in a reduced pressure left 115 mg. of pale yellowoily sb nstance which was dissolved in benzene-hexane (1:1) mixture and chromatographed over 5.0 g. of alumina (Woelm grade II). The fraction eluted with benzene-$CHCl_3$ (1:1) mixture and benzene afforded 79 mg. of a crystalline substance which recrystallized form benzene-hexane to cubic crystals, m.p. 133.5~134°, of 6ξ-methyl-B-norandrost-4-ene-3,17-dione (VIIIf), $[\alpha]_D^{28.5}$ +90.6° (c=2.23). *Anal.* Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.46; H, 9.00. UV: λ_{max}^{EtOH} 239.5 mμ (ε 15,920). IR ν_{max}^{KBr} cm^{-1}: 1738 (17-CO), 1663, 1635 (Δ^4-3-CO).

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Summary

3β,5-Dihydroxy-6β-formyl-B-nor-5β-steroids (IIIa, b, c) of cholestane, pregnane, and androstane series were converted into the corresponding 3β,5-dihydroxy-6β-methyl-B-nor-5β-steroids (VIa, d, e) by reduction of (III) with sodium borohydride, followed by tosylation of 6-hydroxymethyl group and subsequent treatment with lithium aluminium hydride. The compounds (VI) were oxidized to 3-oxo-5-hydroxy-6β-methyl-B-nor-5β-steroid derivatives (VIIa, b, f) which were then dehydrated to 6ξ-methyl-B-norcholest-4-en-3-one (VIIIa), 6ξ-methyl-B-norpregn-4-ene-3,20-dione (VIIIb), and 6ξ-methyl-B-norandrost-4-ene-3,17-dione (VIIIf).

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71. Rinji Takasaki: Steroid Series. VIII.*1 Ozonization of Some Unsaturated Steroid Derivatives.

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In a previous paper of this series,[1] it was shown that cyclic ethylene acetals of cholest-4-en-3-one, pregn-4-ene-3,20-dione, and androst-4-ene-3,17-dione afforded the corresponding 5β,6β-epoxide in 53.5%, 55.5%, and 40.3% yield, respectively, together with 5-hydroxy-6β-formyl-B-nor-5β-steroid derivatives on ozonization and subsequent reduction of the ozonide followed by alumina chromatography.

Peracid oxidations of these steroid compounds are known to afford predominantly α-epoxides, along with a smaller amount of the β-epimers. The formation of epoxide by the action of ozone on an ethylenic linkage has sometimes been recognized when the double bond is sterically hindered on one side.[2] It should be noted, however, that epoxidation reaction proceeded selectively to form the β-epimer with ozone, in contrast to the peracid oxidation of the unsaturated steroid compounds. Early reports suggest that catalytic hydrogenation of 3-oxo-Δ^4-steroid generally affords 3-oxo-5β-*H*-steroid, while 5α-*H*-epimer is obtained, clearly due to the steric environment, when it possesses

