **10**, **11**, and the acidic substances **12a**, **13a** being obtained only under a moderate pressure of oxygen.

According to the experimental results, the order on the oxidation position of cholesterol **1** is: hydroxyl group at C-3 > allylic hydrogen at C-7 > 5,6-double

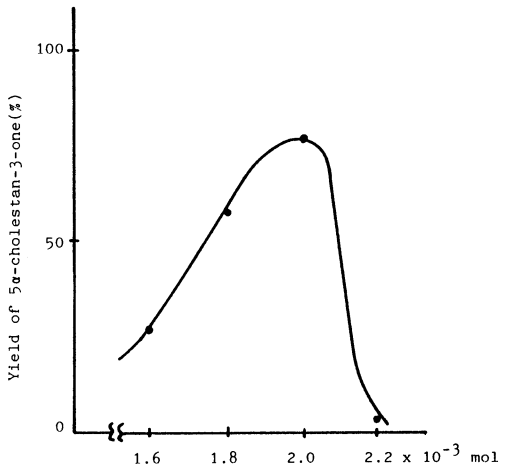

Fig. 1. Catalyst activity of platinum catalyst. Reaction conditions. Substrate: 5α-cholestane-3β-ol (100 mg, 2.5×10^{-4} mol); catalyst: PtO_2 (100 mg, 4.4×10^{-4} mol); O_2-absorption volume (10 ml, 4.5×10^{-4} mol); solvent: EtOAc (3 ml); temperature: room temp; reaction time: 24 h.

Table 1. Composition of the Catalytic Oxygenation Products

Substrate	Composition of the oxygenation products (%)											
	Recov.	Neutral products									Acidic products		Others
	1	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12a**	**13a**	
1[a]	24.7	3.8	16.4	24.9	7.7	3.9	4.9	8.9					4.8
1[b]	36.9	2.7	12.4	11.7	2.8	3.9	1.7	13.0	3.5	1.3	1.8	2.7	5.6

a) Ratio of **1**: Pt (1 : 1); temp 80 °C; O_2-pressure 1 atm; solvent EtOAc; time 24 h. b) Ratio of **1**: Pt (1 : 0.1); temp 90 °C; O_2-pressure 20—25 atm; solvent *t*-BuOH; time 24 h.

Table 2. Composition of the Catalytic Oxygenation Products for Some Steroids

Substrates	Recov. substrate	Composition of the oxygenation products (%)								
		6	**7**	**8**	**9**	**10**	**11**	**12a**	**21**	Others
6[a]		37.9						47.9		14.2
10[a]						11.0	79.9			9.1
16[c]			56.2	2.6	39.7					1.5
18[b]	29.2	5.0				59.6	4.5			1.7
20[c]			6.0						94.0	

a) Ratio of **1**: Pt (1 : 1); O_2-pressure 20—25 atm; solvent *t*-BuOH; temp 80 °C; time: 24 h.
b) Ratio of **1**: Pt (1 : 1); O_2-pressure 1 atm; solvent 2%-aq. Me_2CO; temp 80 °C; time 24 h.
c) Ratio of **1**: Pt (1 : 1); O_2-pressure 1 atm; solvent *t*-BuOH; temp: room temp; time 24 h.

