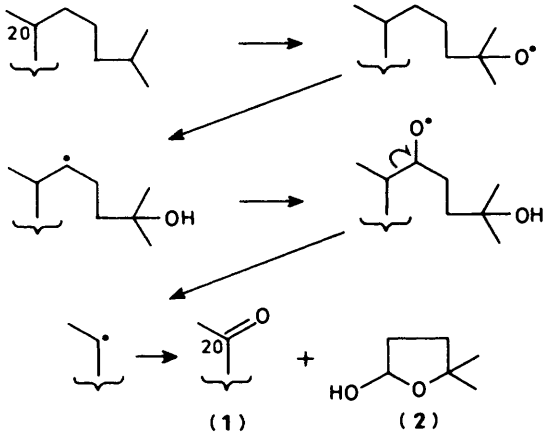
Functionalisation of Saturated Hydrocarbons. Part 7.[1] On the Mechanism of the Degradation of the Cholesterol Side-chain to 20-Ketone by Oxidation with the Gif System

Derek H. R. Barton,* Jean Boivin, David Crich, and Christopher H. Hill
Institut de Chimie des Substances Naturelles, C.N.R.S. 91190 Gif-sur-Yvette, France

The oxidation by the Gif system of the two dienones (**3**) and (**15**) which lack a 25-H still affords minor amounts of the 20-ketone (**12**). This indicates that there are two mechanisms for the degradation of the cholesterol side-chain, the major route as previously proposed and a minor route the nature of which has been briefly discussed.

Oxidation of cholesterol derivatives by the Gif system (see previous paper) affords the 20-ketone (**1**), usually as the major isolated product. A mechanism has been proposed[2] for this degradation which can be summarised as in Scheme 1. Besides the 20-ketone (**1**) the rest of the side-chain is represented by the tetrahydrofuran derivative[2] (**2**).



Scheme 1.

It seemed to us that a good test for the validity of Scheme 1 would be the oxidation of 25-methylcholesterol derivatives. Lacking the 25-hydrogen necessary for side-chain fragmentation these should afford only oxo derivatives of the parent compound.

25-Methylcholesta-1,4-dien-3-one (**3**) was selected as a suitable candidate, primarily because the corresponding cholesta-1,4-dien-3-one gave a good yield of 20-ketone.[1] In addition, from a synthetic viewpoint, the dienone system could be obtained equally well from either the 5α- or 5β-saturated 3-ketones.

The acetate of lithocholic acid (**4**) was chosen as the starting material. It was readily converted into the acid chloride (**5**) with oxalyl chloride in benzene. This was treated with the sodium salt of *N*-hydroxypyridine-2-thione to form the corresponding heterocyclic ester (**6**), which was radically decarboxylated[3] *in situ*, using bromotrichloromethane as solvent to give the bromonorcholane derivative (**7**) in 71% yield. Conversion of the bromide (**7**) into the corresponding phosphonium salt (**8**) proceeded smoothly in refluxing acetonitrile. Reaction of the phosphonium salt (**8**) successively with butyl-lithium and 2,2-dimethylpropanal resulted in the formation of the olefin (**9**) as a mixture of geometrical isomers in 51% yield. Subsequent reduction of the double bond with 10% palladium charcoal under hydrogen at atmospheric pressure gave the 25-methyl side-chain derivative (**10**). Ester hydrolysis and Jones' oxidation gave the ketone (**11**) in 66% overall yield. The double dehydrogenation of the ketone to the desired dienone (**3**) was achieved in 68% yield with 2 equiv. of benzeneseleninic acid.[4]

Table. Yields (%) of 15- and 20-keto oxidation products based on consumed starting material

Steroid position	(13)	(3)	(15)
15-Ketone	1.0	2.3	
20-Ketone	9.4	2.4	2.7

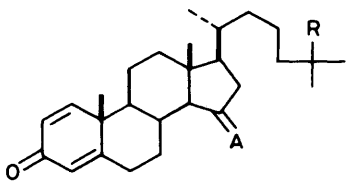
Oxidation of the dienone (**3**), however, did give a minor amount of 20-ketone (**12**) (see Table). Careful isolation of this product showed that it was present in 25% of the quantity obtained in the oxidation of cholesta-1,4-dien-3-one (**13**). Evidently, initial attack at C-25 is not the only route to the 20-ketone, but it does nonetheless appear to be the major pathway. The only other oxidation product isolated from this reaction was the 15-ketone (**14**). The absence of the 24-ketone presumably reflects the increased steric congestion around C-24.