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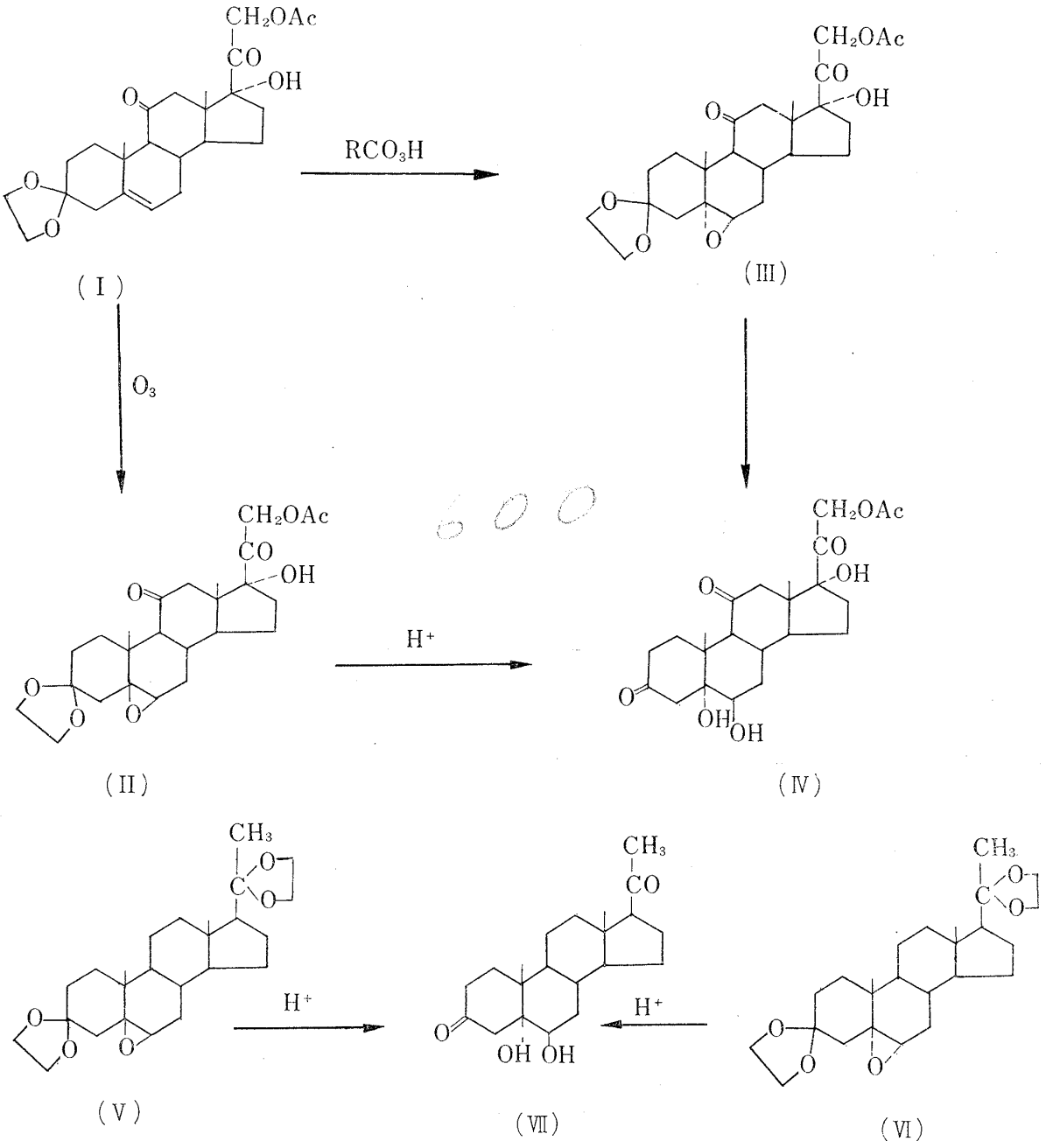
*1 Part VII. : This Bulletin, **10**, 439 (1962).

*2 Nishi-Shinagawa, Shinagawa-ku, Tokyo (高崎林治).

1) K. Tanabe, R. Takasaki, R. Hayashi: This Bulletin, **9**, 7 (1961).
2) P. S. Bailey: Chem. Revs., **58**, 945 (1958).

