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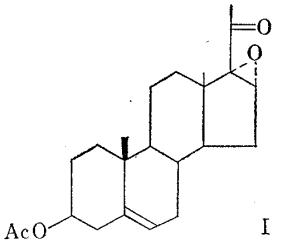
141. Munemitsu Tomoeda, Tetsuya Furuta,*1 and Toshitaka Koga: Studies on Conformation and Reactivity. III.*2 The Polyphosphoric Acid-catalyzed Ring Opening of 4,5-Epoxy-3-oxo Steroids. 3. The Synthesis of 16α,17-Epoxy-4-ethylthiopregn-4-ene-3,20-dione and its Analogs.*3

(*Faculty of Pharmacy, Kanazawa University**4)

It has been reported in the previous papers of this series[1,2] that polyphosphoric acid (PPA) can work as an efficient catalyst, when used in the presence of suitable nucleophiles, for both normal and abnormal ring openings of 4,5-epoxy-3-oxo systems in the cholestane and 17β-acetoxyandrostane series. Particularly with alkylmercaptans as reagent, the reaction began with the selective introduction of a thio-function at C-4 followed by a further substitution at C-3. The types of products thus formed were as follows: 4-ethylthio-4-en-3-oxo, 3,4-bis(ethylthio)-3,5-diene, 3,5-dieno[3,4-*b*]-dithiane and [3,4-*b*]oxathiane systems.

It now appeared to be of interest to apply the reaction to epoxides in the steroid nucleus under different stereochemical environment, such as 16,17-epoxy-20-oxo systems, and also to 4,5-epoxy-3-oxo systems in other biologically active steroid series. The present paper deals with the remarkable inertness of the 16α,17-epoxy-20-oxo system in 3β-acetoxy-16α,17-epoxypregn-5-en-20-one (I) toward the ring opening reaction with alkylmercaptans under PPA catalysis and also with the further genelarization of the selective introduction of a thio-function by alkylmercaptans at C-4 of the 4β,5-epoxy-3-oxo system in 4β,5:16α,17-diepoxy-5β-pregnane-3,20-dione (IIb).

Attempted PPA-catalyzed Ring Opening of 3β-Acetoxy-16α,17-epoxypregn-5-en-20-one (I) with Alkylmercaptans



I

Chart 1.

The 16α,17-epoxy-20-one (I), prepared from 3β-acetoxypregna-5,16-dien-20-one by the method of Julian, *et al.*,[3] was treated with ethanethiol in PPA-dioxane at room temperature or at 90~95°, and also with ethanedithiol in PPA-dioxane at room temperature. The reagents, however, did not react with the epoxide (I) neally at all and the starting material was recovered as the only isolable crystalline product in good yields.

The PPA-catalyzed Normal Ring Opening of 4β,5:16α,17-Diepoxy-5β-pregnane-3,20-dione (IIb) with Alkylmercaptans

The observation of the inertness of the 16α,17-epoxy-20-oxo system toward the catalytic action of PPA at room temperature for the introduction of a thio-function at the D-ring prompted us to attempt the reaction with the 4,5-epoxy-3-oxo derivative of I, 4,5:16α,17-diepoxypregnane-3,20-dione (II). Important motivations of the use of

*1 Present address: Research Laboratories, Yoshitomi Pharmaceutical Co., Fukuoka.
*2 The Part II: This Bulletin, **13**, 769 (1965).
*3 Presented at the Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, on 6th April, 1964.
*4 Takara-machi, Kanazawa (友枝宗光, 古田哲弥, 古賀俊隆).

1) M. Tomoeda, M. Ishizaki, H. Kobayashi, S. Kanatomo, T. Koga, M. Inuzuka, T. Furuta: Tetrahedron. **21**, 733 (1965).
2) The part II*2 published by M. Tomoeda, M. Inuzuka, T. Furuta, and T. Koga.
3) P. L. Julian, E. W. Meyer, I. Ryden: J. Am. Chem. Soc., **72**, 369 (1950).

the diepoxide (Ⅱ) for the reaction were that the reaction would take place only at the ring A of the compound with the 16α,17-epoxy-20-oxo system in the ring D remained unreacted, and that the products thus formed with an oxy function at C-17*[5] would be worthwhile to be put into biological screening.

