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192. Kyosuke Tsuda and Shigeo Nozoe: Steroid Studies. XXI. On the Reaction of 5α,8α-Ethylenic Steroids.

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As a part of studies on alkylation of steroidal skeleton,[1] synthesis and reaction of steroidal compound having ethylenic bridge between 5α and 8α positions were carried out and attempts were also made to derive this compound into a steroid possessing substituents in 5β and 8β positions.[2]

When cholesta-5,7-dien-3-β-ol acetate (I) and methyl acrylate are heated in toluene, in the presence of hydroquinone, an adduct (II) is obtained in a good yield. The infrared spectrum of this substance indicates the presence of acetyl group, caboxylic acid ester, and a *cis*-substituted double bond. The double bond shows its presence by coloration with tetranitromethane but resists hydrogenation in acetic acid over platinum.

The peroxide formed by 1,4-addition of oxygen from the 5,7-diene compound is known to have 5α,8α-configuration.[3] Considering such a fact and steric interference of methyl group at ring juncture against the approach of dienophilic reagent, preferential assumption would be that the adduct (II) has a 5α,8α-ethylene-steroid skeleton[*2] formed by addition of methyl acrylate from the α-side. Therefore, the adduct should have a configuration shown in (IIa). What is interesting in this case is that (i) B-ring takes the partial structure of bicyclo[2.2.2]octene and the α-side of the original B-ring is shielded, and that (ii) the original B-ring takes the boat-form conformation, making the B/C ring juncture *cis* and changing the whole shape of the molecule,[4,5] and the β-side is also shielded by the two methyl groups.

In view of such a fact, examinations were made to see how the reactivity of 5α,8α-ethylene-steroid differed from that of steroids with ordinary skeleton.

Alkaline hydrolysis of the adduct (II) under mild conditions afforded a hydroxy-ester (III) of m.p. 91~92°, while a more drastic conditons gave a hydroxy-acid (IV), m.p. 233°. Methylation of (IV) with diazomethane changed it to (III), while acetylation of (III) reverted it to the adduct (II). Acetylation of (IV) gave an acetoxy-acid (V), m.p. 162~163°, which reverted to (II) on methylation. This shows that the configuration of the carboxyl does not undergo inversion by alkali treatment.

Reduction of (II) or (III) with lithium aluminium hydride produces a diol (VI) of m.p. 169~170°. Attempted partial acetylation of (VI) with one mole of acetic anhydride only afforded a diacetate (VII), m.p. 109°, and the recovered starting material.

Chromic acid oxidation of the hydroxy-ester (III) and hydroxy-acid (IV) was attempted but the starting compounds were recovered with pyridine-chromium trioxide while the starting compound and structurally unknown oily substance were obtained with acetic acid-chromic acid, the objective 3-ketone compound not being obtained. This was considered to be due to blocking of abstraction of hydrogen by the steric or electronic interference on axial hydrogen atom in the 3-position.[6,7]

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*2 The skeleton of the adduct will be named 5α,8α-ethylenecholestane and will be numbered as indicated in formula (IIa).

1) This Bulletin, **7**, 232, 238(1959).
2) A. Windaus, H. H. Inhoffen: Ann., **510**, 260(1934).
3) A. Windaus, *et al.*: Ann., **472**, 195(1929); L. Fieser: Experientia, **6**, 312(1950).
4) C. Djerassi, *et al.*: J. Am. Chem. Soc., **79**, 3835(1957).
5) T. Reichstein: Helv. Chim. Acta, **41**, 1234(1958).
6) D. H. R. Barton: Experientia, **6**, 316(1950); J. Chem. Soc., **1953**, 1027.
7) A. Eschenmoser: Angew. Chem., **67**. 278(1955); Helv. Chim. Acta, **38**, 1529(1955)

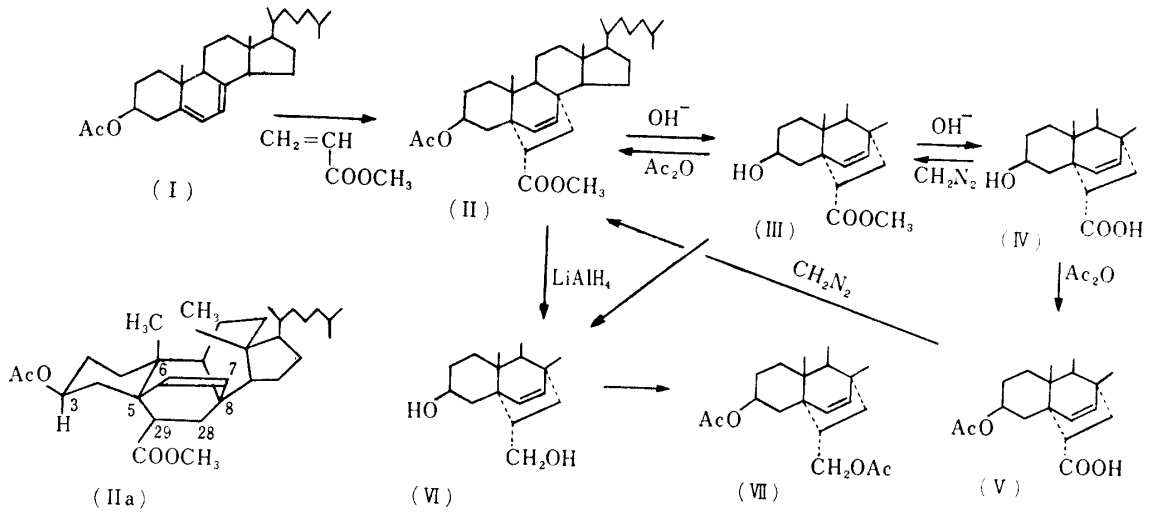

Chart 1.

