Summary

Some 2-ethoxalyl-4-en-3-one was treated with N-halo-succinimide in pyridine to give the corresponding 2 α -halo-4-en-3-one in a good yield. Direct chlorination of testosterone acetate with sulfuryl chloride (1 mole) gave a small amount of 2 α -chloro-testosterone acetate in dry benzene or dry ether, and with sulfuryl chloride (excess) gave mainly 2 α ,4-dichlorotestosterone acetate in dry benzene and mainly 2 α ,6 β -dichlorotestosterone acetate in dry ether. These observations were confirmed by the syntheses of their related compounds through the unequivocal routes.

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170. Hiromu Mori : Studies on Steroidal Compounds. XII.*¹
Stereochemistry of 1,4-Addition of Grignard Reagent
for α,β -Unsaturated Steroidal Ketones. Grignard
Reaction of 3 β -Hydroxycholest-4-en-6-one.

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In the preceding papers, the Grignard reactions of 19-nor-3-oxo-4-ene (I) and 3-oxo-1-ene (II) steroids were described.^{1,2)} 1,4-Addition product was isolated in each case, when Grignard reaction was taken place in the presence of cuprous chloride: 5 β -methyl-3-oxo (III) and 1 α -methyl-3-oxo (IV) compound were obtained respectively as shown in Chart 1. The stereochemical course of the reaction was explained by stereochemical

Chart 1.

interaction. This paper describes further study of stereochemistry of Grignard reaction, in which the reaction of 3 β -hydroxycholest-4-en-6-one (V) will be reported, and discussion will be made concerning the stereochemistry of 1,4-addition of Grignard reagent for α,β -unsaturated ketones.

When 3 β -hydroxycholest-4-en-6-one (V)³⁾ was treated with methyl magnesium iodide in the presence of cuprous chloride or cupric acetate, there was obtained a new compound (VI), m.p. 175.5~177.5° with no characteristic absorption in ultraviolet spectrum.

*¹ H. Mori, J. Yamada : This Bulletin, 11, 1418 (1963).

*² 1604 Shimosakunobe, Kawasaki-shi (森 弘).

1) H. Mori : This Bulletin, 10, 382 (1962).

2) *Idem* : *Ibid.*, 10, 386 (1962).

3) I. M. Heilbron, E. R. H. Jones, F. S. Spring : J. Chem. Soc., 1937, 801.

The infrared spectrum of VI displayed six-membered carbonyl band (1716 cm^{-1}) and a hydroxyl band (3660 cm^{-1}). Mono acetate (VII), m.p. $145.5\sim 146.5^\circ$ was obtained on acetylation of VI with acetic anhydride in pyridine at room temperature. VI or its acetate (VII) was isomerized to the stable isomer, VIII, m.p. $170\sim 171.5^\circ$, or IX, m.p. $120\sim 121.5^\circ$ respectively on treatment with alkali or acid. IX was also obtained from VIII by acetylation with acetic anhydride in pyridine.

In order to assign the structures of these compounds, an attempt to transform the carbonyl group in VIII to methylene group by thioketal formation, followed by Raney nickel desulfuration was undertaken without success. The Huang-Minlon reduction of VIII, however, gave 4β -methyl- 5α -cholestan- 3β -ol (X), the structure of which was easily

Chart 2.

shown by the oxidation of X with chromium trioxide in acetone to known 4β -methyl- 5α -cholestan- 3β -one (XI).⁴⁾ The treatment of XI with acid gave the stable isomer, 4α -methyl- 5α -cholestan- 3β -one (XII).⁴⁾ These observations indicate that the Grignard reaction of V gave undoubtedly 4β -methyl- 6α -oxo compound by 1,4-addition of the Grignard reagent to α,β -unsaturated oxo function, and isomerization of VI to VIII (or VII to IX) was concerned with A/B ring juncture. The configuration of C-5 in VIII would be considered as α from observation described above, but this assignment was proved to be questionable, because the Huang-Minlon reduction of the unstable isomer (VI) gave also 4β -methyl- 5α -cholestan- 3β -ol (X).