Further evidence for the initiation of the side-chain cleavage occurring mainly at the terminal end was obtained by oxidising a steroid with a shortened side-chain. The dienone (**15**) was selected as a suitable substrate, since it contained identical A-ring functionality to the two previous examples and was readily accessible from the acetate of lithocholic acid (**4**) by reductive decarboxylation of the heterocyclic ester (**6**) in the presence of 1,1-dimethylethanethiol.[5] The 3α-acetoxynorcholane (**16**) (79%) thus produced was readily converted into the ketone (**17**) by acetate hydrolysis, followed by Jone's oxidation. This ketone was doubly dehydrogenated to the desired material (**15**) (78%) with benzeneseleninic acid as before. Gif oxidation of (**15**) again yielded the 20-ketone (**12**) with the same reduced yield as in the oxidation of the dienone (**3**).

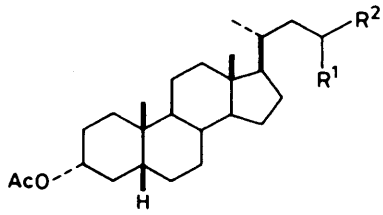
Thus, we propose that a minor pathway for formation of the 20-ketone could involve hydrogen abstraction from the tertiary 20-position with or without formation of an iron–carbon sigma bond[6] (see Scheme 2). There are, of course, other more complex possibilities. Such a pathway would also apply for compounds with a 25-H.

Experimental

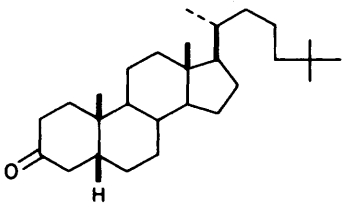
The general Experimental was as in the preceding paper (Part 6). The general oxidation procedure using the Gif system was also as described in Part 6.



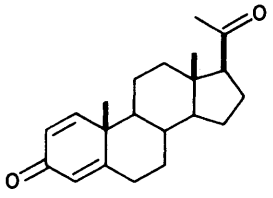
(3) A = H_2, R = Me
(13) A = H_2, R = H
(14) A = O, R = Me



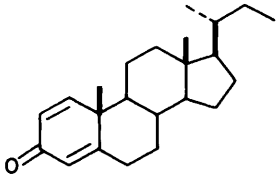
(4) R^1 = CO_2H, R^2 = H
(5) R^1 = COCl, R^2 = H
(6) R^1 = (2-thioxodihydro-1-pyridyl)CO_2, R^2 = H
(7) R^1 = Br, R^2 = H
(8) R^1 = $PPh_3^+Br^-$, R^2 = H
(9) R^1, R^2 = $CHBu^t$
(10) R^1 = CH_2Bu^t, R^2 = H



(11)



(12)



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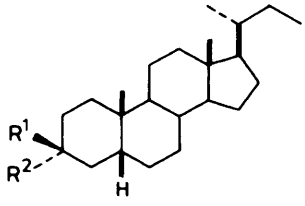
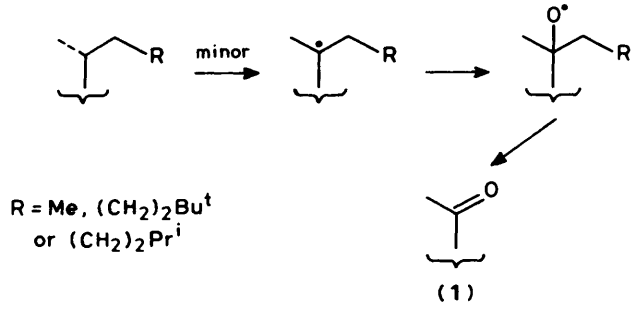


(16) R^1 = H, R^2 = acetoxy
(17) R^1 = R^2 = O



(1)

Scheme 2.