The hydroxy-acid (IV) does not react with *p*-toluenesulfonyl chloride but application of methanesulfonyl chloride affords a neutral substance of m.p. 95°, not containing sulfur. This substance agrees with the molecular formula of $C_{30}H_{46}O_2$, which corresponds to the starting hydroxy-acid minus one mole of water. The absorptions of a hydroxyl (3400 cm^{-1}), carboxylic OH (3000~3200 cm^{-1}), and carboxylic C=O (1692 cm^{-1}) are no longer present in its infrared spectrum and in their stead, a new absorption for lactone appears at 1778 cm^{-1}. The position of this absorption corresponds to that of ordinary γ-lactone. Considering the mechanism of its formation, this absorption must be that of a δ-lactone shifted to a higher wave-number region. In fact, δ-lactone of a spirostane system is known to show a shift of its carbonyl absorption to 1793 cm^{-1}.[8]

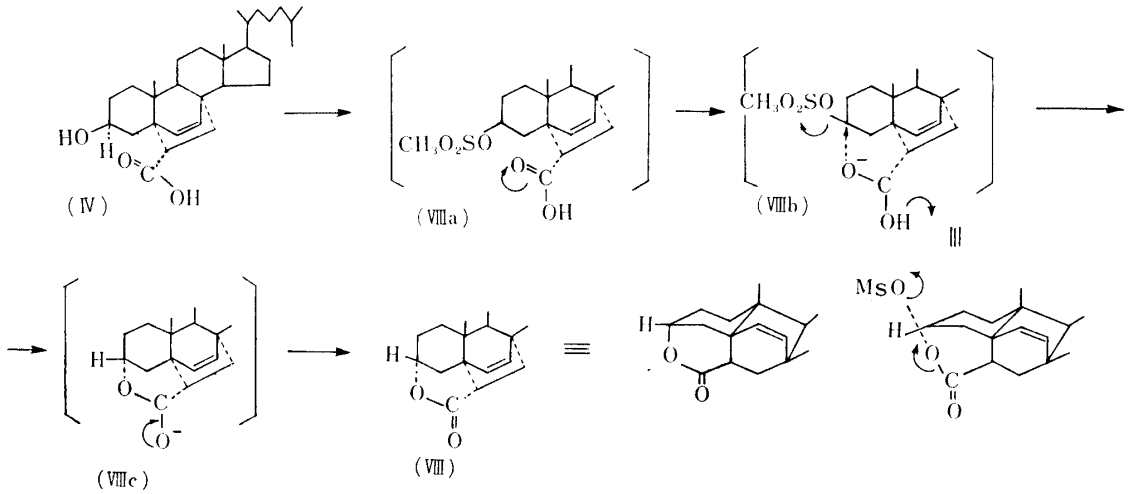

Chart 2.

The hydroxyl in (IV) takes the β-configuration and cannot form a lactone even if the carboxyl is in 29-position. Actually, there is no formation of a lactone on treatment of (IV) with an acid. Consequently, mechanism of the formation of the lactone (VIII) is thought to go through the following route. The action of methanesulfonyl chloride on (IV) first produces 3β-methanesulfonate (VIIIa), from which the methanesulfonyl group is liberated

8) R. N. Jones, F. Herling: J. Org. Chem., **19**, 1252(1954).

by the attack, from the rear, of intramolecular carboxylate ion[9,10] to form (Ⅷb), followed by formation of (Ⅷc) by liberation of a proton, and the lactone (Ⅷ) is finally produced. These experimental results revealed that the position of the carboxyl in (Ⅳ) is not at 28- but at 29-position. It has also been revealed that in the Diels-Alder reaction, the acrylate undergoes addition from the α-side in such a manner that the ester group is oriented nearer to the A-ring.

Reaction of the hydroxy-ester (Ⅲ) with methanesulfonyl chloride in pyridine affords the 3β-methanesulfonate (Ⅸ), m.p. 106°, in a good yield. The infrared spectrum of (Ⅸ) indicates absorption due to the sulfonate at 1352 and 1178 cm^{-1}, in addition to that of ester carbonyl.

Acetolysis of (Ⅸ) by heating in 80% acetic acid, in the presence of potassium acetate, produces two substances, one of m.p. 100° and the other of m.p. 91°. The former was identified with the above-mentioned acetoxy-ester (Ⅱ) and the latter with the hydroxy-ester (Ⅲ), both by the mixed melting point test and infrared spectra.

