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Munemitsu Tomoeda, Akihiko Ishida, and Toshitaka Koga : The Polyphosphoric Acid-Catalyzed Ring Opening of 4,5-Epoxy-3-oxo Steroids. Ⅳ.*1 The Synthesis of 17α-Hydroxy-4-ethylthiopregn-4-ene-3,20-dione and Its Analogs.*2

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In connection of our continuous studies[1~3] on the polyphosphoric acid (PPA)-catalyzed ring opening with suitable nucleophiles of 4,5-epoxy-3-oxo systems in the steroid nucleus, the present paper deals with a generalization of the reaction with the selective introduction of a thio-function by alkylmercaptans into C-4 position of 4β,5-epoxy-17α-hydroxypregnane-3,20-dione, and a further example of remarkable inertness of the carbonyl group at 20-position toward the reaction. Importance of introduction of a hydroxy function at C-17 in the steroid nucleus for pronounced biological activity[4] was also related to the motivation of the present investigation.

4,5-Epoxy-17α-hydroxypregnane-3,20-dione (Ⅱ), chosen as starting material for the present investigation, was obtained by alkaline hydrogen peroxide oxidation of 17α-hydroxypregn-4-ene-3,20-dione (Ⅰ),[5] prepared from pregna-5,16-diene-3,20-dione. The epoxide (Ⅱ) thus obtained was subjected to chromatography on silica gel giving 4α,5-epoxy-17α-hydroxypregnane-3,20-dione (Ⅱa) and its 4β-isomer (Ⅱb), in 24% and 63% yields respectively.

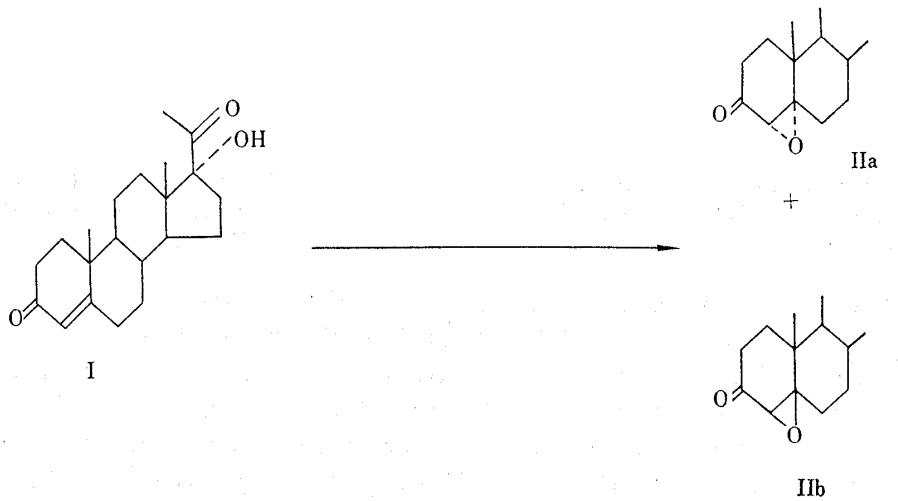

Chart 1.

*1 Part Ⅲ : This Bulletin, **13**, 1078 (1965).
*2 Presented at the meeting of the Hokuriku-Branch of the Pharmaceutical Society of Japan, held at Toyama University on 25th of September, 1965.
*3 Takara-machi, Kanazawa (友枝宗光, 石田昭彦, 古賀俊隆).

1) M. Tomoeda, M. Ishizaki, H. Kobayashi, S. Kanatomo, T. Koga, M. Inuzuka, T. Furuta : Tetrahedron, **21**, 733 (1965).
2) M. Tomoeda, M. Inuzuka, T. Furuta, T. Koga : This Bulletin, **13**, 769 (1965).
3) Part Ⅲ*1 published by M. Tomoeda, T. Furuta, T. Koga.
4) N. Applezweig : "Steroid Drugs," 101 (1962). McGraw Hill Book Co., Inc., New York.
5) H. J. Ringold, B. Löken, G. Rosenkranz, F. Sondheimer : J. Am. Chem. Soc., **78**, 816 (1956).