3α-*Acetoxy*-23-*bromo*-5β-*norcholane* (**7**).—To a stirred solution of lithocholic acid acetate (**4**) (9.00 g, 21.60 mmol) in benzene (125 ml) under nitrogen was added oxalyl chloride (10 ml), and the resulting solution was stirred at room temperature for 14 h. The solvent was removed under reduced pressure and the acid chloride (**5**) was taken up into bromotrichloromethane (80 ml). This solution was added dropwise to a refluxing suspension of 4-dimethylaminopyridine (260 mg, 2.16 mmol) and the sodium salt of *N*-hydroxypyridine-2-thione (3.90 g, 26.20 mmol) in bromotrichloromethane (100 ml) under an argon atmosphere. Reflux was maintained until the reaction was complete (as judged by t.l.c.). The crude reaction mixture was filtered and the filtrate evaporated under reduced pressure. The solid residue was dissolved in dichloromethane, washed with 6M-HCl (3 × 50 ml), dried ($MgSO_4$), and concentrated under reduced pressure. Further purification by flash chromatography [hexane–ether (6:4, v/v)], followed by recrystallisation (MeOH) afforded the bromide (**7**) (6.97 g, 71%), m.p. 183—185 °C (lit.,[7] 186—186.5 °C); $[\alpha]_D^{23}$ +54° (*c* 0.55, $CHCl_3$) (lit.,[7] $[\alpha]_D$ +55°); δ (60 MHz, $CDCl_3$) 0.67 (3 H, s, 18-H), 0.93 (3 H, s, 19-H), 2.05 (3 H, s, CH_3CO_2), 3.49 (2 H, m, 23-H), and 4.72 (1 H, m, 3-H).

3α-*Acetoxy*-23-*norcholanyl*(*triphenyl*)*phosphonium Bromide* (**8**).—The bromide (**7**) (6.50 g, 14.3 mmol) and triphenylphosphine (21.20 g, 81 mmol) were heated to reflux in acetonitrile (250 ml) until all starting material had been consumed as judged by t.l.c. (48 h). The solvent was removed under reduced pressure and the resulting oil triturated with ether to afford virtually pure phosphonium salt (**8**) (9.92 g, 97%), m.p. 144—146 °C; $[\alpha]_D^{24}$ +31° (*c* 0.45, $CHCl_3$); $\nu_{max.}$(CH_2Cl_2) 1 610 (aromatic) and 1 730 cm^{-1} (acetate); δ (60 MHz, $CDCl_3$) 0.62 (3 H, s, 18-H), 0.92 (3 H, s, 19-H), 2.05 (3 H, s, CH_3CO_2), 3.88 (2 H, m, 23-H), 4.72 (1 H, m, 3β-H), and 7.98 (15 H, m, PPh_3).

25-*Methyl*-5β-*cholest*-23-*en*-3α-*yl Acetate* (**9**).—To a suspension of the phosphonium salt (**8**) (9.00 g, 12.5 mmol) in

anhydrous ether (200 ml) under an argon atmosphere was added BuLi (1.6M solution in hexane; 25 ml). The resulting bright orange solution was stirred at room temperature for 15 min after which 2,2-dimethylpropanal (5 ml) was added resulting in an immediate decolourisation. The solution was stirred for a further 30 min at ambient temperature. After removal of the solvent under reduced pressure, the residue was dissolved in pyridine (100 ml) and treated with an excess of acetic anhydride (15 ml). The resulting solution was stirred for 14 h at room temperature and then poured into iced 10% H_2SO_4 and extracted with dichloromethane (150 ml); the extract was then washed with water, 5% aqueous $NaHCO_3$, and water, dried ($MgSO_4$), and evaporated under reduced pressure to afford a yellow oil. The oil was purified by flash chromatography [hexane–ether (8:2, v/v)] to afford the *title compound* (**9**) (2.82 g, 51%) as a mixture of geometrical isomers, m.p. 60—60.5 °C (from acetone); $\nu_{max.}(CH_2Cl_2)$ 1 610 (olefin) and 1 725 cm^{-1} (acetate); δ (60 MHz, $CDCl_3$) 0.65 (3 H, s, 18-H), 0.93 (3 H, s, 19-H), 1.12 (9 H, s, 26-, 27-, and 28-H), 2.01 (3 H, s, CH_3CO_2), 4.72 (1 H, m, 3β-H), and 5.28 (1 H, m, 23- and 24-H); *m/z* 442 (M^+), 427, 382 (Found: C, 81.15; H, 11.3. $C_{30}H_{50}O_2$ requires C, 81.39; H, 11.38%).