Heating of (Ⅸ) in methanol, in the presence of a small amount of acid or alkali, afforded a substance of m.p. 69°, which was found to be the 3-methoxy compound (Ⅹ) from infrared spectrum and elemental analyses. In order to determine the configuration of the methoxyl in (Ⅹ), the hydroxy-ester (Ⅲ), whose configuration at 3-position is known, was submitted to O-methylation by the process which does not involve inversion of configuration, i.e. application of diazomethane in the presence of boron trifluoride catalyst.[11,12] This has shown that the methoxyl compound and (Ⅹ) obtained by methanolysis of (Ⅸ) are the same substances and the configuration of 3-position in (Ⅹ) was determined as β.

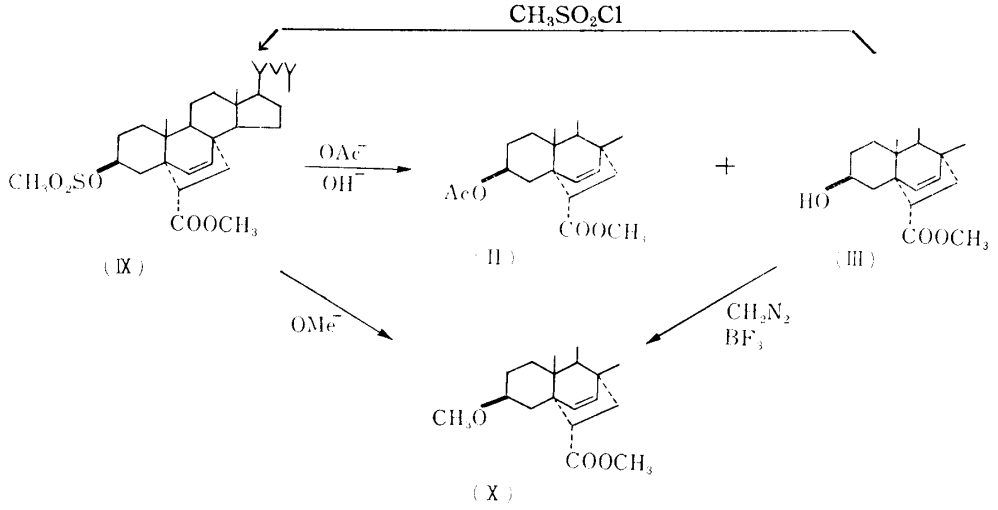

Chart 3.

The fact that the configuration of 3-position was retained in solvolysis, as iterated above, is rather interesting compared to the solvolysis of ordinary saturated steroids.[13] If the reaction progresses by the S_N2 mechanism, as in the case of solvolysis of cholestan-3β-ol tosylate,[13] there should naturally have been inversion of configuration at 3-position.

From the formation of the lactone described above it has been found that the ester carbonyl is situated sufficiently close to the α-side at 3-position and it seems most appropriate to consider the mechanism of this reaction as the intramolecular S_N2-type reaction which is

9) W. A. Cowdrey, E. D. Hughes, C. K. Ingold : J. Chem. Soc., **1937**, 1208.
10) C. D. Vernooy, C. S. Rondestredt : J. Am. Chem. Soc., **77**, 3582(1955).
11) M. Neeman : Tetrahedron, **6**, 36(1959).
12) M. C. Casevio, W. S. Johnson : J. Am. Chem. Soc., **80**, 2584(1958).
13) C. W. Shoppee, D. T. Westcott : J. Chem. Soc., **1955**, 1375; *ibid.*, **1946**, 1138.

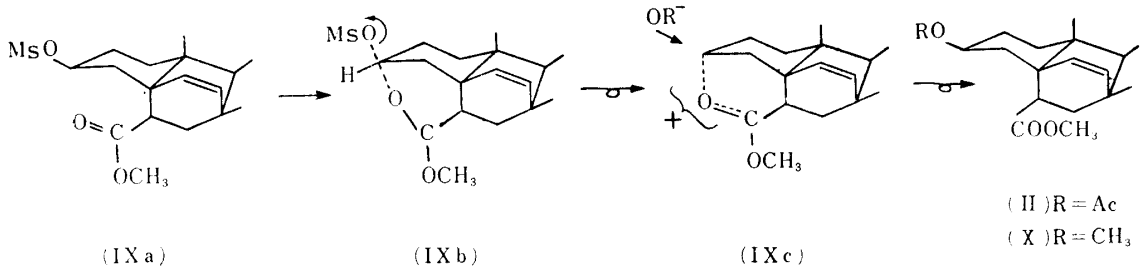

Chart 4.

participated by a neighboring group.[14] This is illustrated in Chart 4. The ester carbonyl situated on the α-side of the carbon atom at 3-position satisfies electrostatic or steric requirements, attacks the methanesulfonyl group at 3β-position from the rear by the intramolecular SN 2 mechanism to accelerate its liberation, and takes the "distributed cation" structure as an intermediate after liberation. Further, it submits to the attack of solvent anion from the β-side and forms the 3β-acetoxy compound (II) or 3β-methoxy compound (X). In other words, there is a double inversion and the configuration at 3-position is retained. The reaction which progresses by the participation of a neighboring group like this requires antiparallel coplanarity to some extent between the liberating group (methanesulfonyl) and the participating group (ester carbonyl),[15] and the α-configuration*3 of the ester at 29-position is more preferable than the β.