The elemental analyses of these epoxides were in agreement with the expected formulae, $C_{21}H_{30}O_4$. The spectroscopic properties of IIa, no characteristic UV absorption of α,β-unsaturated ketone, but only λ_{max} 300 mμ (ε 89), and IR spectrum ν_{max} 3467 (s), and 1695 (s) cm^{-1}, and of IIb, no intensive UV absorption, but λ_{max} 300 mμ (ε 96), and IR spectrum ν_{max} 3476 (s) and 1705 (s) cm^{-1}, supported these structures. The NMR spectrum of IIa showed three singlets at τ 6.93, τ 7.15, and τ 7.72, which could be assigned to C_{17} α-OH group, C_4 β-H, and 21-CH_3 group in the compound respectively, and that of IIb, three singlets at τ 6.97, τ 7.00, and τ 7.72, which could be assigned to C_{17} α-OH group, C_4 α-H, and 21-CH_3 group respectively, supporting the structures.

The α and β configurations at C-4 or C-5 of IIa and IIb were proved by optical rotatory dispersion (ORD) and circular dichroism (CD) analyses that IIa gave a negative Cotton effect curve,[3,6,7] while IIb gave a positive Cotton effect curve. Their symmetrical curves of IIa and IIb with opposite sign are shown in Fig. 1 and 2. In the present study, the 4β,5-epoxide (IIb) was used as the starting material for the subsequent reactions.

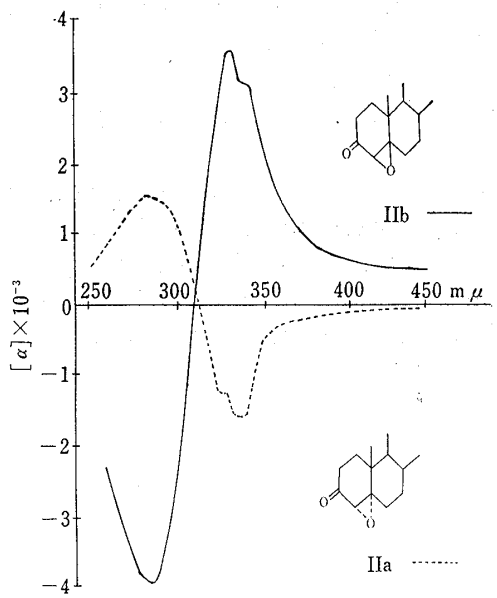

Fig. 1. Optical Rotatory Dispersion Curves of IIa at 11° and IIb at 15° in Dioxane

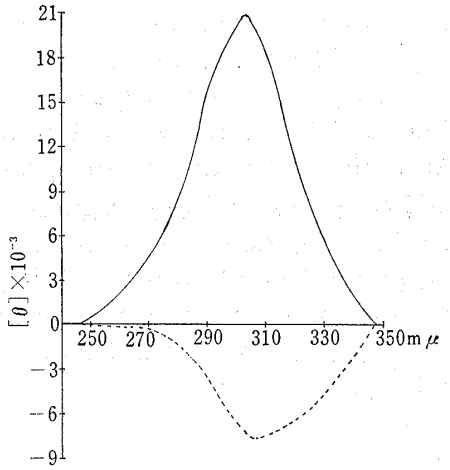

Fig. 2. Circular Dichrorism Curves of IIa and IIb at 18° in MeOH

The reaction of IIb with ethanethiol in PPA-dioxane (room temperature) was first attempted, and was complete in 4 hr. affording 17α-hydroxy-4-ethylthiopregn-4-ene-3,20-dione (III) and a further product, 17α-hydroxy-3,4-bis(ethylthio)pregna-3,5-dien-20-one (IV) as the crystalline products in 61% and 18% yields respectively.

The elemental analyses of these new thio-steroids were in agreement with the expected formulae, $C_{23}H_{34}O_3S$ (III) and $C_{25}H_{38}O_2S_2$ (IV) respectively. The spectroscopic evidence for the structure of III is as follows: the UV absorption spectrum exhibits λ_{max} 249 mμ (ε 12500) and 310 mμ (ε 2300), and IR spectrum ν_{max} 3412 (s), 1703 (s), 1659 (s), 1620 (w), and 1551 (s) cm^{-1}, which support the 17α-hydroxy-4-ethylthiosubstituted 4-en-3-oxo system.[1~3,8] The NMR spectrum does not show any peak in the olefinic proton region but does show peaks at τ 6.22 (doublet, J=14.5 c.p.s.), τ 6.97 (singlet), τ 7.14~7.58 (multiplet), and τ 7.72 (singlet), which can be assigned to C_6 α-H,[9] and C_{17} α-OH, -S-CH_2-, and 21-CH_3