4) Y. Mazur, F. Sondheimer: J. Am. Chem. Soc., 80, 5220 (1958).

Fig. 1. Rotatory Dispersion Curves of VI, VII, VIII, and IX (ethanol)

That the assignment of A/B ring juncture of VIII as *trans* is not the case was shown on the basis of following observations. i) VI was precipitated from 95% ethanol solution as digitonide, when a solution of digitonin in 95% ethanol was added. On the other hand, no insoluble digitonide of VIII was formed on similar treatment. This suggests that A/B ring juncture of VI and VIII are *trans* and *cis*, respectively.⁵⁾ ii) Optical rotatory dispersion curves of VI, VII, VIII, and IX are shown in Fig. 1. The curves for VIII and IX are negative single Cotton effect curves similar as those observed in 3 β -hydroxy-5 α -cholestan-6-one (XIII) or 3 β -hydroxy-5 β -cholestan-6-one (XIV).⁶⁾ The curves for VI and VII should be considered as unusual curves comparing with those for XIII and XIV because of their unusual low amplitude. This fact can be explained naturally by the consideration derived from the assignment described

Chart 3.

above. The conformations of A/B *trans* and *cis* 3 β -hydroxy-4 β -methyl-6-ones are shown as A and B in Chart 3. In conformation A, there is a strong 1,3-diaxial methyl-methyl interaction between 4 β -methyl and 10 β -methyl group, while such a strong interaction is not observed in A/B *cis* series. If unusual curves are considered to be observed in A/B *trans* series, the distortion of ring A or B on account of the strong interaction (1,3-diaxial interaction) will cause the unusual curves.⁷⁾ On the other hand, if the opposite

5) It has been shown that only 3 β -hydroxy-5 α compound is precipitated as digitonide among four isomers of 3-hydroxy saturated compounds (3 α ,5 α ; 3 α ,5 β ; 3 β ,5 α ; 3 β ,5 β). R. N. Jones, F. Herling: J. Org. Chem., 19, 1252 (1954).

6) C. Djerassi, W. Closson: J. Am. Chem. Soc., 78, 3761 (1956).

7) Optical rotatory dispersion curve of 4,4-dimethyl-5 α -cholestan-3-one is known to be an unusual one, and this fact is considered to be due to the distortion of ring A and B. On the other hand, optical rotatory dispersion curves of 4 β - or 2 β -methyl-5 α -cholestan-3-one are positive Cotton effect curves usually observed in A/B *trans*-3-oxo steroids. (C. Djerassi, O. Halpern, V. Halpern, B. Riniker: J. Am. Chem. Soc., 80, 4001 (1958)). Thus it should be considered that the influence of 1,3-diaxial 4 β -methyl-10 β methyl interaction on the conformation is not so serious for 3-oxo Octant diagram, but very serious for 6-oxo diagram.

assignment is made, the unusual curves can not be explained stereochemically. iii) If the stable isomer (VIII) is considered to be A/B *cis* isomer, the fact that the Huang-Minlon reductions of VI and VIII gave the same compound (X) must be considered as follows. The equilibrium mixture (VI $\longleftrightarrow$ VIII) is rapidly produced, only one isomer, 3 β -hydroxy-4 β -methyl-5 α -cholestan-6-one (VI) was transformed to the hydrazone (XV), and the formation of hydrazone of another isomer, 3 β -hydroxy-4 β -methyl-5 β -cholestan-6-one (VIII) was blocked by stereochemical factor. It is generally accepted that rate determining step of hydrazone formation is the addition of hydrazine to ketone ($C=O \rightarrow C \begin{smallmatrix} OH \\ \diagup \\ NNNH_2 \end{smallmatrix}$).⁸⁾ In the case of A/B *trans* isomer (conformation A in Chart 3), if hydrazine attacks from rear