Application of acrolein to (I) under the same reaction conditions as in the case of methyl acrylate affords an adduct of m.p. 111°, whose infrared spectrum indicates absorptions for acetyl group (1734 and 1255 cm^{-1}) and aldehyde (2720 and 1734 cm^{-1}). Reduction of this substance with lithium aluminium hydride gives a diol which was found to be the same as

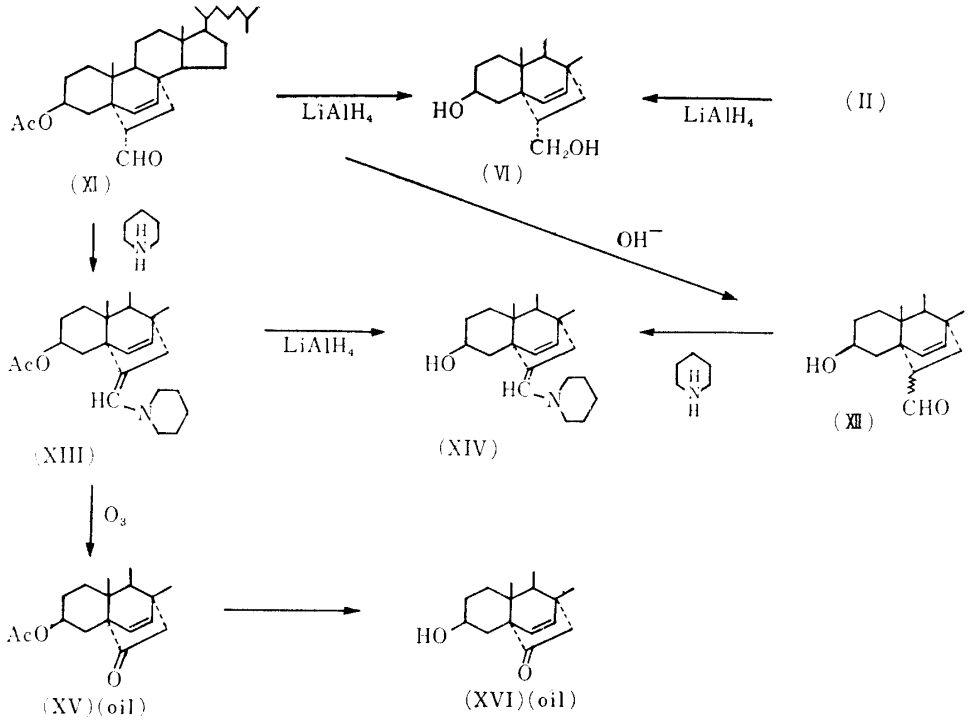

Chart 5.

*3 The *cis*-configuration towards the C_5-C_6 bond is designated as β and *trans*-configuration as α.

14) S. Winstein, L. Goodman, R. Boschan : J. Am. Chem. Soc., **72**, 2311, 4669(1950); T. Taguchi, *et al.* : *Ibid.*, **73**, 5679(1951); D. Taub, R. D. Hoffeomner, N. L. Wendler : *Ibid.*, **81**, 3291(1959).

15) S. Winstein, *et al.* : J. Am. Chem. Soc., **70**, 816(1948).

the diol (VI) described above. It follows, therefore, that the acrolein adduct has the same configuration as that of the acrylate adduct and the structural formula (XI) is given to it.

Alkaline hydrolysis of the acetoxy-formyl compound (XI) gives a mixture (XII) of two kinds of hydroxy-formyl compounds with different configuration at 29-position and application of piperidine to this mixture quantitatively produces hydroxy-enamine (XIV). Application of piperidine to (XI) affords an acetoxy-enamine (XIII) which is derived to (XIV) by treatment with lithium aluminium hydride. Ozonolysis of (XIII) to the ketone compound (XV) and its alkaline hydrolysis affords the hydroxy-ketone compound (XVI). All these compounds failed to undergo crystallization.

Treatment of (XI) with acetic anhydride, in the presence of potassium acetate, affords two kinds of enol acetate (XVII and XVIII) of m.p. 94° and m.p. 160°, in approximately 8:2 ratio. Since (XVII) and (XVIII) form the same product by ozonolysis, they are known to be geometric isomers at the double bond. The ozonolysis product of (XVII) and (XVIII) is a substance (XIX) melting at 170°, corresponding to the molecular formula of $C_{31}H_{48}O_5$, and its infrared spectrum indicates absorptions for aldehyde (2720 cm^{-1}), acetate (1735 and 1245 cm^{-1}), and enol-type β-diketone (3040~3100 and 1580 cm^{-1}), while its ultraviolet spectrum has absorption maxima at 252 and 282 mμ. The substance colors brownish green to ferric chloride solution and also colors with tetranitromethane.

These characteristics suggest that this substance has an enolizable β-diketone structure and indicates the possible presence of at least one hydrogen atom in the carbon atoms situated between the two carbonyl groups. Consequently, it would not be the objective β-diketone compound (XX) but must be a compound formed by rearrangement, having a structure like (XXI) or (XXII). This structure is left undetermined.