6) M. Legrand, R. Viennet, J. Caumartin: Comp. Rend. Acad. Sci., Paris, **253**, 2378 (1961).
7) C. Djerassi, W. Klyne, T. Norin, G. Ohloff, E. Klein: Tetrahedron, **21**, 163 (1965).
8) J. M. Krämer, K. Brüchner, K. Irmscher, Karl-Heinz Bork: Ber., **96**, 2803 (1963).
9) M. Tomoeda, M. Inuzuka, T. Furuta, T. Takahashi: Tetrahedron Letters, **1964**, 1233.

groups in the compound respectively. The positive sign of the specific rotation, $[\alpha]_D^{18}$ +142°, corresponds to 4-thiosubstituted 4-en-3-oxo steroids.[1~3,8]

The spectroscopic evidence of IV is as follows: the UV spectrum exhibits λ_{max} 292 mμ (ε 10300) and IR spectrum ν_{max} 3416 (s), 1708 (s), 1697 (s), 1633 (w), and 1541 (m) cm^{-1}, which correspond to the 3,4-bis(ethylthio)substituted 3,5-diene system with 17α-hydroxy function.[1~3,10] The NMR spectrum shows peaks at τ 3.68 (broad), τ 7.09~7.51 (multiplet), τ 7.12 (singlet), and τ 7.66 (singlet), which can be assigned to C_6-H (vinylic), and -S-CH_2-, C_{17} α-OH, and 21-CH_3 groups respectively.[1~3] The negative sign of the specific rotation, $[\alpha]_D^{21}$ −225°, also corresponds to the 3,4-diethylthiosubstituted 3,5-diene system.[1~3,10]

