Platinum-Catalyzed Oxidation of Cholesterol

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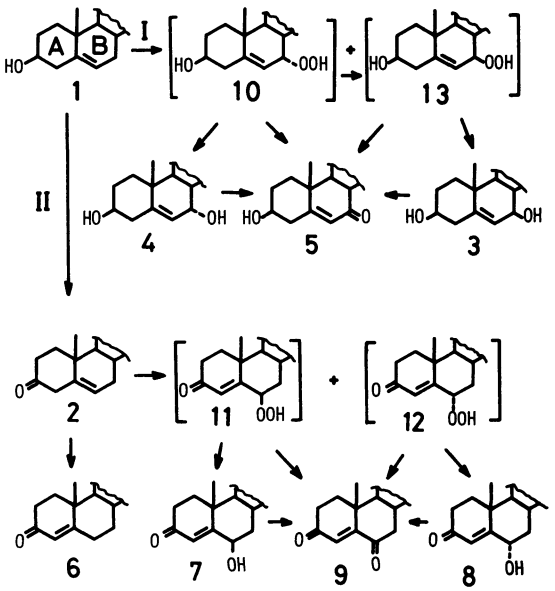
Synopsis. Cholesterol was oxidized (12% conversion) with platinum and oxygen to give several 7-oxygenated products, cholest-5-en-3-one, and cholest-4-en-3-one accompanied with its further oxygenation products at C-6. The pathways and mechanisms of the catalytic oxidation are discussed.

Platinum-catalyzed oxidation[1] has been used successfully for the oxidation of saturated sterols including 5α-cholestan-3β-ol and its 3α-epimer by Sneeden and Turner.[2] The attempts at the oxidation of cholesterol (cholest-5-en-3β-ol, **1**) have, however, met with failure.[2] This paper describes our reinvestigation of the oxidation of **1** with platinum and oxygen, which demonstrated that **1** undergoes catalytic oxidation.

The oxidation of **1** was performed by oxygen over prereduced platinum in ethyl acetate at the ambient pressure and temperature to yield Δ^5- (**2**, **3**, **4**, and **5**) and Δ^4- (**6**, **7**, **8**, and **9**) oxidation products as summarized in Table 1, most of which are known to be autoxidation products of **1**.[3-6] The oxidation of the Δ^5-3-one **2** under the same conditions yielded the Δ^4-3-one **6** and the 6-oxygenated products, **7**, **8**, and **9**, whereas the oxidation of **6** yielded only the unaltered substrate. The controlled oxidation of **1** and **2** in the absence of the catalyst afforded only the unchanged starting material. From the above, it can be assumed that there are two pathways (**I** and **II**) for the catalytic oxidation of **1**, as is illustrated in Scheme 1.

The first, minor, one (**I**) is to form the allylic oxygenation products: **3**, **4**, and **5**. These 7-oxygenated products are well-known radical autoxidation products of **1** and have been established to be formed via the initial formation of the 7-hydroperoxides (**10** and **13**), followed by thermal decomposition.[3-5] Although these hydroperoxides were not detected in the present oxidation of **1**, we suppose that the initial formation of **10** and **13** is also involved in the catalytic oxidation



Scheme 1. Proposed pathways for the platinum-catalyzed oxidation of cholesterol (**1**).

of **1**, which might be, in situ, decomposed over the catalyst to afford the 7-ols **3** and **4** and the 7-ketone **5**. The attempted catalytic oxidation of the 7α-hydroperoxide **10** yielded **3**, **4**, and **5**, with no substrate being recovered, while **10** remained mostly unaltered upon controlled oxidation in the absence of the catalyst, thus suggesting the lability of hydroperoxide over the platinum catalyst. The 7β-ol **3** might arise from **10** through epimerization to the 7β-hydroperoxide **13**, followed by decomposition, the epimerization of which was previously observed in a solution of ethyl acetate and some other solvents.[3]

The second, major pathway (**II**) of the catalytic oxidation of **1** is that proceeding via the dehydrogena-

Table 1. Compositions (%) from the Platinum-Catalyzed Oxidation of Cholesterol and Some Other Steroids[a]