Chart 4.

side of the steroid, no serious interaction is observed, and the attack of the reagent was probably preceded from this direction. On the other hand, in the case of another isomer (conformation B in Chart 3), both rear side and front side attack of the reagent are seriously interacted by 10 β -methyl and 4 β -methyl group, respectively. Thus the behaviour of Huang-Minlon reduction under consideration can be smoothly explained stereochemically.⁹⁾ iv) In order to elucidate the difference of hinderance of C-6 oxo group between VI and VIII, the Grignard reactions (methyl magnesium iodide, at room temperature) of VI and VIII were undertaken. In the case of VIII, the starting material was recovered completely. On the other hand, the same reaction of VI gave an oily substance, the infrared spectrum of which showed that there was obtained an addition product, but isolation in crystalline state was unsuccessful. From this experiment, it became clear that oxo group in VIII is highly sterically hindered.

8) J. Hine: "Physical Organic Chemistry," p. 246 (1956), McGraw-Hill Book Co., Inc. (New York).

9) Similar observations concerning sapogenins having oxygen function at C-15 have been made by C. Djerassi, T. T. Grossnickle, L. B. High (J. Am. Chem. Soc., 78, 3166 (1956)). Digitogenone diacetate (1) is isomerized to thermodynamically stable isomer (2) by treatment with alkali. Both the Huang-Minlon reduction of digitogenone diacetate (1) and its C-14 isomer (2) gave the same 15-deoxo compound, gitogenin (3), the C-14 configuration of which is the same as that for thermodynamically unstable isomer, digitogenin (3).

All observations described above indicate that VI, 1,4-addition product must be formulated as 3 β -hydroxy-4 β -methyl-5 α -cholestan-6-one, and the related compounds, VII, VIII, and IX as shown in Chart 2. It is to be noted that 1,3-diaxial 4 β -methyl; 10 β -methyl interaction inverts the stability order of A/B ring juncture. Generally A/B *trans* compound in decaline system is kinetically more stable than A/B *cis* compound;¹⁰⁾ in fact, Henbest and Wrigley¹¹⁾ found that 5 β -cholestan-6-one is isomerized into kinetically stable isomer, 5 α -cholestan-6-one, on treatment with alumina. In contrast, A/B *cis* compound is more stable in 4 β -methyl-6-oxo series.

Recently House and Thompson found that 1,4-addition of Grignard reagent to 3,4,4 α , 5,6,7-hexahydro-1(2*H*)-naphthalenone (XVIII) gives 8-phenyloctahydro-1(2*H*)-naphthalenone (XIX), in which the configuration of phenyl group is β and ring juncture is *trans* as

Chart 5.

shown in Chart 5.¹²⁾ From this observation they conclude that 1,4-addition of Grignard reagent is comparable to Michael reaction and does not proceed *via* six-membered cyclic transition state (XX). It should be noted that alkyl group introduced newly is axially oriented both in their experiment and also in our case. The hypothesis, that a Grignard reagent attacks from axial direction in which case orbital overlap in the transition state is more favorable, became more acceptable. Moreover, we believe that all examples of 1,4-addition for steroidal α,β -unsaturated ketones can be explained by this concept.

Five types of example in 1,4-addition for steroidal α,β -unsaturated ketones can be seen from literature except our experiment. The most classic example is that for 16-en-20-ones.¹³⁾ Since a methyl group is introduced in five-membered D-ring (16 α), discussion can not be made from this concept.*³ Discussion can be made for the other four examples as follows.

i) 4-En-3-ones. The 1,4-addition for 4-en-3-ones affords 5 β -methyl-3-ones.^{1,14)} It should be noted that 5 α - and 5 β -methyl group are both axially oriented for ring A and the double bond in the starting material exists in A-ring. Thus attack of the reagent should occur from less-hindered β -side.¹⁵⁾

ii) 5 α -1-En-3-ones. From the concept, 1 α -methyl-5 α -3-ones should be the product predicted. In fact, this compounds are obtained almost stereospecifically.²⁾

iii) 5 β -1-En-3-ones. Recently, Wechter¹⁶⁾ has described the Grignard reaction of 5 β -1-en-3-ones, in which 1 β -methyl-5 β -3-ones are obtained as 1,4-addition products. Here again, a methyl group introduced by the reaction is axially oriented.