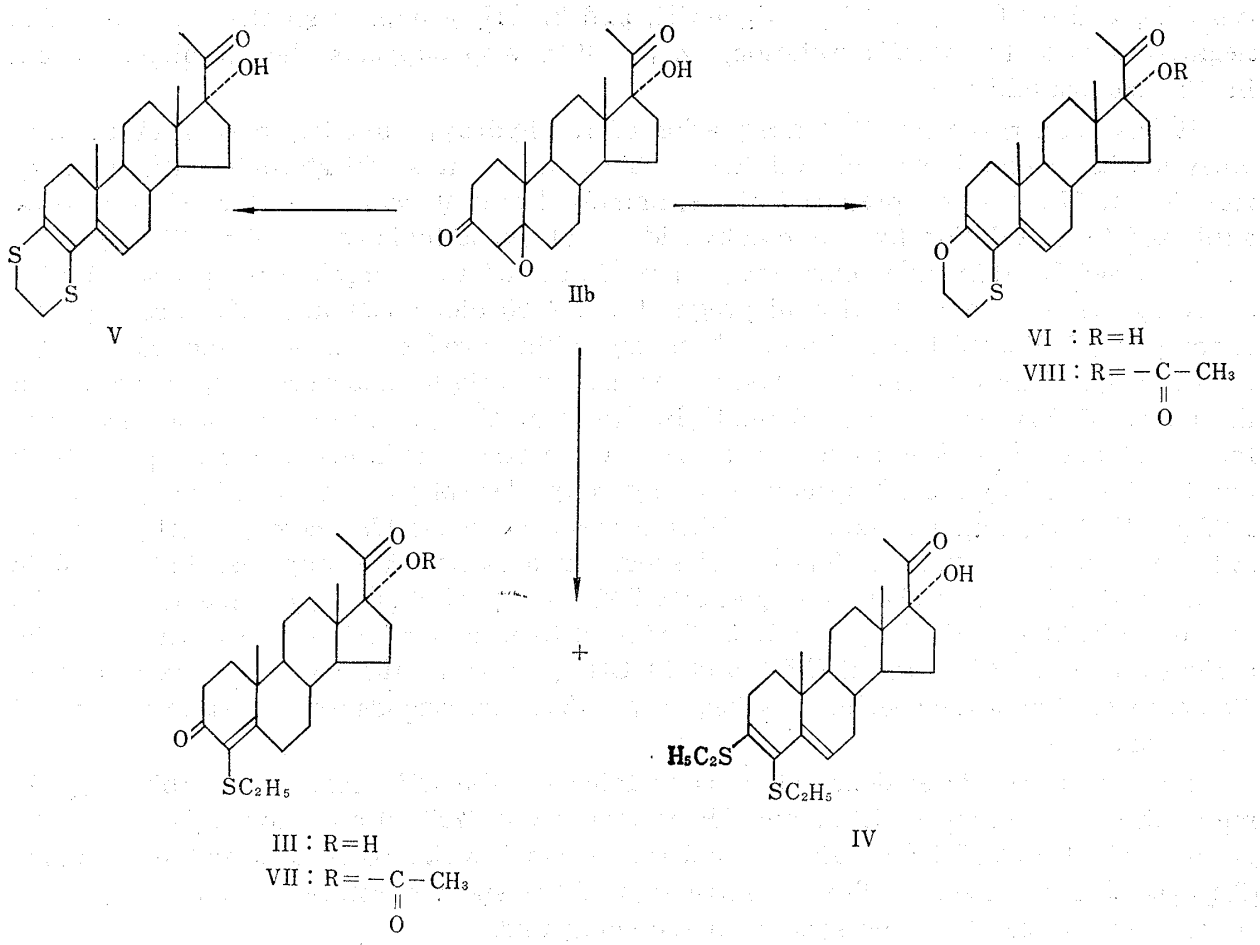

Chart 2.

Ethanedithiol and 2-mercaptoethanol were then used as nucleophiles for the reaction. The reagents reacted, as expected, with one end at C-4 of the 4β,5-epoxy-3-oxo system, followed by a spontaneous intramolecular cyclization with another end at C-3, forming heterocycles, 17α-hydroxy-20-oxopregna-3,5-dieno[3,4-*b*]dithiane (V) and its oxathiane (VI) derivative as the crystalline products in 27% and 53% yields respectively. No thioketalization could be observed. The elemental analyses of these new thiosteroids were in agreement with the expected formulae, $C_{23}H_{32}O_2S_2$ (V) and $C_{23}H_{32}O_3S$ (VI) respectively. The spectroscopic evidence for the structure of V is as follows: the UV spectrum exhibits λ_{max} 240 mμ (ε 10200) and 294 mμ (ε 12300), and IR spectrum ν_{max} 3498 (s), 1695 (s), 1633 (w), and 1570 (m) cm^{-1}, which correspond to the 3,5-dieno[3,4-*b*]dithiane system.[1~3,10] The NMR spectrum shows peaks at τ 4.03 (broad), τ 6.82 (singlet), and τ 7.68 (singlet) which can be assigned to C_6-H (vinylic), and -S-CH_2-CH_2-S- and 21-CH_3 groups[9] respec-

10) L.F. Fieser, C. Yuan, T. Goto: J. Am. Chem. Soc., **82**, 1996 (1961).

tively. The signal due to C_{17} α-OH group could not be identified, possibly, owing to its being marked in the strong peak due to -S-CH_2-CH_2-S- group. The negative sign of the specific rotaion, $[\alpha]_D^{17}$ $-178°$, also corresponds to the 3,4-dithiosubstituted 3,5-diene system in the compound.[1~3,10]

The spectroscopic evidence for the structure of Ⅵ is as follows: the UV spectrum λ_{max} 221 mμ (ε 9300) and 271 mμ (ε 9000), and IR spectrum ν_{max} 3410 (s), 1696 (s), 1638 (w), and 1620 (s) cm^{-1}, which correspond to the 3,5-dieno[3,4-*b*]oxathiane system in the compound.[1~3,10] The NMR spectrum shows peaks at τ 4.45 (broad), τ 5.43~5.93 (multiplet), τ 6.88~7.08 (multiplet), τ 7.08 (singlet) and τ 7.72 (singlet), which can be assigned to C_6-H (vinylic), and -O-CH_2-, -S-CH_2-, C_{17} α-OH, and 21-CH_3 groups respectively.[1~3,10] The negative sign of the specific rotation, $[\alpha]_D^{20}$ $-191°$, also supports the 3,5-diene system in the compound.[1~3,10]