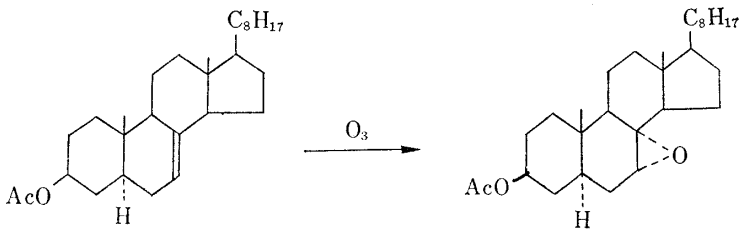
β-hydroxyl or -carbonyl group at C_{11}-position.[3] In order to determine the effect of 11-substituent group on the configuration of the epoxide formed on oxidation with ozone, 17α,21-dihydroxypregn-4-ene-3,11,20-trione 21-acetate 3-(ethylene acetal)[4] (I) was treated with ozone in dichloromethane solution and the resulting mixture was reduced with zinc dust and acetic acid until active oxygen was no longer detected. After chromatographic separation over alumina, there was obtained a crystalline substance melting at 220.5°, $[\alpha]_D$ +34.2°, in 42.7% yield, whose composition, $C_{25}H_{34}O_8$, indicated that one oxygen atom was newly incorporated into (I). The infrared spectrum of this substance showed a band at 841 cm^{-1}, which might be attributable to an epoxide function.[5]



3) J. Pataki, G. Rosenkranz, C. Djerassi: J. Biol. Chem., **195**, 751 (1952), and references cited there.
4) F. Sondheimer, O. Mancera, G. Rosenkranz: J. Am. Chem. Soc., **76**, 5020 (1954).
5) W. A. Patterson: Anal. Chem., **26**, 823 (1954).

Sondheimer, *et al.*[4] prepared 5,6-epoxide (III) with m.p. > 300° by peracid oxidation of (I) and converted it on treatment with perchloric acid into 5,6β,17α,21-tetrahydroxy-5α-pregnane-3,11,20-trione 21-acetate (IV), which was found to be obtainable also from (II) in the same condition. On treatment with perchloric acid, the identical compound, 5,6β-dihydroxy-5α-pregnane-3,20-dione (VII), was formed from 5,6α-epoxy-5α-pregnane-3,20-dione bis (ethylene acetal) (VI) as well as from its epimeric 5β,6β-epoxide (V). On the basis of these observations the compound (II) was concluded to be the epimeric epoxide of (III) obtained by peracid oxidation. For the purpose of comparison, the epoxide (III) was prepared from (I) by oxidation with monoperphthalic acid and it showed m.p. 308°, $[\alpha]_D$ −68.2°, after repeated recrystallization. From the well known fact that peracid oxidation predominantly furnishes α-epoxide and that 5α,6α-epoxide shows negative rotational contribution,[6] it was considered that (III) is most probably α-epoxide and (II) must therefore be β-epoxide. On paper partition chromatography, using carbitol-methanol as a stationary phase and methylcyclohexane as a mobile phase, (III) was found to move faster than (II). This also supported the configuration of the epoxides assigned. This experiment appears to show that 11-carbonyl group exerts no effect on the configuration of the epoxide formed by the action of ozone on cyclic ethylene acetal of 4-en-3-oxosteroid.

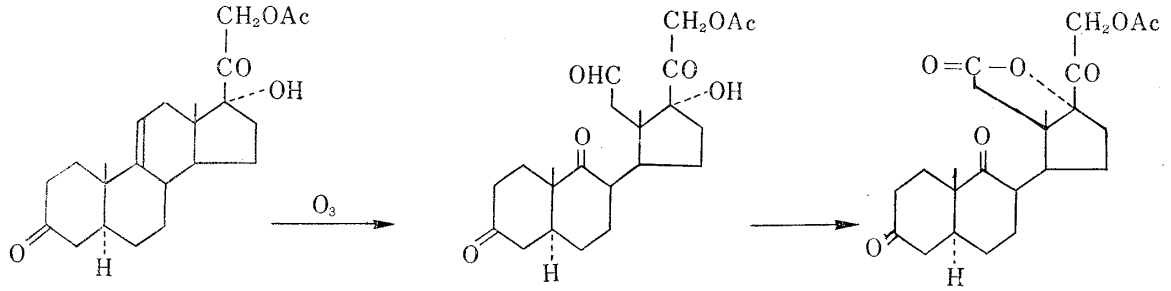
When 5α-cholest-7-en-3β-ol acetate (VIII) was treated with ozone, it afforded a crystalline material of m.p. 95.5~97°, $[\alpha]_D$ +6.95°, in 20% yield, which gave analytical values corresponding to $C_{29}H_{48}O_3$, indicating that one oxygen atom was incorporated into (VIII). The substance showed physical constants closely resembling those of 7α,8α-epoxy-5α-cholestan-3β-ol acetate (IX), and the substance was identified by mixed melting point determination with (IX), which was prepared from (VIII) with monoperphthalic acid according to the method of Fieser and Goto.[7] Such epoxidation reaction with ozone is similar to the formation of the 7,8-epoxide of methyl dihydromasticadienoate.[8]