*³ In this case, it may, only, be considered that Grignard reagent attacks from less hindered rear side.

10) W. Klyne: "Progress in Stereochemistry, I," p. 47 (1954), Butterworth Scientific Publications (London).

11) H. B. Henbest, T. I. Wrigley: J. Chem. Soc., 1957, 4596.

12) H. O. House, H. W. Thompson: J. Org. Chem., 28, 360 (1963).

13) R. E. Marker, H. M. Crooks: J. Am. Chem. Soc., 64, 1280 (1942).

14) A. J. Birch, M. Smith: Proc. Chem. Soc., 356 (1962).

15) Concerning the stereochemical consideration, see ref. 1).

16) W. J. Wechter: J. Org. Chem., 29, 163 (1964). He described in the original paper that the configuration of the methyl group of the product is α , but according to his private communication, the configuration of the 1-methyl group described in his paper should be revised to 1 β -methyl.

iv) 1(10)-En-2-one. The reaction of 1(10)-en-2-one (XXI) has been described by Torigoe and Fishman¹⁷⁾ who obtained 10 α -methyl-2-one (XXII) as 1,4-addition product. Both 10 α - and 10 β -methyl group are axially oriented for A-ring, in which the double bond of the starting material has existed (see Chart 7). This case is resemble to the case i), and the less hindered side attack should occur. It is easy to show that α -side is less hindered from models shown in Chart 7. In conformation C, main interactions for the 10-methyl group are three 1,3-diaxial methyl-hydrogen and one 1,2-methyl-hydrogen interactions, while in D, two 1,3-diaxial methyl-hydrogen*⁴ and two 1,2-methyl-hydrogen interactions. As interactions for conformation D are smaller than those for C, the product predicted from the concept is 10 α -methyl compound and this agrees with the experimental result.

Chart 6.

Chart 7.

From these considerations, it may be concluded that the configuration of a newly introduced alkyl group on an 1,4-addition reaction of a Grignard reagent to α,β -unsaturated ketone is predicted to be axial, and if both configurations are axial for the ring in which the double bond has existed, the product can be predicted only from stereochemical interactions.

The oxidations of VI and VIII with chromium trioxide in acetone afforded the corresponding 3,6-diones, XXIII and XXIV, respectively. Both XXIII and XXIV were isomerized into the same diketone. As the most stable isomer must be considered to be 4 α -methyl-5 α -compound, the diketone can be formulated as 4 α -methyl-5 α -cholestane-3,6-dione. Similar observation has been made on the compounds derived from santonin by Tahara.¹⁸⁾ Fieser¹⁹⁾ has described that 4-methylcholest-4-ene-3,6-dione, which is obtained from cholest-4-ene-3,6-dione by the reaction with diazomethane followed by heating, is transformed into saturated compounds by reduction with zinc dust in acetic acid. He isolated two isomers of 4-methylcholestane-3,6-dione, m.p. 190° and 124°, but no assignment of the configurations of these compounds at C-4 and C-5 was given. From the comparison of melting points and optical rotations, Fieser's diketones, m.p. 190° and 124° are considered to be the same as XXIV and XXV, respectively.

Experimental*⁵

3 β -Hydroxy-4 β -methyl-5 α -cholestan-6-one (VI). a) By Cu₂Cl₂ Catalyzed Reaction—Finely powdered

*⁴ The interaction between 10 α -methyl and 11 α -hydrogen is shown as an 1,3-diaxial interaction, because the interatomic distance between these groups is the same as that for 1,3-diaxial relationship.