It has been revealed[5] that acetylation of 17α-hydroxy function may lead to derivatives with higher biological activities. Two of the new thiosteroids with hydroxy function at 17α-position prepared above, namely Ⅲ and Ⅵ, were therefore chosen to be subjected to acetylation by acetic anhydride-*p*-toluenesulfonic acid at 80°. The reaction was followed by thin-layer chromatography (TLC) and was complete in a few minutes affording 17α-acetoxy-4-ethylthiopregn-4-ene-3,20-dione (Ⅶ) and 17α-acetoxy-20-oxopregna-3,5-dieno[3,4-*b*]oxathiane (Ⅷ) as crystalline products in 46% and 25% yields respectively. The elemental analyses of these new thiosteroids were in agreement with the expected formulae, $C_{25}H_{36}O_4S$ and $C_{25}H_{34}O_4S$ respectively. The spectroscopic evidence for the structure of Ⅶ is as follows: the UV spectrum exhibits λ_{max} 247 mμ (ε 11000) and 315 mμ (ε 2100), and IR spectrum, no hydroxy absorption, but ν_{max} 1728 (s), 1710 (s), 1677 (s), 1640 (w), and 1553 (s) cm^{-1}, which correspond to the 17α-acetoxy-4-ethylthiosubstituted 4-en-3-oxo system. The NMR spectrum does not show any peak in the olefinic proton region but does show a singlet at τ 7.95 for C_{17} α-O-CO-CH_3 group and also peaks at τ 6.22 (doublet, J=14.5 c.p.s.) τ 7.09~7.56 (multiplet) and τ 7.87 (singlet), which can be assigned to C_6 α-H,[9] and -S-CH_2- and 21-CH_3 groups in the compound respectively. The positive sign of the specific rotation, $[\alpha]_D^{26}$ $+133°$, corresponds well to 4-thiosubstituted 4-en-3-oxo steroids.

The spectroscopic evidence of Ⅷ is as follows: the UV spectrum exhibits λ_{max} 222 mμ (ε 9500) and 271 mμ (ε 9400), and IR spectrum ν_{max} 1727 (s) cm^{-1} for C_{17} α-O-CO-CH_3 group, and also at 1703 (s), 1640 (w), and 1620 (s) cm^{-1}, which correspond to the 3,5-dieno-[3,4-*b*]oxathiane system. The negative sign of the specific rotation, $[\alpha]_D^{24}$ $-171°$, also corresponds to the 3,5-diene system in the compound.

Examination of biological activities of the new steroids sofar synthesized in the series of our studies is underway, and its result will be reported elsewhere.

Experimental*4

4α,5-Epoxy-17α-hydroxypregnane-3,20-dione (IIa) and 4β,5-Epoxy-17α-hydroxypregnane-3,20-dione (IIb) To a solution of 17α-hydroxyprogesterone[5] (m.p. 218~220°, 1.20 g.) (I) in MeOH (144 ml.), 1*N* NaOH (7.2 ml.) and 30% H_2O_2 (13 ml.) were added successively at 18°, and the mixture was kept at 5° for 8 hr. when the reaction was complete (TLC). To the reaction mixture $CHCl_3$ was added, and the $CHCl_3$ layer was separated, washed with water and dried (anhyd. Na_2SO_4). Concentration of the filtrate afforded a colorless solid of m.p. 100~114° (wt. 1.24 g.). This was chromatographed on silica gel (Kanto Chemical

*4 Melting points were taken on a Kofler-type hot-stage, and are uncorrected. $[\alpha]_D$ refers to chloroform, UV absorption spectra to 95% ethanol, and IR spectra to nujol unless otherwise stated. NMR spectra were run on a Varian Associates A-60 high resolution spectrometer, and the intensities or peak areas were measured by the integrator. ORD and CD measuremeants were made on a Japan Opitics Spectroscopic Co. ORD/UV-5 Automatic Spectrophotometer.

Co.) (124 g.) when elution with 4:1 benzene–ether (150 ml.) afforded 4α,5-epoxy-17α-hydroxypregnane-3,20-dione (IIa) as colorless prisms, m.p. 212~215° (wt. 266 mg., 21%). Further recrystallization from acetone gave material of m.p. 216~217°. *Anal.* Calcd. for $C_{21}H_{30}O_4$: C, 72.81; H, 8.73. Found: C, 72.52; H, 8.46. $[\alpha]_D^{20}$ −89°(c=0.93); RD in dioxane (c=0.148) at 11°, $[\alpha]_{400}$ −237°, $[\alpha]_{350}$ −861°, $[\alpha]_{336}$ −1740°, $[\alpha]_{328}$ −1351°, $[\alpha]_{324}$ −1318°, $[\alpha]_{312}$ 0°, $[\alpha]_{310}$ +179°, $[\alpha]_{286}$ +1520°, $[\alpha]_{250}$ +507°; CD in dioxane (c=0.096) at 18°, $[\theta]_{347}$ 0°, $[\theta]_{330}$ −4884°, $[\theta]_{306}$ −7744°, $[\theta]_{290}$ −3217°, $[\theta]_{270}$ −238°, $[\theta]_{247}$ 0°; UV λ_{max} mμ (ε): 300 (89) (C=O); IR ν_{max} cm^{-1}: 3467 (s), 1695 (s); NMR τ: 6.93 (one proton, singlet) (C_{17} α-OH), 7.15 (one proton, singlet) (C_4 β-H), 7.72 (three protons, singlet) (21-CH_3), 8.92 (three protons, singlet) (19-CH_3), 9.26 (three protons, singlet) (18-CH_3).