16α,17-Epoxypregn-4-ene-3,20-dione (Ⅲ),[3] derived from I by Oppenauer-oxidation reaction, was subjected to alkaline hydrogen peroxide oxidation in methanol under cooling and the oxidation was followed by thin-layer chromatography (TLC). The reaction was complete in 22 hr. The diepoxide (Ⅱ) thus obtained was subjected to chromatography on silica gel and repeated recrystallization to give 4α,5:16α,17-diepoxy-5α-pregnane-3,20-dione (Ⅱa) and its 4β-isomer (Ⅱb) in 0.76% and 30.6% yields respectively. The elemental analyses of these diepoxides were in agreement with the expected for-

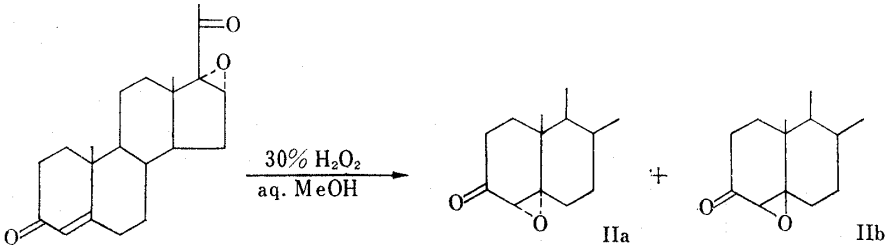


Chart 2.

mulae, $C_{21}H_{28}O_4$. The spectroscopic properties of Ⅱa, no characteristic ultraviolet absorption of $\alpha\beta$-unsaturated ketone, and IR ν_{max}^{KBr} cm^{-1}: 1703 (s), and of Ⅱb, no characteristic ultraviolet absorption of $\alpha\beta$-unsaturated ketone, and IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1704 (s), supported their structures. The nuclear magnetic resonance spectrum of Ⅱb showed three singlets at τ 6.30, τ 7.03, and τ 7.97, which could be assigned to $C_{16}\beta$-H, $C_4\alpha$-H, and $C_{17}\beta$-$COCH_3$ in the compound respectively. The α and β configurations at C-4 or C-5 of Ⅱa and Ⅱb were proved by optical rotatory dispersion analysis*[6] that Ⅱa gives a negative Cotton effect curve while Ⅱb gives a positive Cotton effect curve.[1,5,6] Their symmetrical curves of Ⅱa and Ⅱb with opposite sign are shown in Fig. 1.

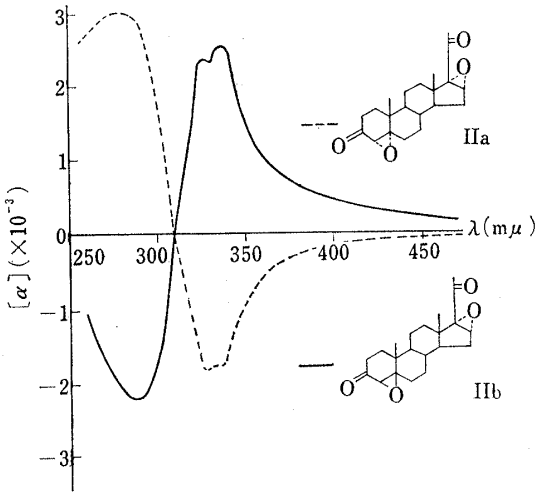


Fig. 1. Optical Rotatory Dispersion Curves of Ⅱa at 13° and Ⅱb at 20° in Dioxane

For the present study, the 4β,5-epoxide (Ⅱb) was chosen as starting material for the subsequent reactions.