*⁵ All optical rotations were measured in CHCl₃, and all melting points were uncorrected.

17) M. Torigoe, J. Fishman: Tetrahedron Letters, 1963, 1251.

18) A. Tahara: J. Org. Chem., 21, 442 (1956).

19) L. F. Fieser: J. Am. Chem. Soc., 75, 4386 (1953).

Cu_2Cl_2 (500 mg.) was added to a solution of 3 β -hydroxycholest-4-en-6-one (V, 3.0 g.) in Et_2O (180 ml.). To the resulting suspension, a Grignard reagent prepared from Mg (1.55 g.), CH_3I (4.35 ml.) and Et_2O (75 ml.) was added dropwise with vigorous stirring at room temperature. After stirring was continued for an hour, excess Grignard reagent was decomposed by addition of ice. Organic layer was washed with 10% NH_4Cl , 5% Na_2CO_3 and H_2O , and dried (Na_2SO_4). The solvent was removed by evaporation, and the residue was recrystallized from Me_2CO - Et_2O to give 3 β -hydroxy-4 β -methyl-5 α -cholestan-6-one (VI, 1.1 g.), m.p. 150~165°. Twice recrystallization from Me_2CO afforded an analytical sample as colorless needles, m.p. 175.5~177.5°. $[\alpha]_D^{25} + 29^\circ$ ($c=1.20$), IR $\nu_{\text{max}}^{\text{CS}_2}$ cm^{-1} : 3660 ($-\text{OH}$), 1716 ($\text{C}=\text{O}$). ORD ($c=0.14$, EtOH): $[\alpha]_{318} -103^\circ$ (trough), $[\alpha]_{274} +441^\circ$ (peak). Anal. Calcd. for $\text{C}_{28}\text{H}_{48}\text{O}_2$: C, 80.71; H, 11.61. Found: C, 80.75; H, 11.71.

b) By $\text{Cu}(\text{OAc})_2$ Catalyzed Reaction—To a Grignard reagent prepared from Mg (6.4 g.), CH_3I (17 ml.) and Et_2O (200 ml.), a solution of 3 β -hydroxycholest-4-en-6-one (V, 8.8 g.) and $\text{Cu}(\text{OAc})_2$ (0.88 g.) in tetrahydrofuran (210 ml.) was added dropwise with vigorous stirring at 0~-5°. After stirring was continued at the same temperature for 3 hr., the resulting suspension was allowed to stand overnight at room temperature. The excess Grignard reagent was decomposed by addition of ice, and the organic layer was washed with 10% NH_4Cl , 5% Na_2CO_3 , and H_2O . After drying (Na_2SO_4), the solvent was evaporated and the residue was recrystallized from Me_2CO to give 3 β -hydroxy-4 β -methyl-5 α -cholestan-6-one (VI, 4.3 g.), m.p. 161~169°. Recrystallization from the same solvent afforded a pure sample, m.p. 175~177° (3.4 g.), which was identical with the compound obtained above in all respects.

3 β -Acetoxy-4 β -methyl-5 α -cholestan-6-one (VII)—A solution of 3 β -hydroxy-4 β -methyl-5 α -cholestan-6-one (VI, 200 mg.) in pyridine (3.0 ml.) and Ac_2O (3.0 ml.) was allowed to stand overnight at room temperature, and poured into H_2O . The product was extracted with Et_2O , and Et_2O layer was washed with 10% HCl , 5% Na_2CO_3 and H_2O , and dried (Na_2SO_4). After evaporation of the solvent, the residue was recrystallized from Me_2CO - MeOH to give the acetate (VII, 160 mg.), m.p. 142~144°. Recrystallization from the same solvent afforded an analytical sample as colorless needles, m.p. 145~146.5°. $[\alpha]_D^{25} -2^\circ$ ($c=1.12$), IR $\nu_{\text{max}}^{\text{CS}_2}$ cm^{-1} : 1742 ($-\text{OAc}$), 1720 ($\text{C}=\text{O}$). ORD ($c=0.15$, EtOH): $[\alpha]_{316} -224^\circ$ (trough), $[\alpha]_{270} +368^\circ$ (peak). Anal. Calcd. for $\text{C}_{30}\text{H}_{50}\text{O}_3$: C, 78.55; H, 10.99. Found: C, 78.34; H, 10.84.