25-*Methyl*-5β-*cholestan*-3α-*yl Acetate* (**10**).—To a stirred solution of the olefin (**9**) (2.60 g, 5.88 mmol) in ethanol (60 ml) was added 10% palladium on charcoal catalyst (250 mg). The resulting suspension was stirred under a hydrogen atmosphere until no further hydrogen up-take was observed. The catalyst was filtered off through a thin pad of silica and the filtrate was concentrated under reduced pressure. Crystallisation from methanol afforded the *title compound* (**10**) as a white solid (1.98 g, 76%), m.p. 85—87 °C (from MeOH); $[\alpha]_D^{23}$ +44° (*c* 1.8, $CHCl_3$); $\nu_{max.}(CH_2Cl_2)$ 1720 cm^{-1} (acetate); δ (400 MHz, $CDCl_3$) 0.65 (3 H, s, 18-H), 0.87 (9 H, s, 26-, 27-, and 28-H), 0.91 (3 H, d, *J* 7 Hz, 21-H), 0.93 (3 H, s, 19-H), 2.04 (3 H, s, CH_3CO_2), and 4.72 (1 H, m, 3β-H); *m/z* 444 (M^+), 429, 384, and 369 (Found: C, 80.8; H, 11.6. $C_{30}H_{52}O_2$ requires C, 81.02; H, 11.79%).

25-*Methyl*-5β-*cholestan*-3-*one* (**11**).—To a stirred solution of the acetate (**10**) (1.75 g, 5.0 mmol) in ethanol (150 ml) was added 40% aqueous sodium hydroxide (2 ml). After 2 h t.l.c. indicated that all starting material had been consumed. The reaction mixture was added to iced dilute HCl (200 ml) and the resulting precipitate filtered off, washed with water, and dissolved in acetone. The acetone solution was cooled to 0 °C, and Jones' reagent was added dropwise until the solution remained brown. Stirring was continued for 3 h. The reaction mixture was diluted with water (600 ml), filtered, and the resulting solid washed with water (2 × 100 ml). Purification was effected by flash chromatography [hexane–ether (75:25, v/v)] and recrystallisation from methanol to give the *ketone* (**11**) (1.33 g, 87%), m.p. 123—126 °C; $[\alpha]_D^{23}$ +38° (*c* 0.45, $CHCl_3$); $\nu_{max.}(CH_2Cl_2)$ 1 705 cm^{-1} (ketone); δ (400 MHz, $CDCl_3$) 0.69 (3 H, s, 18-H), 0.87 (9 H, s, 26-, 27-, and 28-H), 0.92 (3 H, d, *J* 6 Hz, 21-H), and 1.02 (3 H, s, 19-H); *m/z* 400 (M^+) and 385. (Found: C, 83.95; H, 12.1. $C_{28}H_{48}O$ requires C, 83.93; H, 12.07%).