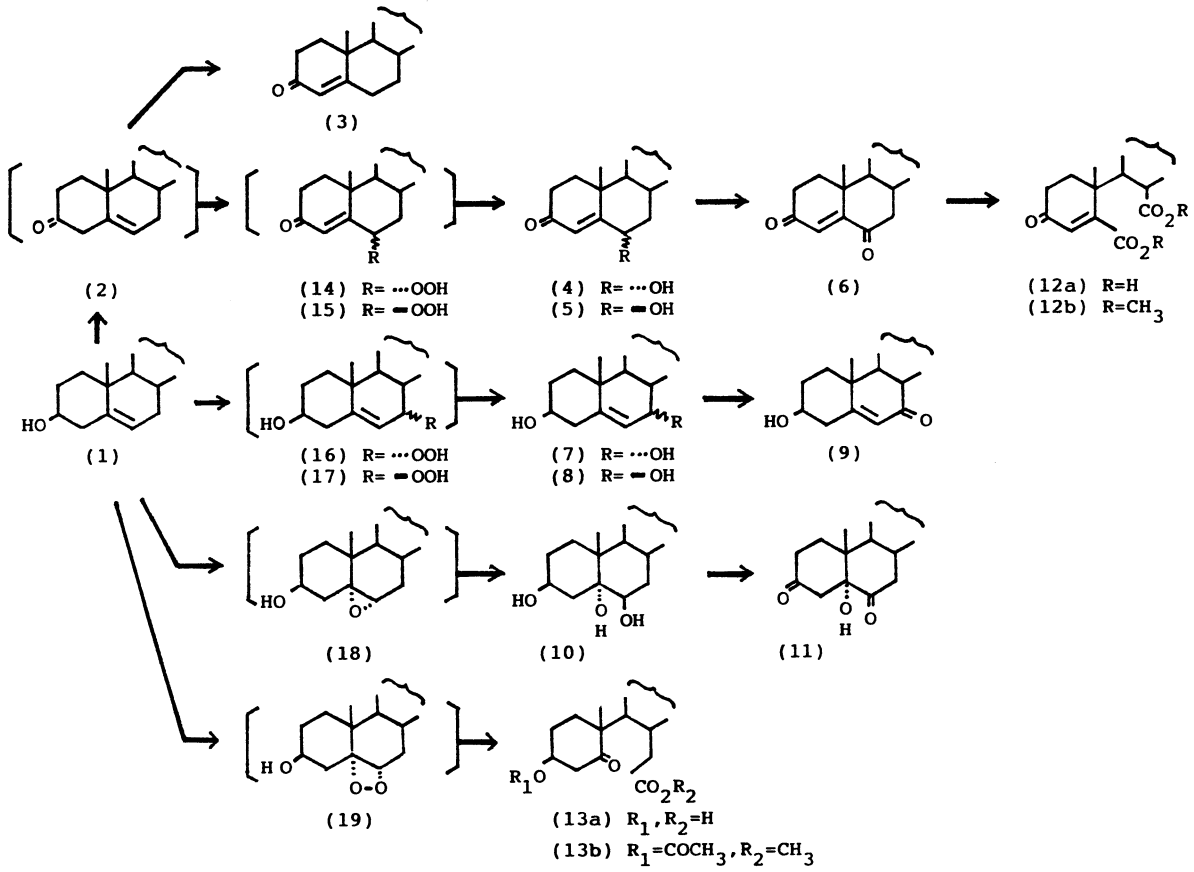

Fig. 2. Proposed pathways for the catalytic oxygenation of cholesterol (**1**).

bond.

The pathway of this catalytic oxygenation under moderate pressure of oxygen, presumed from the obtained oxidation product, is shown in Fig. 2. The courses of formation from **1** to **3** and **6** were shown in our previous paper.[3] In order to confirm the formation of the 6,7-seco acid **12a**, we performed catalytic oxygenation of diketone **6** with a platinum catalyst under a moderate pressure of oxygen with the result that **12a** was formed in a yield of 47%, as shown in Table 2. Therefore, **12a** was confirmed to be formed from **1** via **6**.

As for the formation of the 7-oxo compound **9**, it was assumed that there are two pathways: one is the pathway in which the 7α-hydroperoxide (**16**)[8] is directly formed and another is the course in which the 5α-hydroperoxide (**20**)[7a] is formed as is known to be formed by autoxidation[1a,b] and photoxidation.[7a,b] In order to confirm these pathways, the catalytic oxygenation of **16** with a platinum catalyst under ordinary pressure of oxygen was performed to give 3β,7α-diol **7** and **9** in yields of 56.2 and 39.7% respectively. On the other hand, 3β,5α-diol (**21**)[7a] was formed at a yield of 94% by catalytic oxygenation of **20** under these same conditions.