(VIII) (IX)

Ozone oxidation of 17α,21-dihydroxy-5α-pregn-9(11)-ene-3,20-dione 21-acetate[9] (X) in dichloromethane solution at 0° resulted in cleavage of the double bond at 9(11)-position to afford a substance of m.p. 178~180° with composition of $C_{23}H_{32}O_7$, to which the structure of 17α,21-dihydroxy-9,11-seco-5α-pregnane-3,9,20-trion-11-al 21-acetate (XI) was assigned. A probable alternative 11,17-hemiacetal structure of (XI) might be excluded, since it was recovered unchanged on attempting acetylation and benzoxylation. Oxidation of (XI) with chromium trioxide in acetic acid afforded a material melting at 172~173°, whose analytical values were consistent with $C_{23}H_{30}O_7$. In the infrared spectrum of this compound no hydroxyl band was exhibited and an absorption band attributable to a carbonyl group of γ-lactone appeared newly at 1780 cm^{-1} and, therefore, this substance was

6) A. Bowers, L.C. Ibanez, H.J. Ringold: Tetrahedron, **7**, 138 (1959).
7) L.F. Fieser, T. Goto: J. Am. Chem. Soc., **82**, 1693 (1960).
8) D.H.R. Barton, E. Seoane: J. Chem. Soc., **1956**, 4150.
9) R.M. Evans, G.F.H. Green, J.S. Hunt, A.G. Long, B. Moonly, G.H. Phillips: *Ibid.*, **1958**, 1529.



(X) (XI) (XII)

assumed to be 17α,21-dihydroxy-9,11-seco-5α-pregnane-3,9,20-trione-11-carboxylic acid 11,17-lactone 21-acetate (XII).

Experimental*3

Ozonization of 17α,21-Dihydroxypregn-4-ene-3,11,20-trione 21-Acetate 3-(Ethylene acetal) (I)——A solution of 4.0 g. of (I) in 2 L. of CH_2Cl_2 was ozonized by passing a stream of ozonized air at about −60° to −70° by chilling with Dry Ice-Me_2CO mixture until the solution turned pale violet. To the reaction mixture, zinc dust (8.0 g.) and AcOH (32 cc.) were added and the solution was stirred at room temperature until it became negetive to the KI test. After filtration of inorganic substance, the filtrate was washed with H_2O to remove AcOH and dried. Evaporation of the solvent at a reduced pressure gave 4.53 g. of a white solid, which was chromatographed on 200 g. of acid-washed alumina. Elution with $CHCl_3$ afforded 1.768 g. (42.7%) of a crystalline material, which was recrystallized from hexane-Me_2CO to 17α,21-dihydroxy-5,6β-epoxy-5β-pregnane 3,11,20-trion 21-acetate 3-(ethylene acetal) (II) as leaf lets of m.p. 218.5～220.5°, $[\alpha]_D^{28}$ +34.2° (c=2.86 pyridine). *Anal.* Calcd. for $C_{25}H_{34}O_8$: C, 64.92; H,7.41. Found : C, 64.99; H, 7.15. IR ν_{max}^{KBr} cm^{-1} : 3340 (OH), 1745 (AcO), 1725 (20-CO), 1675 (11-CO), 841(-O-).