3 β -Hydroxy-4 β -methyl-5 β -cholestan-6-one (VIII)—A solution of 3 β -hydroxy-4 β -methyl-5 α -cholestan-6-one (VI, 100 mg.) and KOH (100 mg.) in MeOH (10 ml.) was refluxed for 2 hr., and poured into 10% HCl . The product was extracted with Et_2O , and Et_2O layer was washed with 5% Na_2CO_3 and H_2O , and dried (Na_2SO_4). The solvent was evaporated to dryness, and the residue was recrystallized from MeOH - Me_2CO to give 3 β -hydroxy-4 β -methyl-5 β -cholestan-6-one (VIII, 60 mg.), m.p. 169~170.5°. Further recrystallization from the same solvent afforded an analytical sample as colorless needles, m.p. 170~171.5°. $[\alpha]_D^{25} -16^\circ$ ($c=0.57$), IR $\nu_{\text{max}}^{\text{CS}_2}$ cm^{-1} : 3625 ($-\text{OH}$), 1704 ($\text{C}=\text{O}$). ORD ($c=0.16$, EtOH): $[\alpha]_{310} -825^\circ$ (trough), $[\alpha]_{272} +1065^\circ$ (peak). Anal. Calcd. for $\text{C}_{28}\text{H}_{48}\text{O}_2$: C, 80.71; H, 11.61. Found: C, 80.53; H, 11.80.

3 β -Acetoxy-4 β -methyl-5 β -cholestan-6-one (IX). **a) By Isomerization of 3 β -Acetoxy-4 β -methyl-5 α -cholestan-6-one (VII)**—A solution of VII (200 mg.) in AcOH (20 ml.) containing 2 drops of H_2SO_4 was warmed on steam bath for 2 hr., and poured into H_2O . The product was extracted with Et_2O , and Et_2O layer was washed with H_2O , 5% Na_2CO_3 and H_2O , and dried (Na_2SO_4). The solvent was evaporated to dryness, and the residue was recrystallized from MeOH - Me_2CO to give 3 β -acetoxy-4 β -methyl-5 β -cholestan-6-one (IX, 110 mg.), m.p. 118~121°. Further recrystallization from MeOH gave an analytical sample as colorless plates, m.p. 120~121.5°. $[\alpha]_D^{25} 0^\circ$ ($c=1.02$), IR $\nu_{\text{max}}^{\text{CS}_2}$ cm^{-1} : 1738 ($-\text{OAc}$), 1705 ($\text{C}=\text{O}$). ORD ($c=0.17$, EtOH): $[\alpha]_{309} -771^\circ$ (trough), $[\alpha]_{238} +711^\circ$ (peak). Anal. Calcd. for $\text{C}_{30}\text{H}_{50}\text{O}_3$: C, 78.55; H, 10.99. Found: C, 78.60; H, 10.91.

b) By Acetylation of 3 β -Hydroxy-4 β -methyl-5 β -cholestan-6-one (VIII)—A solution of VIII (1.3 g.) in pyridine (10 ml.) and Ac_2O (10 ml.) was allowed to stand overnight at room temperature, and poured into H_2O . The product was extracted with Et_2O , and Et_2O layer was washed with 10% HCl , 5% Na_2CO_3 and H_2O , and dried (Na_2SO_4). The solvent was evaporated to dryness, and the residue was recrystallized from MeOH - Me_2CO to give colorless plates (IX, 1.1 g.), m.p. 104~120°. Further recrystallization from the same solvent afforded a pure sample, m.p. 118~121°, which was identical with the compound obtained above in all respects.