Therefore, in the catalytic oxygenation of **1**, it has become clear that the intermediate **16** is formed by the direct abstraction of the hydrogen of the allylic position at C-7 with the platinum catalyst, and an attack of oxygen; then **7** is formed with the reduction by hydrogen on the platinum catalyst and is further oxidized to give **9**.

In order to investigate the course of formation of hydroxy diketone **11**, catalytic oxygenation of 5,6α-epoxycholestan-3β-ol (**18**)[9] with a platinum catalyst in 2%-aqueous acetone at 80 °C under ordinary pressure of oxygen was performed to afford triol **10** with a yield of 59.6%. Furthermore, catalytic oxygenation of **10** with the platinum catalyst in *t*-butyl alcohol at room temperature under ordinary pressure of oxygen was performed to give **11** with a yield of 79.9%. These experimental results showed that the epoxide **18** was an intermediate in the formation of **11**.

Finally, regarding the pathway of the formation 5,6-seco acid **13a**, we have presumed that it is formed via the 5,6-dioxetane (**19**).[10a,b] We have inferred that the catalytic oxygenation of **1** with the platinum catalyst is considered a radical reaction, including the four pathways (Fig. 2).

Experimental

All melting points are uncorrected. IR spectra were obtained in KBr on a JASCO IR-G instrument. ^{1}H NMR were measured at 100 MHz using deuteriochloroform as the solvent. The chemical shift are given in ppm using tetramethylsilane (TMS) as an internal standard on a JNM-FX100 instrument. The mass spectra were recorded on a Hitachi RMU-7M system at 70 eV. GLC was performed on a Shimadzu GC-9A gas chromatography equipped 2%OV-17 (3 m×5 mm) at 300 °C and a SCOT OV-17 glass capillary column (30 m×0.3 mm).