25-*Methylcholesta*-1,4-*dien*-3-*one* (**3**).—To a stirred solution of the ketone (**11**) (1.32 g, 4.4 mmol) in chlorobenzene (**11**) 20 ml) was added benzeneseleninic acid (1.83 g, 0.68 mmol). The resulting colourless solution was heated to 95 °C for 2 h, when t.l.c. indicated that the starting material had been consumed. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography [hexane–ether (7:3, v/v)] to give the *title compound* (**3**) (886 mg, 68%), m.p. 119—121 °C (from MeOH); $[\alpha]_D^{23}$ +45° (*c* 1.8, $CHCl_3$); $\lambda_{max.}$(EtOH) 245 nm (ε 14 000); $\nu_{max.}(CH_2Cl_2)$ 1 630 (olefins) and 1 670 cm^{-1} (unsaturated ketone); δ (400 MHz, $CDCl_3$) 0.75 (3 H, s, 18-H), 0.87 (9 H, s, 26-, 27-, and 28-H), 0.92 (3 H, d, *J* 7 Hz, 21-H), 1.23 (3 H, s, 19-H), 6.06 (1 H, s, 4-H), 6.22 (1 H, d, *J* 10 Hz, 2-H), and 7.05 (1 H, d, *J* 10 Hz, 1-H); *m/z* 396 (M^+) and 381. (Found: C, 84.6; H, 11.15. $C_{28}H_{44}O$ requires C, 84.79; H, 11.18%).

Gif Oxidation of 25-*Methylcholesta*-1,4-*dien*-3-*one* (**3**).—The crude oxidation mixture (see Part 6 [1]) was chromatographed on silica gel and eluted with hexane–ether (8:2, v/v) to give first unchanged starting material (780 mg, 66%), followed by the product mixture. This was further purified by h.p.l.c. [normal phase: hexane–ethyl acetate (7:3, v/v), 3 ml/min and reverse phase: acetonitrile, 3 ml/min] to afford the 15-*ketone* (**14**) (9.9 mg, 2.3%), m.p. 101—105 °C (from MeOH); $[\alpha]_D^{23}$ +80° (*c* 0.45, $CHCl_3$); $\lambda_{max.}$(EtOH) 245 nm (ε 13 600); $\nu_{max.}(CH_2Cl_2)$ 1 600, 1 620 (olefin), 1 660 (unsaturated ketone) and 1 735 cm^{-1} (ketone); δ (400 MHz, $CDCl_3$) 0.84 (3 H, s, 18-H), 0.87 (9 H, s, 26-, 27-, and 28-H), 1.00 (3 H, d, *J* 6 Hz, 21-H), 1.24 (3 H, s, 19-H), 2.99 (1 H, m, 14-H), 6.07 (1 H, s, 4-H), 6.23 (1 H, d, *J* 10 Hz, 2-H), and 7.02 (1 H, d, *J* 10 Hz, 1-H); *m/z* 410 (M^+), 405 (Found: *m/z* 410.3310. $C_{28}H_{42}O_2$ requires 410.3185); and the 20-ketone (**12**) (7.8 mg, 2.4%); m.p. and mixed m.p. 148—150 °C (from MeOH) (lit.,[8] 152—153 °C); $[\alpha]_D^{24}$ +119° (*c* 0.5, $CHCl_3$) (lit.,[8] $[\alpha]_D$ +120°); *m/z* 312 (M^+), 297.

3α-*Acetoxy*-5β-*norcholane* (**16**).—To a stirred solution of lithocholic acid acetate (**4**) (2.50 g, 6.00 mmol) in benzene (50 ml) under a nitrogen atmosphere was added oxalyl chloride (3 ml) and the resulting solution stirred at room temperature for 14 h. The acid chloride (**5**) solution was concentrated under reduced pressure and the residue dissolved in toluene (30 ml). The resulting solution was added over a 30 min period to a stirred suspension of 4-dimethylaminopyridine (60 mg, 0.5 mmol) and the sodium salt of *N*-hydroxypyridine-2-thione (1.07 g, 7.2 mmol) at reflux in toluene (50 ml), in the presence of 1,1-dimethylethanethiol (3 ml) under an argon atmosphere. Reflux was maintained for 45 min, after the addition was complete and the cooled reaction mixture was filtered and evaporated under reduced pressure. The residue was dissolved in dichloromethane, washed with 6M-HCl (3 × 25 ml), dried ($MgSO_4$), and concentrated under reduced pressure. Further purification was effected by flash chromatography (hexane–ether 75:25, v/v) to give the *title compound* (**16**) (1.75 g, 79%), m.p. 87—89 °C (from MeOH); $[\alpha]_D^{24}$ +57° (*c* 1.15, $CHCl_3$); $\nu_{max.}(CH_2Cl_2)$ 1 725 cm^{-1} (acetate); δ (400 MHz, $CDCl_3$) 0.65 (3 H, s, 18-H), 0.93 (3 H, s, 19-H), 2.03 (3 H, s, CH_3CO_2), and 4.72 (1 H, m, 3β-H); *m/z* 374 (M^+), 314, and 299 (Found: C, 79.9; H, 11.05. $C_{25}H_{42}O_2$ requires C, 80.16; H, 11.30%).