Further elution with 4:1 benzene–ether (150 ml.) afforded a colorless solid, m.p. 156~161° (wt. 295 mg.). Recrystallization from MeOH gave colorless prisms of m.p. 200~212° (wt. 76 mg.), and colorless needles of m.p. 163~170° (wt. 191 mg.). The former prisms were recrystallized twice from acetone to give α-epoxide (IIa), m.p. 213~216° (wt. 37 mg., 3%). The total yield of α-epoxide (IIa) then reached 24%. The latter needles were further recrystallized from MeOH to give 4β,5-epoxy-17α-hydroxypregnane-3,20-dione (IIb) as colorless needles, m.p. 169~172° (wt. 149 mg., 12%).

Continuous elution with the same solvent (300 ml.) afford further β-epoxide (IIb) as colorless needles, m.p. 170~173° (wt. 645 mg., 51%). The total yield of β-epoxide (IIb) then reached 63%. Recrystallization from MeOH gave material of m.p. 173~174°. *Anal.* Calcd. for $C_{21}H_{30}O_4$: C, 72.81; H, 8.73. Found: C, 72.63; H, 8.56. $[\alpha]_D^{20}$ +137°(c=0.96); RD in dioxane (c=0.112) at 15°, $[\alpha]_{400}$ +580°, $[\alpha]_{350}$ +1875°, $[\alpha]_{340}$ +3080°, $[\alpha]_{334}$ +3169°, $[\alpha]_{328}$ +3571°, $[\alpha]_{310}$ +179°, $[\alpha]_{309}$ 0°, $[\alpha]_{296}$ −4018°, $[\alpha]_{250}$ −2455°; CD in dioxane (c=0.096) at 18°, $[\theta]_{348}$ 0°, $[\theta]_{330}$ +5480°, $[\theta]_{303}$ +20968°, $[\theta]_{290}$ +15964°, $[\theta]_{270}$ +4527°, $[\theta]_{247}$ 0°; UV λ_{max} mμ (ε): 300 (96) (C=O); IR ν_{max} cm^{-1}: 3476 (s), 1705 (s); NMR τ: 6.97 (one proton, singlet) (C_{17} α-OH), 7.00 (one proton, singlet) (C_4 α-H), (three protons, singlet) (21-CH_3), 8.83 (three protons, singlet) (19-CH_3), 9.27 (three protons, singlet) (18-CH_3).

PPA Catalyzed Ring Opening of 4β,5-Epoxy-17α-hydroxypregnane-3,20-dione (IIb) with Ethanethiol: Formation of 17α-Hydroxy-4-ethylthiopregn-4-ene-3,20-dione (III), and 17α-Hydroxy-3,4-bis(ethylthio)-pregna-3,5-dien-20-one (IV)

A solution of IIb (490 mg.), ethanethiol (4.0 ml.), and PPA (4.0 g.) in dioxane (80 ml.) was kept at room temperature for 4 hr. when the reaction was complete (TLC). The mixture was poured into ice-water depositing a colorless solid, m.p. 167~174° (wt. 517 mg.). This was chromatographed on silica gel (Kanto Chemical Co.) (16 g.) when elution with 19:1 benzene–ether (200 ml.) afforded 17α-hydroxy-3,4-bis(ethylthio)-pregna-3,5-dien-20-one (IV) as pale yellow crystals, m.p. 184~187° (wt. 109 mg., 18%). Further recrystallization from MeOH gave colorless needles, m.p. 190~191.5° (wt. 18 mg., 3%). *Anal.* Calcd. for $C_{25}H_{38}O_2S_2$: C, 69.07; H, 8.82; S, 14.75. Found: C, 69.32; H, 8.40; S, 14.94. $[\alpha]_D^{21}$ −225°(c=0.44); UV λ_{max} mμ (ε): 292 (10300); IR λ_{max}^{KBr} cm^{-1}: 3416 (s), 1708 (s), 1697 (s), 1633 (w), 1541 (m); NMR τ: 3.68 (one proton, broad) (C_6-H), 7.09~7.51 (multiplet) (-S-CH_2-), 7.12 (one proton, singlet) (C_{17} α-OH), 7.66 (three protons, singlet) (21-CH_3), 9.05 (three protons, singlet) (19-CH_3), 9.24 (three protons, singlet) (18-CH_3).