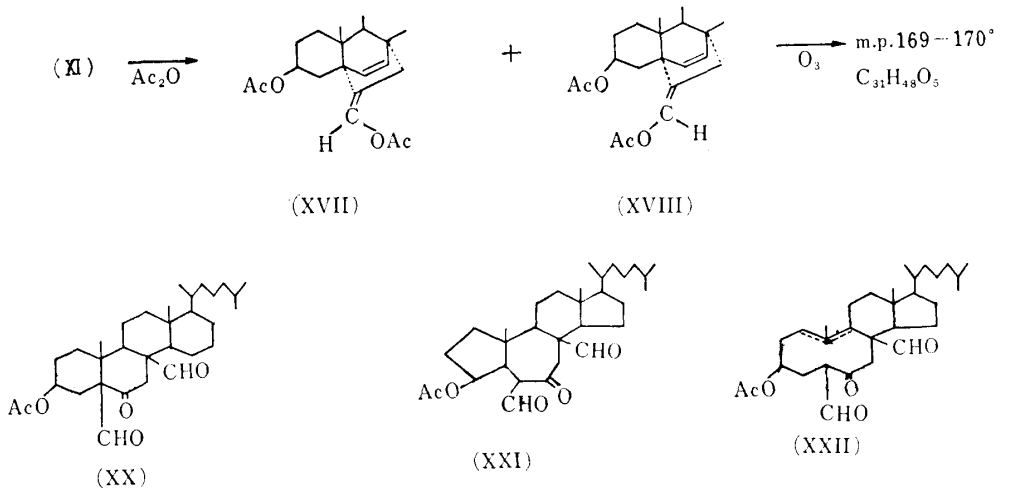

Chart 6.

Experimental

All melting points are uncorrected. Infrared spectra were obtained in Nujol with Koken Model DS-301 Spectrophotometer and ultraviolet spectra were measured in MeOH with Beckman Model DK-2 Spectrophotometer. Rotations were determined for $CHCl_3$ solution at room temperature unless otherwise stated.

29α-Methoxycarbonyl-5α,8α-ethylenecholest-6-en-3β-ol Acetate (II)—A solution of 20 g. of cholesta-5,7-dien-3-ol acetate (I), 20 g. of freshly distilled methyl acrylate, and 40 mg. of hydroquinone in 30 cc. of dry xylene was heated at 170° in a stainless autoclave for 17 hr. under magnetical stirring. After cooling the reaction mixture, removal of the excess methyl acrylate and solvent *in vacuo* gave colorless oily product, which was triturated with 20 cc. of MeOH and stood for one day at 0°. The resulting crystals were collected and washed with MeOH. Recrystallization from MeOH gave 11 g. of colorless prisms of (II). The filtrate was evaporated to dryness *in vacuo* and residual oil was chromatographed on silica gel and elution with benzene gave colorless oil, which was recrystallized

by trituration with MeOH. Recrystallization from MeOH gave 4 g. of (II) melting at 100~101°. *Anal.* Calcd. for $C_{33}H_{52}O_4$: C, 77.29; H, 10.22. Found: C, 77.24; H, 10.18. $[\alpha]_D^{25}$ −103°(c=1.22). IR λ_{max} cm^{-1}: 1737, 1245, 1193, 1067, 1033.

29α-Methoxycarbonyl-5α,8α-ethylenecholest-6-en-3β-ol (III) and 29α-Carboxy-5α,8α-ethylenecholest-6-en-3β-ol (IV)—A solution of 4 g. of (II), 5 g. of KOH, and 5 cc. of H_2O in 30 cc. of MeOH was heated under reflux for 15 min. on a water bath. When cool, the reaction mixture was diluted with 100 cc. of H_2O and extracted with Et_2O. The extract was washed with 10% KOH solution and H_2O, and dried over Na_2SO_4. The solvent was evaporated to dryness *in vacuo* and residual oily substance was passed through alumina column eluted with petr. ether-benzene. From the first eluted portion, 500 mg. of the starting material was recovered. The oily substance obtained from the second eluate was dissolved in a minimum quantity of MeOH and refrigerated. The resulting crystals were collected and recrystallized from MeOH to give 2 g. of (III) as colorless needles, m.p. 91~92°. *Anal.* Calcd. for $C_{31}H_{50}O_3$: C, 79.10; H, 10.71. Found: C, 78.96; H, 10.60. $[\alpha]_D^{25}$ −91°(c=1.23). IR λ_{max} cm^{-1}: 3300, 1734, 1332, 1194, 1180, 1157, 1062, 1047.

The alkali solution was acidified with 2*N* HCl and extracted with Et_2O, which was washed with H_2O, dried over Na_2SO_4, and evaporated *in vacuo*. Recrystallization from AcOEt afforded 1 g. of (IV) as colorless needles, m.p. 233~234° (decomp.).

On the other hand, a solution of 4 g. of (II) and 5 g. of KOH in 30 cc. of MeOH was heated under reflux for 6 hr. After cooling the reaction mixture, it was acidified with 10% HCl, resulting white precipitate was collected by filtration, washed with H_2O, and dried. Recrystallization from AcOEt gave 3.5 g. of (IV), described above. *Anal.* Calcd. for $C_{30}H_{48}O_3$: C, 78.89; H, 10.59. Found: C, 78.91; H, 10.59. $[\alpha]_D^{25}$ −88°(EtOH, c=0.61). IR λ_{max} cm^{-1}: 3400, 3000~3200, 1692, 1185, 1042.