4 β -Methyl-5 α -cholestan-3 β -ol (X). **a) From 3 β -Hydroxy-4 β -methyl-5 β -cholestan-6-one (VIII)**—A solution of VIII (200 mg.) and KOH (400 mg.) in diethyleneglycol (8 ml.) and 80% $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (1.2 ml.) was heated at 140~160° for 30 min., and 190~210° for 2 hr., and poured into H_2O . The product was extracted with Et_2O , and Et_2O layer was washed well with H_2O , and dried (Na_2SO_4). After evaporation of the solvent, the residue was chromatographed on alumina (4.0 g.). 4 β -Methyl-5 α -cholestan-3 β -ol (X, 98 mg.), m.p. 160.5~161.5° was eluted by hexane-benzene (1:1). $[\alpha]_D^{18} +14^\circ$ ($c=0.94$), IR: $\nu_{\text{max}}^{\text{CS}_2}$ cm^{-1} : 3630 ($-\text{OH}$), no carbonyl band. Anal. Calcd. for $\text{C}_{28}\text{H}_{50}\text{O} \cdot \frac{1}{2}\text{H}_2\text{O}$: C, 81.68; H, 12.49. Found: C, 81.95; H, 12.38.

b) From 3 β -Hydroxy-4 β -methyl-5 α -cholestan-6-one (VI)—VI (200 mg.) was reduced as the same manner described above. X (83 mg.), m.p. 158~161° was obtained, the infrared spectrum of which was the same as that for the compound obtained above.

4 β -Methyl-5 α -cholestan-3-one (XI)—8*N* CrO₃ solution (0.1 ml.)²⁰⁾ was added to a solution of 4 β -methyl-5 α -cholestan-3 β -ol (X, 80 mg.) in alcohol free Me₂CO (20 ml.) at 5~10°. After the resulting suspension was stirred for 5 min. at the same temperature, H₂O was added and the product was extracted with Et₂O. Et₂O layer was washed with 5% Na₂CO₃ and H₂O, and dried (Na₂SO₄). The solvent was removed by evaporation, and the residue was recrystallized from Et₂O-MeOH to give 4 β -methyl-5 α -cholestan-3-one (XI, 52 mg.), m.p. 125~126.5°, $[\alpha]_D^{24} + 34^\circ$ (c=0.94) as colorless needles. (reported⁴⁾ m.p. 126~127°, $[\alpha]_D + 36^\circ$).

4 α -Methyl-5 α -cholestan-3-one (XII)—A solution of 4 β -methyl-5 α -cholestan-3-one (XI, 50 mg.) in EtOH (5 ml.) and 10% H₂SO₄ (0.1 ml.) was refluxed for 2 hr., and poured into H₂O. The product was extracted with Et₂O, and Et₂O layer was washed with 5% Na₂CO₃ and H₂O, and dried (Na₂SO₄). The solvent was evaporated to dryness, and the residue was recrystallized from Et₂O-MeOH to give 4 α -methyl-5 α -cholestan-3-one (XII), m.p. 114~116°. Further recrystallization from the same solvent gave a pure sample as colorless needles. m.p. 121~123.5°, $[\alpha]_D^{24} + 24^\circ$ (c=1.03). (reported⁴⁾ m.p. 121~123°, $[\alpha]_D + 26^\circ$).