The reaction of Ⅱb with ethanethiol in PPA-dioxane at room temperature was first attempted, and was followed by TLC; it was complete in 54.5 hr. affording 16α,17-epoxy-4-ethylthioandrost-4-ene-3,20-dione (Ⅳ) and 3,4-bis(ethylthio)-16α,17-epoxyandrosta-3,5-dien-20-one (Ⅴ) as the crystalline products in 11.9% and

*[5] Importance of the presence of α-hydroxyl function at C-17 on the steroid nucleus for pronounced biological activity is well known.[4]

*[6] We are indebted to Dr. K. Sasaki of the Research Laboratories, Shionogi and Co. for valuable discussions on the analysis.

4) N. Applezweig: "Steroid Drugs," 101 (1962). McGraw Hill Book Co., Inc., New York.
5) M. Legrand, R. Viennet, J. Caumartin: Compt. Rend. Acad. Sci., Paris, **253**, 2378 (1961).
6) C. Djerassi, W. Klyne, T. Norin, G. Ohloff, E. Klein: Tetrahedron, **21**, 163 (1965).

25.5% respectively. The elemental analyses of these new thiosteroids were in agreement with the expected molecular formulae, $C_{23}H_{32}O_3S$ and $C_{25}H_{36}O_2S_2$, respectively. The spectroscopic evidence for the structure of Ⅳ is as follows: the ultraviolet absorption spectrum exhibits λ_{max} 247 mμ (ε 10600) and 314 mμ (ε 1800), and the infrared spectrum ν_{max} 1698 (s), 1676 (s), and 1560 (w) cm^{-1}, which support the 4-ethylthiosubstituted 4-en-3-oxo system.[1,2,7] The nuclear magnetic resonance spectrum does not show any peak in the olefinic proton region but does show a doublet at τ 6.22, a singlet at τ 6.29, a multiplet at τ 7.25~7.61, and a singlet at τ 7.97 which can be assigned to $C_6\alpha$-H,[8] $C_{16}\beta$-H, -S-CH_2-, and $C_{17}\beta$-$COCH_3$ in the compound respectively. The positive sign of the specific rotation, $[\alpha]_D^{20}$ +146°, corresponds well to 4-thiosubstituted 4-en-3-oxo steroids.[1,2,7]

The spectroscopic evidence for the structure of Ⅴ is as follows: the ultraviolet spectrum exhibits λ_{max} 292 mμ (ε 12300), and the infrared spectrum ν_{max} 1696 (s), and 1546 (w) cm^{-1}, which corresponds to the 3,4-bis(ethylthio)substituted 3,5-diene system.[1,2,9] The nuclear magnetic resonance spectrum does show a broad signal at τ 3.72, which can be attributed to the C-6 vinylic hydrogen, and a singlet at τ 6.29, a multiplet at τ 7.00~7.57, and a singlet at τ 7.95, which can be assigned to $C_{16}\beta$-H, -S-CH_2- and $C_{17}\beta$-$COCH_3$ respectively. The negative sign of the specific rotation, $[\alpha]_D^{21}$ −142°, also corresponds to the 3,4-dithiosubstituted 3,5-diene system.[9]

That the PPA-catalyzed ring opening introduces a mercapto group at C-4 of the diepoxide (Ⅱb) was also proved by the reaction with ethanedithiol as nucleophile. As has been observed in the cholestane and 17β-acetoxyandrostane series, the reagent reacted with one end at C-4 of the 4,5-epoxy-3-oxo system followed by a spontaneuous intramolecular cyclization at C-3, forming a heterocycle, 16α,17-epoxy-20-oxoandrosta-3,5-dieno[3,4-*b*]dithiane (Ⅵ) as the sole crystalline product in 36% yield; no thioketalization was observed. The elemental analyses of the compound were in agreement with the expected molecular formula, $C_{23}H_{30}O_2S_2$. The spectroscopic evidence for the structure of Ⅵ is as follows: the ultraviolet spectrum exhibits λ_{max} 239 mμ (ε 10800) and