Esterification of (IV) with CH_2N_2—A suspension of 4.57 g. of (IV) in 200 cc. of dry Et_2O containing 10 cc. of MeOH was treated with dropwise addition of CH_2N_2 in Et_2O solution until a yellow color persisted. After completion of the addition, the pale yellow solution was allowed to stand for 1 hr. at room temperature. Evaporation of the solvent *in vacuo* gave an oily product, which crystallized on trituration with MeOH. Recrystallization from MeOH gave 4.5 g. of colorless silky needles, m.p. 90~91°, undepressed on admixture with (III).

Acetylation of (III)—Acetylation of (III) with Ac_2O in pyridine gave colorless needles, which showed no depression on admixture with (II).

29α-Carboxy-5α,8α-ethylenecholest-6-en-3β-ol Acetate (V)—To a solution of 457 mg. of (IV) in 5 cc. of pyridine, 5 cc. of Ac_2O was added dropwise. After usual processing, 290 mg. of crude (V) was obtained. Recrystallization from AcOEt gave (V) as needles, m.p. 162~163°(decomp.). *Anal.* Calcd. for $C_{32}H_{50}O_4$: C, 77.06; H, 10.11. Found: C, 76.94; H, 10.10. $[\alpha]_D^{25}$ −128°(c=0.84). IR λ_{max} cm^{-1}: 3020~3080, 1730, 1685, 1250, 1196, 1040, 1036, 884.

29α-Hydroxymethyl-5α,8α-ethylenecholest-6-en-3-ol—To a cold solution of 1 g. of acetoxy-ester (II) in 50 cc. of dehyd. Et_2O an excess of $LiAlH_4$ in Et_2O solution was added and the reaction mixture was then allowed to stand at room temperature overnight. After decomposition of unreacted $LiAlH_4$ by adding H_2O, the solution was acidified with 10% HCl and extracted with Et_2O. The Et_2O layer was washed successively with 10% HCl, 10% $NaHCO_3$, and H_2O, dried over Na_2SO_4, and evaporated to leave colorless crystals. Recrystallization from AcOEt gave silky needles of (VI) melting at 169~170°. *Anal.* Calcd. for $C_{30}H_{50}O_2$: C, 81.69; H, 11.38. Found: C, 81.60; H, 11.36. $[\alpha]_D^{25}$ −141° (c=0.83). IR λ_{max} cm^{-1}: 3320, 1070, 1037, 1026.

Diacetate (VII)—Acetylation of (VI) under the usual condition employing pyridine-Ac_2O gave (VII), which was recrystallized from MeOH; m.p. 108~109°. *Anal.* Calcd. for $C_{34}H_{54}O_4$: C, 77.52; H, 10.33. Found: C, 77.68; H, 10.34. $[\alpha]_D^{25}$ −88°(c=0.9). IR λ_{max} cm^{-1}: 1747, 1250, 1034.

29α-Carboxy-5α,8α-ethylenecholest-6-en-3α-ol Lactone (VIII)—1.5 g. of hydroxy-carboxylic acid (IV) was dissolved in 30 cc. of anhydrous pyridine and the solution was cooled to 0°. 2 cc. of methanesulfonyl chloride was added dropwise with stirring in N_2. The reaction mixture was then allowed to stand overnight. The resulting brown solution was poured into a large amount of H_2O, the collected precipitate was washed with H_2O, and dried. The crude product was dissolved in Et_2O and washed successively with 10% HCl, 10% $NaHCO_3$, and H_2O. Evaporation of the solvent *in vacuo* gave 1.45 g. of yellow oil, which was chromatographed on 50 g. of Florisil. Elution with benzene-Et_2O (99 : 5) and crystallization from MeOH gave 200 mg. of the lactone (VIII), m.p. 94~95°. *Anal.* Calcd. for $C_{30}H_{46}O_2$: C, 82.13; H, 10.57. Found: C, 82.17; H, 10.55. $[\alpha]_D^{25}$ +26°(c=0.76). IR λ_{max} cm^{-1}: 1778, 1152, 1016, 1007, 1007, 1000, 990.

29α-Methoxycarbonyl-5α,8α-ethylenecholest-6-en-3β-ol Mesylate (IX)—A solution of 1.5 g. of hydroxy-ester (III) dissolved in 30 cc. of anhydrous pyridine was cooled to 0°, 1 cc. of methanesulfonyl chloride was added dropwise with stirring, and the mixture was allowed to stand overnight at 0°. The reaction mixture was poured into a large amount of H_2O, extracted with Et_2O. The extract was washed successively with 10% HCl, 10% $NaHCO_3$, and H_2O, dried and evaporated *in vacuo* to leave 2 g. of pale yellow oil. The residual oil was dissolved in a small amount of MeOH, chilled in

ice, and the resulting crystals were collected. Recrystallization from Et_2O-MeOH gave 1.9 g. of colorless silky needles of the mesylate (IX), m.p. 106~107°. *Anal.* Calcd. for $C_{32}H_{52}O_5S$: C, 70.04; H, 9.55; S, 5.55. Found : C, 70.06; H, 9.52; S, 5.75. $[\alpha]_D^{25}$ −97°(c=1.03). IR λ_{max} cm^{-1} : 1726, 1352, 1177, 970, 950.