17α,21-Dihydroxy-5,6α-epoxy-5α-pregnane-3,11,20-trione 21-Acetate 3-(Ethylene acetal) (III)——A mixture of 3.0g. of (I) in 330 cc. of Et_2O and 300 cc. of Et_2O solution of 2 mol. equiv. of monoperphthalic acid was set aside for 20 hr. at room temperature. The solution was then washed with 2% $NaHCO_3$ solution, H_2O, and dried. Evaporation of the solvent afforded a residue, which was crystallized from hexane to 2.38 g. of a crystalline material of m.p. 278～292° (decomp.). Recrystallization from $CHCl_3$-hexane gave 17α,21-dihydroxy-5,6α-epoxy-5α-pregnane-3,11,20-trione 21-acetate 3-(ethylene acetal) (III) of m.p. 308°, $[\alpha]_D^{28.5}$ −68.2° (c=0.61 pyridine). (reported[4] m.p.>300° $[\alpha]_D$+62°) *Anal.* Calcd. for $C_{25}H_{34}O_8$: C, 64.92; H, 7.41. Found : C, 64.91; H, 7.34. IR ν_{max}^{KBr} cm^{-1} : 3420 (OH), 1750 (AcO), 1730(20-CO), 1710 (11-CO).

5,6β,17α,21-Tetrahydroxy-5α-pregnane-3,11,20-trione 21-Acetate (IV)——a) A mixture of 300 mg. of 5β,6β-epoxide (II) in 20 cc. of Me_2CO and 1.4 cc. of 1.5*N* $HClO_4$ was stirred for 18 hr. at room temperature, then poured into H_2O, and extracted with $CHCl_3$. The extract was washed with H_2O and dried. Ramoval of the solvent afforded 290 mg. of a residue, which was recrystallized from hexane-Me_2CO to (IV), m.p. 280～281°. *Anal.* Calcd. for $C_{23}H_{32}O_8$: C, 63.28; H, 7.39. Found : C, 62.91; H, 7.62. IR ν_{max}^{KBr} cm^{-1} : 3460, 3400 (OH), 1745, 1720, 1702 (CO).

b) A mixture of 300 mg. of 5α,6α-epoxide (III) in 20 cc. of Me_2CO and 1.4 cc. of 1.5*N* $HClO_4$ was stirred for 18 hr. at room temperature, then poured into H_2O, and the precipitate, separated by filtration, was washed with H_2O, and dried. Recrystallization from hexane-Me_2CO gave 290 mg. of crystals melting at 278～279°, which was identified with the sample obtained as in (a) by mixed m.p. and infrared spectra.

5,6β-Dihydroxy-5α-pregnane-3,20-dione (VII)——a) To a solution of 500 mg. of 5,6β-epoxy-5β-pregnane-3,20-dione bis (ethylene acetal) (V) in 20 cc. of Me_2CO, 1.4 cc. of 1.5*N* $HClO_4$ was added. The mixture was stirred for 18 hr. at room temperature, during which a crystalline material separated from the solution, which was collected and washed with H_2O. Recrystallization from MeOH afforded (VII) with m.p. 287～289° (decomp.).

b) A solution of 500 mg. of 5,6α-epoxy-5α-pregnane-3,20-dione bis(ethylene acetal) (VI) in 20 cc. of Me_2CO and 1.4 cc. of 1.5*N* $HClO_4$ was treated as described above, and (VII), m.p. 290～293°, was obtained which was identified with the sample obtained as in (a) by mixed m.p. and infrared spectra.

*3 All m.p.s are uncorrected. Rotations were measured in $CHCl_3$.

$[\alpha]_D^{29.5}$ +52.0°(c=2.49 pyridine). *Anal.* Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.34; H, 9.23.