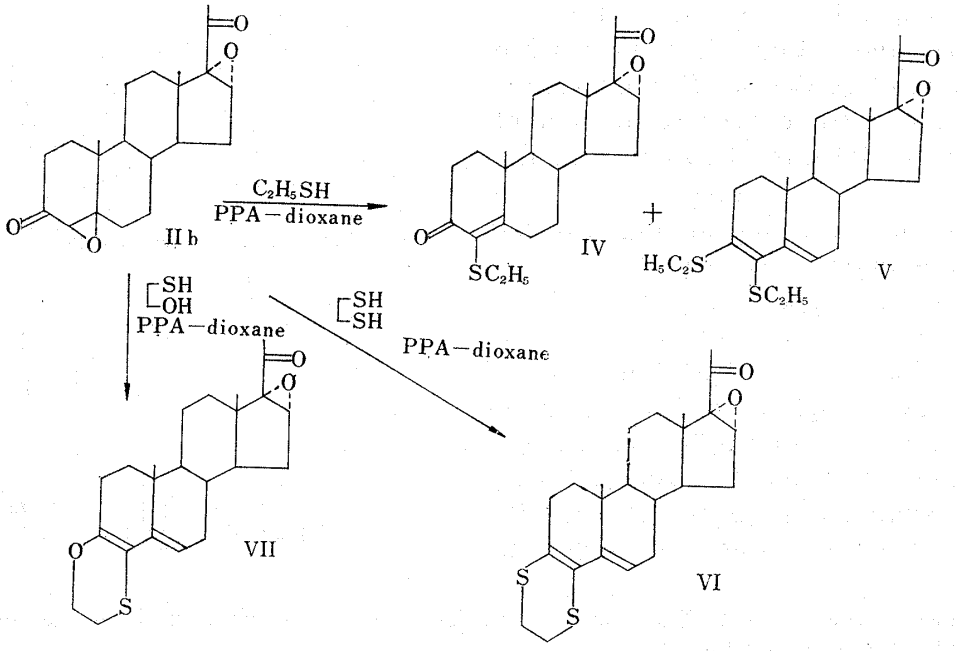


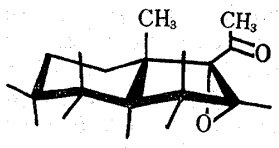
Chart 3.

7) J. M. Krämer, K. Brüchner, K. Irmscher, Karl-Heinz Bork: Ber., **96**, 2803 (1963).
8) M. Tomoeda, M. Inuzuka, T. Furuta, T. Takahashi: Tetrahedron Letters, **1964**, 1233.
9) L. F. Fieser, C. Yuan, T. Goto: J. Am. Chem. Soc., **82**, 1996 (1961).

293 mμ (ε 12700), and the infrared spectrum ν_{max} cm^{-1}: 1695 (s), and 1580 (w), which support the 3,5-dieno[3,4-*b*]dithiane system.[1,2,9] The nuclear magnetic resonance spectrum does show a broad peak at τ 4.11 which can be attributed to the vinylic C_6-H and three singlets at τ 6.31, τ 6.83, and τ 7.97 which can be assigned to $C_{16}\beta$-H, -S-CH_2CH_2-S- and $C_{17}\beta$-$COCH_3$ respectively. The negative sign of the specific rotation, $[\alpha]_D^{22}$ −77°, corresponds to the 3,4-dithiosubstituted 3,5-diene system.[1,2,9]

The selective introduction of a thio function at C-4 of the 4β,5:16α,17-diepoxide (IIb) was further confirmed by the reaction of IIb with 2-mercaptoethanol. The ring opening took place readily affording 16α,17-epoxy-20-oxoandrosta-3,5-dieno[3,4-*b*]oxathiane (VII) in 50% yield. No other product could be isolated. The elemental analyses of the compound were in agreement with the expected molecular formula, $C_{23}H_{30}O_3S$. The spectroscopic evidence for the structure of VI is as follows: the ultraviolet spectrum exhibits λ_{max} 216~219 mμ (ε 9900) and 271 mμ (ε 8700), and the infrared spectrum ν_{max} cm^{-1}: 1696 (s), 1642 (w), and 1618 (m), which support the 3,5-dieno[3,4-*b*]oxathiane system.[1,2,9] The nuclear magnetic resonance spectrum shows a broad peak at τ 4.46 which can be attributed to the vinylic C_6-H, and a multiplet at τ 5.60~5.92, a singlet at τ 6.31, a multiplet at τ 6.90~7.07, and a singlet at τ 7.97 which can be assigned to -O-CH_2-, $C_{16}\beta$-H, -S-CH_2-, and $C_{17}\beta$-$COCH_3$ respectively. The negative sign of the specific rotation, $[\alpha]_D^{19}$ −79°, corresponds to the 3,5-dieno[3,4-*b*]oxathiane system.[1,2,9]