Acetolysis of the Mesylate (IX)—A solution of 400 mg. of the mesylate (IX) in 200 cc. of 80% aq. AcOH, containing 5 g. of KOAc, was heated under reflux for 4 hr. The reaction mixture was poured into H_2O and allowed to stand overnight. Filtration of the resulting crystals and recrystallization from MeOH gave 190 mg. of colorless needles, m.p. 99~100°, which was identical in all respects with the 3β-acetate (II) mentioned before. The filtrate was extracted with Et_2O and the extract was washed with 10% $NaHCO_3$ solution to remove AcOH. Evaporation of Et_2O to dryness gave 60 mg. of colorless oil, which crystallized on addition of MeOH and chilled in ice. Recrystallization from MeOH gave 40 mg. of needles, m.p. 89~90°, which was identical in all respect with the 3β-hydroxy compound (III) mentioned above.

29α-Methoxycarbonyl-5α,8α-ethylenecholest-6-en-3β-ol Methyl Ether (X)—i) A solution of 485 mg. of mesylate (IX) dissolved in 40 cc. of MeOH containing 40 mg. of KOH, was heated under reflux for 1 hr. After cooling the reaction mixture, crystals of K-methanesulfonate so formed were filtered off. Neutralization of the filtrate with 10% HCl, dilution with H_2O, and extraction with Et_2O gave a yellow oil, which was chromatographed on Florisil. Elution with benzene and recrystallization from MeOH gave 170 mg. of the methoxy-ester (X), m.p. 68~69°. *Anal.* Calcd. for $C_{32}H_{52}O_3$: C, 79.28; H, 10.81. Found : C, 79.28; H, 10.74. $[\alpha]_D^{25}$ −102°(c=0.76). IR λ_{max} cm^{-1} : 1732, 1192, 1110, 1104, 1010.
ii) A solution of 300 mg. of the mesylate (IX) dissolved in 30 cc. of MeOH, containing 1 drop of conc. HCl, was heated under reflux for 3 hr. in N_2. The reaction mixture was concentrated to 5 cc. in volume, diluted with H_2O, extracted with Et_2O, and the extract was washed with 10% $NaHCO_3$ solution and H_2O. Evaporation of Et_2O gave 250 mg. of oil, which crystallized on addition of MeOH and chilling in ice. Recrystallization from MeOH gave 210 mg. of (X), m.p. 67~68°.
iii) O-Methylation of 3β-hydroxy compound (III) : A solution of 100 mg. of (III) in 10 cc. of dehyd. Et_2O was cooled in dry ice-acetone bath, 1 cc. of 47.5% BF_3-Et_2O was added to the solution, and a large excess of CH_2N_2 in Et_2O was added dropwise with vigorous stirring. The reaction mixture was diluted with Et_2O, polymer formed was removed by filtration, and the filtrate was washed with 10% $NaHCO_3$ solution and H_2O. Evaporation of the solvent to dryness gave 105 mg. of colorless oil, which was purified by alumina chromatography. Elution with benzene and recrystallization from MeOH gave 70 mg. of (X), m.p. 68~69°, which was identical with the sample prepared by methanolysis of the mesylate (IX).

29α-Formyl-5α,8α-ethylenecholest-6-en-3β-ol Acetate (XI)—A solution of 10 g. of cholesta-5,7-dien-3-ol acetate (I), 10 g. of freshly distilled acrolein, and 100 mg. of hydroquinone in 30 cc. of anhyd. xylene was treated by the same procedure as described for preparation of (II). After cooling the reaction mixture, the solvent was evaporated to dryness *in vacuo*. The residue was purified by chromatography over 200 g. of silica gel, and the fraction eluted first with benzene was crystallized from Et_2O-MeOH to give 4.8 g. of the formyl derivative (XI) as needles, m.p. 110~111°. *Anal.* Calcd. for $C_{32}H_{50}O_3$: C, 79.62; H, 10.44 Found : C, 79.40; H, 10.40. $[\alpha]_D^{20}$ −95°(c=0.63). IR λ_{max} cm^{-1}: 2738 (doublet), 1735, 1256, 1030.

$LiAlH_4$ Reduction of the Formyl Derivative (XI)—To a solution of 483 mg. of (XI) in 15 cc. of anhyd. Et_2O, 100 mg. of $LiAlH_4$ in 20 cc. of Et_2O was added under stirring. The reaction mixture was treated by the same processing as described for reduction of (II). Recrystallization from AcOEt gave 380 mg. of diol, m.p. 168~169°, undepressed on admixture with the diol (VI).