3-*Oxo*-5β-*norcholane* (**17**).—To a stirred solution of the acetate (**16**) (1.80 g, 4.82 mmol) in ethanol (50 ml) was added 40% squeous sodium hydroxide (5 ml). The resulting solution was stirred at room temperature for 14 h and poured into iced dilute HCl. The resulting precipitate was filtered off and washed with water. The white solid was dissolved in acetone (100 ml) and Jones' reagent was added to the stirred, cooled (0 °C) solution until the brown colouration persisted. The reaction mixture was stirred for a further hour at 0 °C, poured into water, and the solid filtered off and dried. The product was purified by flash chromatography (CH_2Cl_2) to afford the *pure ketone* (**17**) (1.29 g, 81%), m.p. 141—142 °C (CH_2Cl_2–MeOH); $[\alpha]_D^{23}$ +36° (*c* 0.5, $CHCl_3$); $\nu_{max.}(CH_2Cl_2)$ 1 705 cm^{-1} (ketone); δ (400 MHz, $CDCl_3$) 0.69 (3 H, s, 18-H), 0.83 (3 H, t, J 7 Hz, 21-H), and 1.03 (3 H, s, 19-H); *m/z* 330 (M^+), 315, 296, 260, and 231 (Found : C, 83.3; H, 11.55. $C_{23}H_{38}O$ requires C, 83.57; H, 11.59%).

3-*Oxonorchola*-1,4-*diene* (**15**).—To a stirred solution of the ketone (**17**) (1.28 g, 4.88 mmol) in chlorobenzene (5 ml) was

added benzeneseleninic acid and the resulting solution heated to 95 °C until all starting material had been consumed (t.l.c.). The solution was evaporated under reduced pressure and the product purified by flash chromatography (hexane–ether 1:1, v/v) to afford the *dienone* (**15**) (1.00 g, 78%), m.p. 168—170 °C (from MeOH); $[\alpha]_D^{23}$ +32° (*c* 0.6, $CHCl_3$); $\lambda_{max.}$(EtOH) 244 nm (ε 13 500); $\nu_{max.}$(CH_2Cl_2) 1 600, 1 620 (olefin), and 1 660 cm^{-1} (unsaturated ketone); δ (400 MHz, $CDCl_3$) 0.74 (3 H, s, 18-H), 0.82 (3 H, t, *J* 8 Hz, 23-H), 0.90 (3 H, d, *J* 7 Hz, 21-H), 1.23 (3 H, s, 19-H), 6.27 (1 H, s, 4-H), 6.43 (1 H, d, *J* 10 Hz, 2-H), and 7.29 (1 H, d, *J* 10 Hz, 1-H); *m/z* 326 (M^+), 311, 297, 285, and 269 (Found; C, 84.35; H, 10.5. $C_{23}H_{34}O$ requires C, 84.60; H, 10.50%).

Gif Oxidation of 3-*Oxonorchola*-1,4-*diene* (**15**).—The crude oxidation mixture (see Part 6 [1]) was chromatographed on silica gel and eluted with hexane–ether (8:2, v/v) to give first unchanged starting material (655 mg, 67%). Further elution gave the crude 20-ketone (**12**), which was purified by h.p.l.c. [normal phase, hexane–ethyl acetate (7:3, v/v), 3 ml/min] and reverse phase, acetonitrile, 3 ml/min to give the pure 20-*ketone* (see above) (8.4 mg, 2.7%), m.p. and mixed m.p. 148—150 °C (from MeOH), $[\alpha]_D^{22}$ +119° (*c* 0.8, $CHCl_3$), *m/z* 312 (M^+), 297.

Acknowledgements

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