It has thus been proved that PPA can catalyze selectively the ring opening at C-4 of 4,5:16α,17-diepoxy-3,20-dioxo steroids without inducing any substancial ring opening at another reactive site or the 16α,17-epoxy-20-oxo system (VIII) in the compound. The observed difference in reactivity of these epoxides in the PPA-catalyzed ring opening reaction appears to be of interest both from the mechanistic and synthetic standpoints of view as it is in marked contrast with the well-known fact[10] that 16,17-epoxy-20-oxo systems open under such acid catalysis as sulfuric acid, hydrohalides, or acetic acid, as 4,5-epoxy-3-oxo systems do. The present paper therefore represents a good example of the mild and selective catalytic action of PPA for the ring opening reaction of α,β-epoxy ketone systems under different steric environment in the steroid nucleus.



VIII
Chart 4.

The products thus formed still have a reactive epoxy function on the D-ring. This would be of value in providing a further opportunity of structural change of the compounds.

Experimental*7

3β-Acetoxy-16α,17-epoxypregn-5-en-20-one (I)——Prepared from 3β-acetoxypregna-5,16-dien-20-one by the method of Julian, *et al.*[3] as colorless prisms, m.p. 159~161°; $[\alpha]_D^{17}$ −9.0 (c=1.11); no characteristic UV absorption of αβ-unsaturated ketone; IR ν_{max} cm^{-1}: 1725 (s), 1691 (s), 1655 (w).

Attempted Polyphosphoric Acid-catalyzed Ring Opening of I with Ethanethiol: Recovery of the Starting Material——A solution of the epoxide (I) (100 mg.), ethanethiol (0.2 ml.) and PPA (200 mg.) in dioxane (3.8 ml.) was kept at room temperature for 132 hr. when the TLC of the reaction mixture gave

*7 Melting points were taken on a Kofler-type hot-plate, 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 Valian Associates A-60 high resolution spectrometer, and the intensities or peak areas were measured by the integrator. ORD measurements were made on a Rudolf photoelectric spectropolarimeter and also on a Japan Optics Spectroscopic Co. ORD/UV-5 Automatic Spectropolarimeter.

10) For instance, see Refs. cited in C. Djerassi, (Ed.): "Steroid Reactions," 618~630 (1963). Holden-Day, Inc., San Francisco.

only one spot of the same Rf value with that of the starting material (I). The mixture was poured into ice-water affording I as colorless crystals, m.p. 150~159° (wt. 87 mg., 87%). Recrystallization from methanol gave colorless prisms, m.p. 159~161°, alone and on admixture with a specimen of I (wt. 65 mg., 65%). Their IR spectra were superposable.

Attempted Polyphosphoric Acid-catalyzed Ring Opening of I with Ethanedithiol : Recovery of the Starting Material——A solution of I (100 mg.), ethanedithiol (0.2 ml.), and PPA (200 mg.) in dioxane (3.8 ml.) was kept at room temperature for 132 hr. when the TLC of the reaction mixture gave only one spot of the same Rf value with that of the starting material (I). The mixture was poured into ice-water, depositing I as colorless crystals, m.p. 145~150° (wt. 83 mg., 83%). Recrystallization from methanol gave colorless prisms, m.p. 158~160°, alone and on admixture with a specimen of I (wt. 61 mg., 61%). Their IR spectra were identical.