29-[(N-Piperidinyl)methylene]-5α,8α-ethylenecholest-6-en-3β-ol Acetate (XII)—To a solution of 4.83 g. of formyl derivative (XI) and 400 mg. of *p*-toluenesulfonic acid in 60 cc. of anhyd. benzene, a large excess (5 cc.) of piperidine was added, and the mixture was heated at reflux in N_2 atmosphere, using moisture trap. After 1.5 hr., theoretical amount of H_2O had collected, and the reaction mixture was evaporated to dryness *in vacuo*. Trituration with MeOH and recrystallization from AcOEt-MeOH gave 5 g. of enamine (XII) as needles, m.p. 137~138°. *Anal.* Calcd. for $C_{37}H_{59}O_2N$: C, 80.82; H, 10.82; N, 2.55. Found : C, 80.62; H, 10.79; N, 2.69. $[\alpha]_D^{25}$ −178°(c=1.16). IR λ_{max} cm^{-1} : 1738, 1652, 1250, 1175, 1126, 1037, 1018, 868.

29-[(N-Piperidinyl)methylene]-5α,8α-ethylenecholest-6-en-3-ol (XIV)—i) Via hydroxy-formyl derivative (XIII) : A solution of 2.8 g. of (XI) in 20 cc. of MeOH was refluxed with 500 mg. of KOH for 20 min. in N_2 atmosphere. Extraction with Et_2O and evaporation of the solvent gave 2.02 g. of oil, which is an isomeric mixture of hydroxy-formyl derivative. A solution of the oily substance in 30 cc. of benzene was treated with 2 cc. of piperidine and 200 mg. of *p*-toluenesulfonic acid by the same procedure as described for preparation of enamine (XII) to give 1.8 g. of (XIV), m.p. 133~135°. *Anal.* Calcd. for $C_{35}H_{57}ON$: C, 82.78; H, 11.31; N, 2.76. Found : C, 82.76; H, 11.20; N, 2.77. $[\alpha]_D^{25}$ −166°(c=0.96). IR λ_{max} cm^{-1} : 3200, 1660, 1160, 1131, 1080.
ii) A solution of 100 mg. of (XIII) in 15 cc. of Et_2O and 10 mg. of $LiAlH_4$ was allowed to stand overnight.

After usual processing, 52 mg. of (XIV) was obtained.

29-Acetoxymethylene-5α,8α-ethylenecholest-6-en-3β-ol Acetate A (XVII) and B (XVIII)—A mixture of 9.66 g. of formyl derivative (XI), 200 cc. of Ac_2O, and 5.0 g. of freshly fused NaOAc was heated at reflux for 5 hr. in N_2. The reaction mixture was evaporated to dryness *in vacuo*. The residue was redissolved in 200 cc. of Et_2O and washed with 10% $NaHCO_3$ solution and H_2O. Evaporation of the solvent and trituration with MeOH gave 9.02 g. of crude crystal. Recrystallization from MeOH–AcOEt gave 1.6 g. of enol acetate B (XVIII) as silky needles, m.p. 159~160°. *Anal.* Calcd. for $C_{34}H_{52}O_4$: C, 77.82; H, 9.99. Found: C, 77.59; H, 9.87. $[\alpha]_D^{25}$ −145° (c=1.16). IR λ_{max} cm^{-1}: 1765, 1670, 1250, 1222, 1092, 1033, 828.

On the other hand, concentration of the filtrate gave colorless crystals. Recrystallization from MeOH–AcOEt gave 6 g. of enol acetate A (XVII), m.p. 94~95°. *Anal.* Calcd. for $C_{34}H_{52}O_4$: C, 77.82; H, 9.99. Found: C, 77.61; H, 9.89. $[\alpha]_D^{25}$ −116° (c=1.00). IR λ_{max} cm^{-1}: 1759, 1740, 1242, 1220, 1105, 1040, 1670.

Ozonization of Enol Acetate (XVII or XVIII)—A solution of 1.84 g. of the enol acetate (XVII or XVIII) in 150 cc. of CH_2Cl_2 was chilled in dry ice-acetone bath. A stream of ozone-rich oxygen (28.8 mg. of ozone/min.) was passed into the cold solution. After 2.2 moles of ozone was absorbed, ozonization was stopped. To a well stirred suspension of 3 g. of zinc dust in this reaction mixture, 100 cc. of HOAc was added and stirring was continued for 2 hr. at room temperature. After removal of zinc dust by filtration, the solvent wes concentrated to 100 cc., diluted with a large amount of H_2O, and extracted with Et_2O. The extract was washed with 10% $NaHCO_3$ solution to remove HOAc and dried over Na_2SO_4. Evaporation of the solvent gave 1.64 g. of brown oily substance, which crystallized on trituration with MeOH and chilling in ice. Recrystallization from MeOH gave 200 mg. of (XIX) as needles, m.p. 169~170°. *Anal.* Calcd. for $C_{31}H_{48}O_5$: C, 74.36; H, 9.66. Found: C, 74.21; H, 9.59. $[\alpha]_D^{25}$ −12° (c=1.18). UV λ_{max} mμ: 252 (6800), 282 (shoulder). IR λ_{max} cm^{-1}: 3050~3100 (broad), 2680, 2720, 1740, 1710, 1560, 1250.

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Summary

Diels–Alder reaction of methyl acrylate and acrolein on cholesta-5,7-dien-3β-ol acetate was carried out and the structure of the adduct thereby obtained was determined. Solvolysis of 3-methanesulfonate of these 5α,8α-ethylene-steroids was carried out and retention of configuration was found to take place, whose mechanism was considered.

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