Substrate	Substrate reacted	Composition/% of the products								
		2	**3**	**4**	**5**	**6**	**7**	**8**	**9**	Others, unidentified
Cholesterol (**1**)	12.2	0.8	1.6	0.8	0.4	0.8	15.5	31.1	31.1	17.9
Cholest-5-en-3-one (**2**)	89.5					1.8	20.0	18.3	29.3	30.6
Cholest-5-ene-3β,7β-diol (**3**)	13.9				32.4					67.9
Cholest-5-ene-3β,7α-diol (**4**)	26.3				4.2					95.8
Cholest-4-en-3-one (**6**)	0									
6β-Hydroxycholest-4-en-3-one (**7**)	48.1								62.8	37.2
6α-Hydroxycholest-4-en-3-one (**8**)	20.1								58.7	41.3
7α-Hydroperoxycholest-5-en-3β-ol (**10**)	100		18.4	53.9	29.7					
6β-Hydroperoxycholest-4-en-3-one (**11**)	100						56.4		36.6	7.0
6α-Hydroperoxycholest-4-en-3-one (**12**)	100							62.9	29.1	8.0

a) **5**, 3β-Hydroxycholest-5-en-7-one; **9**, cholest-4-ene-3,6-dione.

Table 2. Melting Points, Chromatographic Data, and ^{1}H NMR Data of Some Steroids

Steroid	Mp θ_m/°C	RRT		^{1}H NMR data[b]					
		GLC[a]	HPLC	18-H_3(*s*)	19-H_3(*s*)	3α-H(*m*)	4-H	6-H	7-H
1	149—150	1.00	1.00	0.69	1.02	3.53(26)	—	5.35(m, 9)	—
2	130—131	1.92	0.80	0.71	1.19	—	—	5.33(m, 9)	—
3	170—174	1.19	0.18	0.70	1.04	3.53(25)	—	5.29(br. s)	3.86(m, 18)
4	178—182	0.82	0.17	0.69	1.01	3.50(25)	—	5.61(d, 4.8)	3.86(m,13)
5	168—170	2.49	0.29	0.68	1.20	3.63(26)	—	5.69(s)	—
6	80—82	1.92	0.64	0.71	1.18	—	5.72(s)	—	—
7	197—199	1.67	0.92	0.74	1.37	—	5.80(s)	4.35(m, 8)	—
8	161—164	2.41	0.20	0.71	1.18	—	6.17(d, 2)	4.33(m, 20)	—
9	123—125	3.30	0.22	0.72	1.16	—	6.17(s)	—	—
10	154—155	3.30	0.14	0.66	0.99	3.60(22)	—	5.73(d, 4.9)	4.16(m, 10)
11	176—178	3.30	0.23	0.71	1.33	—	5.88(s)	4.44(m, 7)	—
12	150—154	3.30	0.18	0.71	1.20	—	6.14(d, 2)	4.62(m, 22)	—

a) The RRTs of **2**, **6**, and **9** corresponded to the ketones, and those of the other steroids corresponded to the TMSE derivatives. The RRTs of **10**, **11**, and **12** were for GLC decomposition products. b) Gvien as δ values. Figures in parentheses denote *J* values (Hz) for doublet signals, whereas $W_{1/2}$ values (Hz) for multiplet signals. The signals at δ 0.87 (6H, *d*, *J*~6 Hz, 26-H_3, 27-H_3) and 0.92 (3H, *d*, *J*~5 Hz, 21-H_3) also were observed for all of the steroids. s: singlet, d: doublet, m: multiplet.

tion to afford the ketone **2** as the primary product. Upon isomerization, this yields conjugated ketone **6**, not further oxidized, and upon a second oxidation it yields the epimeric 6-hydroxy ketones **7** and **8**. These 6-ols are known to be formed from the ketone **2**, accompanied by the 6-hydroperoxides **11** and **12** and other products, by irradiation in air using ^{60}Co gamma radiation,[6] and by autoxidation in acetic acid.[7] Although we did not detect the 6-hydroperoxides **11** and **12** in the present oxidation of **1**, we consider the involvement of the 6-hydroperoxides in the catalytic oxidation to be as likely as in the autoxidation of **1**;[6] they may be involved as intermediates which might be decomposed, in situ, to form the epimeric 6-ols **7** and **8** and diketone **9**. The attempted oxidation of **11** and **12** in the presence of platinum yielded the 6-ols **7** and **8** respectively in addition to **9**, while no starting material was recovered. The formation of the ketones **6** and **9** is also known in the oxidation of **1** promoted by the Ni-Cr-O catalyst in xylene under reflux.[8]