Attempted Polyphosphoric Acid-catalyzed Ring Opening of I with Ethanethiol at 90~95° : Recovery of the Starting Material——A solution of I (100 mg.), ethanethiol (0.4 ml.) and PPA (200 mg.) in dioxane (8.0 ml.) was heated at 90~95° for 40 hr. The reaction mixture, after cooling, was poured into ice-water, depositing a solid precipitate. The precipitate was extracted into chloroform, and the chloroform layer was washed with satd. $NaHCO_3$ aq. and water and dried (anhyd. Na_2SO_4). Concentration of the filtrate under reduced pressure afforded a pale yellow oil (wt. 206 mg.). This was chromatographed on silica gel (Davison Co.) (6.18 g.) and elution with 1:2 petr. ether-benzene (70 ml.) afforded an unidentified brown oil (wt. 50 mg.). Further elution with 19:1 benzene-ether (60 ml.) afforded the crude starting material (I) as pale brown crystals, m.p. 132~142° (wt. 54 mg., yield 54%). The IR spectrum of the crystals was almost identical with that of I. TLC of the crystals on Kiesel Gel G (Merck Co.) (9.0 g.) with 19:1 benzene-ethyl acetate as eluent afforded I as colorless prisms, m.p. 147~156 (wt. 29 mg., 29%). Recrystallization from methanol gave material of m.p. 160~161°, alone and on admixture with a specimen of I (wt. 26 mg., 26%). Their IR spectra were completely identical.

4α,5:16α,17-Diepoxy-5α-pregnane-3,20-dione (IIa) and 4β,5:16α,17-Diepoxy-5β-pregnane-3,20-dione (IIb)——To a solution of 16α,17-epoxypregn-4-ene-3,20-dione (III)[3] (2.50 g.) in methanol (200 ml.), 4*N* NaOH(5.0 ml.) and 30% H_2O_2 (10.0 ml.) was added successively at 5°, and the mixture was kept under cooling for 23 hr. when the reaction was complete (TLC). The reaction mixture was poured into ice-water, and the mixture was extracted into chloroform. The chloroform layer was washed with water, and dried (anhyd. Na_2SO_4). Concentration of the filtrate afforded a colorless solid of m.p. 112~139° (wt. 1.468 g.). This was chromatographed on silica gel (Kanto Chemical Co.) (190 g.) when elution with 19:1 benzene-ether (200 ml.) afforded a colorless solid (wt. 1.238 g.), which was recrystallized once from petr. ether-ether to give colorless prisms, m.p. 119~159° (wt. 1.01 g.). Their physical properties, $[\alpha]_D^{21}$ +171°(c=1.05), no characteristic UV absorption of αβ-unsaturated ketone and IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1704 (s), suggested them to be the crude diepoxide (II) consisting almost of the 4β-isomer. The prisms (890 mg.) were recrystallized from methanol to give 4β,5:16α,17-diepoxy-5β-pregnane-3,20-dione (IIb) as colorless plates, m.p. 153~159.5° (wt. 803 mg., total yield 30.6%). Further recrystallization from the same solvent afforded material, m.p. 160~161°. *Anal.* Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found : C, 72.97; H, 8.09. $[\alpha]_D^{16}$ +185° (c=0.90); RD in dioxane (c=0.291) at 20°, $[\alpha]_{700}$ +103°, $[\alpha]_{337.5}$ +2620°, $[\alpha]_{331}$ +2420°, $[\alpha]_{327}$ +2503°, $[\alpha]_{320}$ +1329°(sh.), $[\alpha]_{315}$ +862°(sh.), $[\alpha]_{305}$ −758°, $[\alpha]_{287}$ −1868°, $[\alpha]_{250}$ −558°; no characteristic UV absorption of αβ-unsaturated ketone; IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1704 (s); NMR τ : 6.30 (one proton, singlet) ($C_{16}\beta$-H), 7.03 (one proton, singlet) ($C_4\alpha$-H), 7.97 (singlet, three protons) ($C_{17}\beta$-$COCH_3$), 8.82 (three protons, singlet) (19-CH_3), 8.93 (three protons, singlet) (18-CH_3).