Further elution with 4:1 benzene–ether (225 ml.) afforded 17α-hydroxy-4-ethylthiopregn-4-ene-3,20-dione (III) as pale yellow crystals, m.p. 184~186° (wt. 336 mg., 61%). Recrystallization from MeOH gave colorless needles, m.p. 185~186°. *Anal.* Calcd. for $C_{23}H_{34}O_3S$: C, 70.73; H, 8.77; S, 8.21. Found: C, 71.03; H, 8.71; S, 8.11. $[\alpha]_D^{18}$ +142°(c=0.87); UV λ_{max} mμ (ε): 249 (12500) and 310 (2300); IR ν_{max} cm^{-1}: 3412 (s), 1703 (s), 1659 (s), 1620 (w), 1551 (s); NMR τ: 6.22 (one proton, doublet (J=14.5 c.p.s.)) (C_6 α-H),[9] 6.97 (one proton, singlet) (C_{17} α-OH), 7.14~7.58 (multiplet) (-S-CH_2-), 7.72 (three protons, singlet) (21-CH_3), 8.76 (three protons, singlet) (19-CH_3), 9.24 (three protons, singlet) (18-CH_3).

PPA-Catalyzed Ring Opening of (IIb) with Ethanedithiol: Formation of 17α-Hydroxy-20-oxopregna-3,5-dieno[3,4-*b*]dithiane (V)

A solution of IIb (498 mg.), ethanedithiol (2.0 ml.) and PPA (4 g.) in dioxane (40 ml.) was kept at room temperature for 5 hr. when the reaction was complete (TLC). The reaction mixture was poured into ice-water depositing a colorless oil which was extracted into $CHCl_3$. The chloroform layer was washed with sat. $NaHCO_3$ aq. and water, and dried (anhyd. Na_2SO_4). Concentration of the chloroform filtrate afforded a colorless oily residue (wt. 783 mg.), which was treated with benzene affording 17α-hydroxy-20-oxopregna-3,5-dieno[3,4-*b*]dithiane (V) as colorless needles, m.p. 246~247° (wt. 99 mg., 17%). Concentration of the benzene filtrate afforded a residue which was subjected to chromatography on silica gel (Kanto Chemical Co.) (24 g.) when elution with 19:1 benzene–ether (75 ml.) afforded further V as colorless needles, m.p. 245~246° (wt. 57 mg., 10%). The total yield of V then reached 27%. Recrystallization from benzene gave material, m.p. 246~247°. *Anal.* Calcd. for $C_{23}H_{32}O_2S_2$: C, 68.26; H, 7.97; S, 15.85. Found: C, 67.96; H, 7.91; S, 16.02. $[\alpha]_D^{17}$ −178°(c=0.86); UV λ_{max} mμ (ε): 240 (10200), 294 (12300); IR ν_{max} cm^{-1}: 3498 (s), 1695 (s), 1633 (w), 1570 (m); NMR τ: 4.03 (one proton, broad) (C_6-H), 6.82 (four protons, singlet) (-S-CH_2-CH_2-S-), C_{17} α-OH unidentified, 7.68 (three protons, singlet) (21-CH_3), 8.98 (three protons, singlet) (19-CH_3), 9.23 (three protons, singlet) (18-CH_3).

PPA-Catalyzed Ring Opening of IIb with 2-Mercaptoethanol : Formation of 17α-Hydroxy-20-oxopregna-3,5-dieno[3,4-*b*]oxathiane (VI)