Thus, **1** has undergone catalytic oxidation with platinum and oxygen under ambient pressure and temperature to yield several dehydrogenated and oxygenated products. The oxygenation of **1** in the catalytic oxidation is considered to proceed by means of a free-radical-type reaction promoted by platinum catalyst. Although saturated sterols have been oxidized successfully by the catalytic oxidation,[2] the reactivity of **1** in the catalytic oxidation was found to be extremely low (12% conversion) in this study. Such a low reactivity of **1** might be attributed to its 3β-hydroxy-Δ^5 structure since the other 3β-hydroxy-Δ^5-sterols **3** and **4**, which possess an additional hydroxyl group at C-7, also remained mostly unaltered by the catalytic oxidation. The oxidation has been found to proceed preferentially on the axial hydroxyl group rather than on the equatorial one as for the epimeric 6-hydroxy steroids **7** and **8** although the selectivity was not so clear cut as that of carbohydrates.[1] Table 2 showed the melting points, and chromatographic and ^{1}H NMR spectroscopic data of twelve steroids (**1**—**12**). The ^{1}H NMR spectroscopy has distinguished unequevocally between each of the double bond- and stereo-isomers of steroids. The ketone **2** was indistinguishable from conjugated ketone **6** in GLC which suggested the formation of **6** from **2** by thermal isomerization during GLC. The GLC peaks of the hydroperoxides **10**, **11**, and **12** were considered to be corresponded to the thermal decomposition products.[9]

Experimental

General Methods and Materials. The melting points are uncorrected. The HPLC was carried out on a Partisil 5 ODS-2 column (25 cm×10 mm i.d., two columns in series) using a UV detector (monitored at 212 nm) or a RI detector with MeOH as mobile phase. The GLC was performed with a SCOT OV-17 glass capillary column (30 m×0.3 mm i.d.) at 260 °C. The RRTs (relative retention times) in the HPLC and GLC were expressed relative to **1** and the trimethylsilyl ether (TMSE) derivative of **1**, respectively. The EI-MS spectra (70 eV) were taken by means of a probe injection. The ^{1}H NMR spectra (100 MHz) were obtained in a $CDCl_3$ solution, with Me_4Si as the internal standard. The thin-layer chromatography (TLC) was performed on plates of precoated silica gel. A commercial sample of **1** was purified through the dibromide by the method of Shoenheimer.[10,11] The other steroids were prepared from **1** as has previously been described.[12] All the steroid samples for the oxidation, which were identified on the basis of the mp, and the chromatographic and spectroscopic data, were recrystallized from MeOH or from MeOH-H_2O mixture several times and did not contain any detectable levels of autoxidation products.

Oxidation of Steroids and Analysis of the Oxidation Products. The oxidation was performed in a way similar to that described by Sneeden and Turner.[2] A suspension of PtO_2 (50 mg) in EtOAc (15 ml) was first reduced to Pt in an atmosphere of H_2, after which the H_2 was carefully replaced with air by repeated evacuation. The system was then filled with O_2, and the catalyst suspension was stirred until the uptake of O_2 ceased. The sample (50 mg) was added, the system was filled again with O_2, and the reaction was continued for 24 h at ambient pressure and temperature. The product was then passed through a short Florisil column in

order to remove the catalyst. A portion of the product was analyzed and fractionated by HPLC, while the other portion was analyzed by GLC as the TMSE derivatives. Steroid hydroperoxides were detected on TLC by spraying with *N,N*-dimethyl-*p*-phenylenediamine.[6] The oxidation products were identified on the basis of mp, and the chromatographic and spectroscopic data after isolation.

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