4 β -Methyl-5 α -cholestane-3,6-dione (XXIII)—8*N* CrO₃ solution (0.25 ml.) was added to a solution of 3 β -hydroxy-4 β -methyl-5 α -cholestan-6-one (VI, 200 mg.) in alcohol free Me₂CO (15 ml.) at 5~10°, and stirring was continued for 3 min. at the same temperature. The resulting suspension was poured into H₂O, and the precipitates were collected by filtration, washed with H₂O, and dried. Recrystallization from MeOH-Me₂CO gave 4 β -methyl-5 α -cholestane-3,6-dione (XXIII, 120 mg.), m.p. 182~186°. Recrystallization from the same solvent afforded an analytical sample as colorless leaflets. m.p. 181~183°, $[\alpha]_D^{28} - 2^\circ$ (c=1.20), IR: $\nu_{\text{max}}^{\text{CS}_2}$ 1720 cm⁻¹ (C=O). Anal. Calcd. for C₂₈H₄₆O₂: C, 81.10; H, 11.18. Found: C, 81.06; H, 11.29.

4 β -Methyl-5 β -cholestane-3,6-dione (XXIV)—8*N* CrO₃ solution (0.2 ml.) was added to a solution of 3 β -hydroxy-4 β -methyl-5 β -cholestan-6-one (VIII, 100 mg.) in alcohol free Me₂CO (10 ml.) at 5~10°, and stirring was continued for 10 min. at the same temperature. The resulting suspension was poured into H₂O, and the product was extracted with Et₂O. Et₂O layer was washed with 5% Na₂CO₃ and H₂O, and dried (Na₂SO₄). The solvent was evaporated, and the residue was recrystallized from MeOH-Me₂CO to give 4 β -methyl-5 β -cholestane-3,6-dione (XXIV, 80 mg.), m.p. 191~192°. Further recrystallization from the same solvent afforded an analytical sample as colorless needles. m.p. 191~192°, $[\alpha]_D^{23} - 91^\circ$ (c=0.54). IR: $\nu_{\text{max}}^{\text{CS}_2}$ 1710 cm⁻¹ (C=O). Anal. Calcd. for C₂₈H₄₆O₂: C, 81.10; H, 11.18. Found: C, 81.25; H, 11.30.

4 α -Methyl-5 α -cholestane-3,6-dione (XXV). a) **From 4 β -Methyl-5 α -cholestane-3,6-dione (XXIII)**—A solution of XXIII (100 mg.) in AcOH (10 ml.) containing 3 drops of H₂SO₄ was heated on steam bath for 1 hr., and poured into H₂O. The product was extracted with Et₂O, and Et₂O layer was washed with 5% Na₂CO₃ and H₂O, and dried (Na₂SO₄). After evaporation of the solvent, the residue was recrystallized from MeOH-Me₂CO to give 4 α -methyl-5 α -cholestane-3,6-dione (XXV, 60 mg.), m.p. 120~124°. Further recrystallization from the same solvent afforded an analytical sample as colorless needles. m.p. 121.5~124°, $[\alpha]_D^{23} - 21^\circ$ (c=0.46), IR: $\nu_{\text{max}}^{\text{CS}_2}$ 1710 cm⁻¹ (C=O). Anal. Calcd. for C₂₈H₄₆O₂: C, 81.10; H, 11.18. Found: C, 81.28; H, 11.23.

b) **From 4 β -Methyl-5 β -cholestane-3,6-dione (XXIV)**—XXIV (34 mg.) was treated as the same manner described above, and the same compound, m.p. 121~124° was obtained as colorless needles.

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Summary

The Grignard reaction of 3 β -hydroxycholest-4-en-6-one (V) was undertaken in the presence of cuprous chloride or cupric acetate. 1,4-Addition product was isolated, and its structure was proved to be 3 β -hydroxy-4 β -methyl-5 α -cholestan-6-one (VI). Some transformations related to this compound were made. From observations of the Grignard reaction and other reactions of α,β -unsaturated steroidal ketones reported in literature, it may be concluded that the configuration of alkyl group newly introduced by 1,4-addition should be axially oriented.

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20) A solution of CrO₃ (26.72 g.) in H₂SO₄ (23 ml.) diluted with H₂O to a volume of 100 ml. was used.