A solution of IIb (503 mg.), 2-mercaptoethanol (2.0 ml.), and PPA (2.0 g.) in dioxane (40 ml.) was kept at room temperature for 5 hr. when the reaction was complete (TLC). The reaction mixture was poured into ice-water depositing a colorless oil which was extracted into $CHCl_3$. The chloroform layer was separated and washed with sat. $NaHCO_3$ aq. and water, and dried (anhyd. Na_2SO_4). Concentration of the filtrate gave a colorless oil (wt. 441 mg.), which was chromatographed on silica gel (Kanto Chemical Co.) (16 g.) when elution with 19:1 benzene-ether (175 ml.) afforded 17α-hydroxy-20-oxopregna-3,5-dieno[3,4-*b*]oxathiane (VI) as colorless needles, m.p. 205~210° (wt. 299 mg., 53%). Recrystallization from MeOH gave material of m.p. 230~231.5° (wt. 177 mg., 31%). Further recrystallization from the same solvent gave m.p. 231~232.5°. *Anal.* Calcd. for $C_{23}H_{32}O_3S$: C, 71.09; H, 8.30; S, 8.25. Found : C, 70.90; H, 8.29; S, 8.03. $[\alpha]_D^{20}$ −191° (c=0.94); UV λ_{max} mμ (ε) : 221 (9300), 271 (9000); IR ν_{max} cm^{-1} : 3410 (s), 1696 (s), 1638 (w), 1620 (s); NMR τ : 4.45 (one proton, broad) (C_6-H), 5.43~5.93 (two protons, multiplet) (-O-CH_2-), 6.88~7.08 (two protons, multiplet) (-S-CH_2-), 7.08 (one proton, singlet) (C_{17} α-OH), 7.72 (three protons, singlet) (21-CH_3), 8.98 (three protons, singlet) (19-CH_3), 9.25 (three protons, singlet) (18-CH_3).

17α-Acetoxy-4-ethylthiopregn-4-ene-3,20-dione (VII)

A solution of III (571 mg.) and *p*-toluenesulfonic acid (140 mg.) in acetic anhydride (11.5 ml.) was kept at 80° for 10 min., and the reaction mixture was poured into ice-water depositing an amorphous brown solid which was filtrated off. The solid was dissolved in $CHCl_3$, and the chloroform layer was washed with sat. $NaHCO_3$ aq. and water, and dried (anhyd. Na_2SO_4). Concentration of the filtrate under reduced pressure afforded a colorless solid, m.p. 190~203° (wt. 750 mg.), which was chromatographed on silica gel (Kanto Chemical Co.) (80 g.) when elution with 19:1 benzene-ether (1250 ml.) afforded 17α-acetoxy-4-ethylthiopregn-4-ene-3,20-dione (VII) as colorless needles, m.p. 222~223° (wt. 288 mg., 46%). Further recrystallization from acetone gave material of m.p. 224~225°. *Anal.* Calcd. for $C_{25}H_{36}O_4S$: C, 69.41; H, 8.39; S, 7.64. Found : C, 69.52; H, 8.34; S, 7.38. $[\alpha]_D^{26}$ +133°(c=0.86); UV λ_{max} mμ (ε) : 247 (11000), 315 (2100); IR ν_{max} cm^{-1} : 1728 (s), 1710 (s), 1677 (s), 1640 (w), 1553 (s); NMR τ : 6.22 (one proton, doublet (J=14.5 c.p.s.)) (C_6 α-H),[9] 7.09~7.56 (multiplet) (-S-CH_2-), 7.87 (three protons, singlet) (21-CH_3), 7.95 (three protons, singlet) (17α-O-CO-CH_3), 8.73 (three protons, singlet) (19-CH_3), 9.31 (three protons, singlet) (18-CH_3).

17α-Acetoxy-20-oxopregna-3,5-dieno[3,4-*b*]oxathiane (VIII)

A solution of VI (404 mg.) and *p*-toluenesulfonic acid (96 mg.) in acetic anhydride (8.0 ml.) was kept at 80° for 30 min., and the reaction mixture was poured into ice-water depositing a colorless oil which was extracted into $CHCl_3$. The chloroform layer was washed with water, sat. $NaHCO_3$ aq. and water, and dried (anhyd. Na_2SO_4). Concentration of the filtrate gave an amorphous yellow solid, m.p. 240~255° (wt. 262 mg.). This was chromatographed on silica gel (Kanto Chemical Co.) (45 g.) when elution with 19:1 benzene-ether (500 ml.) afforded 17α-acetoxy-20-oxopregna-3,5-dieno[3,4-*b*]oxathiane (VIII) as colorless needles, m.p. 272~274° (wt. 229 mg., 51%). Recrystallization from benzene gave material of m.p. 277~279° (wt. 100 mg., 25%). Further recrystallization from the same solvent gave m.p. 281~282°. *Anal.* Calcd. for $C_{25}H_{34}O_4S$: C, 69.73; H, 7.94; S, 7.45. Found : C, 70.00; H, 7.99; S, 7.22. $[\alpha]_D^{24}$ −171°(c=0.91); UV λ_{max} mμ (ε): 222 (9500), 271 (9400); IR ν_{max}^{KBr} cm^{-1} : 1727 (s), 1703 (s), 1640 (w), 1620 (s).

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