Material and Authentic Specimens. Cholesterol (**1**) was a commercial source (Riken Vitamin Co. (Tokyo)) and purified by acetylation, hydrolysis and repeated recrystallization from methanol. The authentic specimens of cholest-4-en-3-one (**3**, mp 76—79 °C),[4a] 6α-hydroxycholest-4-en-3-one (**4**, mp 155—156 °C),[4b] 6β-hydroxycholest-4-en-3-one (**5**, mp 184—185 °C,[4b] cholest-4-ene-3,6-dione (**6**, mp 124—125 °C),[4b,c] cholest-5-ene-3β,7α-diol (**7**, mp 188—189 °C),[4d] cholest-5-ene-3β,7β-diol (**8**, mp 177—178 °C),[4d] 3β-hydroxycholest-5-en-7-one (**9**, mp 169—170 °C),[4d,e] cholestane-3β,5α,6β-triol (**10**, mp 236—238 °C),[4f] IR(KBr) ν 3400 cm^{-1} (OH); ^{1}H NMR ($CDCl_3$) (diacetate) δ=0.69 (3H, s, 18-CH_3), 1.15 (3H, s, 19-CH_3), 2.02 (3H, s, 6-OCOCH_3), 2.07 (3H, s, 3-OCOCH_3), 4.69 (1H, br.s *w*/2=6 Hz, 6-H), 5.15 (1H, m, *w*/2=24 Hz, 3-H); MS Found: *m*/*z* 420.3572. Calcd for $C_{27}H_{48}O_3$: M, 420.3591; 5α-hydroxycholestane-3,6-dione (**11**, mp 230—231 °C),[4b] IR(KBr) ν 3300 cm^{-1} (OH), 1710 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ=0.68 (3H, s, 18-CH_3), 1.01 (3H, s, 19-CH_3); MS Found: *m*/*z* 416.3245. Calcd for $C_{27}H_{44}O_3$: M, 416.3279; dimethyl 3-oxo-6,7-seco-cholest-4-ene-6,7-dioate (**12b**, mp 137—139 °C),[5] IR(KBr) ν 1735, 1720 cm^{-1} (OAc), 1690 cm^{-1} (C=O), 1660 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$) δ=0.64 (3H, s, 18-CH_3), 1.37 (3H, s, 19-CH_3), 3.67 (3H, s, 7-CO_2CH_3), 3.81 (3H, s, 6-CO_2CH_3), 6.49 (1H, s, 4-H); MS Found: *m*/*z* 474.3293. Calcd for $C_{29}H_{46}O_5$: M, 474.3333; methyl 3β-acetoxy-5-oxo-5,6-seco-cholestan-6-oate (**13b**, amorphous),[6] IR(KBr) ν 1735 cm^{-1} (OAc), 1715 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ=0.68 (3H, s, 18-CH_3), 1.04 (3H, s, 19-CH_3), 2.01 (3H, s, 3-OCOCH_3), 3.58 (3H, s, CO_2CH_3); MS Found: *m*/*z* 430.3429. Calcd for $C_{30}H_{50}O_5$: M, 490.3435, M−CH_3CO_2H, 430.3435; 7α-hydroperoxycholest-5-en-3β-ol (**16**, mp 150—152 °C),[8] 5α-hydroperoxycholest-6-en-3β-ol (**20**, mp 149—150 °C),[7a,b] 5,6α-epoxycholestan-3β-ol (**18**, mp 141—142 °C),[9] IR(KBr) ν 3380 cm^{-1} (OH); ^{1}H NMR ($CDCl_3$) δ=0.68 (3H, s, 18-CH_3), 1.18 (3H, s, 19-CH_3), 3.54 (1H, br.s *w*/2=6 Hz, 6-H); MS Found: *m*/*z* 402.3492. Calcd for $C_{27}H_{46}O_2$: M, 402.3486; cholest-6-ene-3β,5α-diol (**21**, mp 148—149 °C)[7a,b] IR(KBr) 3610, 3400, 3300 cm^{-1} (OH); ^{1}H NMR ($CDCl_3$) δ=0.70 (3H, s, 18-CH_3), 0.95 (3H, s, 19-CH_3), 4.07 (1H, m *w*/2=24 Hz, 3-H), 5.59 (2H, br.s, *w*/2=4.5 Hz, CH=CH); MS Found: *m*/*z* 402.3482. Calcd for $C_{27}H_{46}O_2$: M, 402.3486; were prepared and purified as reported in references.

Catalytic Oxygenation of Cholesterol with Platinum Catalyst under Moderate Pressure of Oxygen. Platinum oxide (200 mg) was reduced to platinum black with hydrogen (60 ml) in *t*-butyl alcohol (10 ml) and then hydrogen was carefully replaced with air. The system filled with oxygen and catalyst was absorbed with oxygen (10 ml).

A solution of *t*-butyl alcohol (100 ml), platinum catalyst (200 mg), and cholesterol (**1**, 2g) was added to autoclave and the system was filled with oxygen (20—25 atm) and stirred at 90 °C for 24 hours. After reaction ceased, catalyst was removed by filtration and then the filtrate was concentrated to dryness at 40 °C under reduced pressure. Resulting reaction products were poured into ether and a treatment with 5%-Na_2CO_3 solution gave an acidic portion (160 mg, 8%) and a neutral portion (1.8 g, 90%). A portion of neutral product was separated on alumina column chromatography, TLC, and HPLC, while the other portion was analyzed by GLC as TMSE derivative. Acidic product was methylated with diazomethane and then acetylated with acetic anhydride-pyridine. A portion of the acidic products were separated on silica gel column chromatography, while the other portion was analyzed by GLC. All of the above oxidation products were identified by comparing with authentic sample by a known method.[4-6]

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