7α,8α-Epoxy-5α-Cholestan-3β-ol Acetate (IX)——A solution of 5.0 g. of 5α-cholest-7-en-3β-ol acetate (VIII) in 300 cc. of CH_2Cl_2 was ozonized by passing a stream of an ozonized air at about −60° to −70° by chilling with dry ice-Me_2CO mixture until the solution turned pale violet. Zinc dust (10 g.) and AcOH(40 cc.) were added to the reaction mixture and the solution was stirred for 1.5 hr. at room temperature. After filtration of inorganic substance, the filtrate was washed with H_2O, 1% $NaHCO_3$ solution, and dried. Evaporation of the solvent at a reduced pressure gave 5.6 g. of a pale yellow oily residue, which was chromatographed on 200 g. of alumina (Woelm grade II). Elution with petr. ether-benzene (1:1) and benzene afforded 1.598 g. of 7α,8α-epoxy-5α-cholestan-3β-ol acetate (IX), which, after recrystallized from MeOH, melted at 95.5~97°. $[\alpha]_D^{30}$ + 6.95° (c=1.94 $CHCl_3$) (reported m.p. 96~97°, $[\alpha]_D$ +8.5°).[7] *Anal.* Calcd. for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found: C, 78.29; H, 10.54.

Ozonization of 17α,21-Dihydroxy-5α-pregn-9(11)-ene-3,20-dione 21-Acetate(X)——A solution of 2.0 g. of (X) in 1 L. of CH_2Cl_2 was ozonized by passing a stream of ozonized air (0.6 mmol. O_3/min.) for 1.5 hr. at about 0° by chilling with ice. Zinc dust (4.5 g.) and AcOH (20 cc.) were added to the reaction mixture and the solution was stirred for 3 hr. at room temperature. After filtration of inorganic substance, filtrate was washed with H_2O, 1% $NaHCO_3$ solution, and dried. Evaporation of the solvent afforded syrup, which recrystallized from petr. ether-benzene to give 1.1 g. of 17α,21-dihydroxy-9,11-seco-5α-pregnane-3,9,20-trion-11-al 21-acetate (XI) with m.p. 172~174°. Recrystallization from the samesolvent, it showed m.p. 178~180°. *Anal.* Calcd. for $C_{23}H_{32}O_7$: C, 65.69; H, 7.67. Found: C, 65.62; H, 7.59. IR ν_{max}^{Nujol} cm^{-1}: 3460 (OH), 1750, 1740, 1700 (CO).

17α,21-Dihydroxy-9,11-seco-5α-pregnane-3,9,20-trione-11-carboxylic Acid 11,17-Lactone 21-Acetate (XII)——A solution of 65 mg. of CrO_3 in 2 cc. of AcOH was added to a solution of 100 mg. of (XI) in 5 cc. of AcOH. The mixture was kept for 4.5 hr. at room temperature and then EtOH was added to decompose the excess reagent. After dilution with H_2O, the mixture was extracted with $CHCl_3$, the extract was washed with 5% $NaHCO_3$ solution and H_2O, and dried. Removal of the solvent gave 77 mg. of a residue, which was recrystallized from petr. ether-benzene to (XII), m.p. 172~173°. *Anal.* Calcd. for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23. Found: C, 66.32; H, 6.92. IR ν_{max}^{Nujol} cm^{-1}: 1780 (γ-lactone), 1750, 1730, 1715, 1685 (CO).

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Summary

17α,21-Dihydroxypregn-4-ene-3,11,20-trione 21-acetate and 5α-cholest-7-en-3β-ol acetate were treated with ozone to afford the corresponding 5β,6β- and 7α,8α-epoxide, respectively. 17α,21-Dihydroxy-5α-pregn-9(11)-ene-3,20-dione 21-acetate gave 17α,21-dihydroxy-9,11-seco-5α-pregnane-3,9,20-trion-11-al 21-acetate on ozone oxidation, which was converted into 17α,21-dihydroxy-9,11-seco-5α-pregnane-3,9,20-trione-11-carboxylic acid 11, 17-lactone 21-acetate by oxidation with chromium trioxide.

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