Concentration of the ethereal recrystallization mother liquor of the crude diepoxide, m.p. 119~159°, afforded a colorless solid (wt. 216 mg.), which was recrystallized once from ether, and further twice from methanol to give 4α,5:16α,17-diepoxy-5α-pregnane-3,20-dione (IIa) as colorless needles, m.p. 162~168° (wt. 20 mg., 0.76%). Further recrystallization from methanol gave material, m.p. 171~171.5°. *Anal.* Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found : C, 72.76, H, 8.16. $[\alpha]_D^{16}$ −8.9°(c=0.09, dioxane);[*8] RD in dioxane (c=0.09) at 13°, $[\alpha]_{400}$ −178°, $[\alpha]_{350}$ −867°, $[\alpha]_{336}$ −1843°, $[\alpha]_{330}$ −1840°, $[\alpha]_{326}$ −1910°, $[\alpha]_{316}$ −978°(sh.), $[\alpha]_{312}$ −578°(sh.), $[\alpha]_{310}$ −312°, $[\alpha]_{300}$ +1510°; IR ν_{max}^{KBr} cm^{-1} : 1703 (s).

Concentration of the recrystallization mother liquor of both diepoxides afforded a mixture of the 4α- and 4β-diepoxides, m.p. 117~151° (wt. 146 mg., 5.6%).

Polyphosphoric Acid-catalyzed Ring Opening of 4β,5:16α,17-Diepoxy-5β-pregnane-3,20-dione (IIb) with Ethanethiol : Formation of 16α,17-Epoxy-4-ethylthiopregn-4-ene-3,20-dione (IV) and 3,4-Bis(ethylthio)-16α,17-epoxypregna-3,5-dien-20-one (V)——A solution of IIb (700 mg.), ethanethiol (2.8 ml.), and PPA (2.8 g.) in dioxane (56 ml.) was kept at room temperature; the reaction was complete in 64.5 hr. (TLC). The reaction mixture was poured into ice-water depositing a yellow oil which was extracted into ether. The ethereal layer was washed with satd. $NaHCO_3$ aq. and water and dried (anhyd. Na_2SO_4). Concentration of the ethereal filtrate afforded a yellow solid residue (wt. 1.169 g.). This was chromatographed

[*8] The measurement was made on a Yanagimoto OR-20 Recording Spectropolarimeter, for which we are indebted to Professor S. Yamada of the Faculty of Pharmaceutical Sciences, University of Tokyo.

on silica gel (Merck Co.) (36 g.) and elution with benzene (400 ml.) afforded pale yellow crystals (wt. 409 mg.). Recrystallization from ether gave 3,4-bis(ethylthio)-16α,17-epoxypregna-3,5-dien-20-one (V) as pale yellow needles, m.p. 170~171.5°(wt. 224 mg., 25.5%). Further recrystallization from the same solvent gave material, m.p. 172.5~173.5°. *Anal.* Calcd. for $C_{25}H_{36}O_2S_2$: C, 69.39; H, 8.39; S, 14.82. Found : C, 69.25; H, 8.49; S, 14.60. $[\alpha]_D^{21}$ −142°(c=1.09); UV λ_{max} mμ (ε) : 292 (12300); IR ν_{max} cm^{-1} : 1696 (s), 1546 (w); NMR τ : 3.72 (one proton, broad) (C_6–H), 6.29 (one proton, singlet) ($C_{16}\beta$–H), 7.00~7.57 (multiplet)*9 (–S–CH_2–), 7.95 (three protons, singlet) ($C_{17}\beta$–$COCH_3$), 8.92 (three protons, singlet) (19–CH_3), 9.03 (three protons, singlet) (18–CH_3). A further crop of V, m.p. 162~165°, was obtained from the recrystallization mother liquor (wt. 45 mg., 5.1%). The total yield of V then reached 30.6%.

Further elution of the chromatogram of the crude product with 19:1 benzene–ether (250 ml.) afforded a pale yellow oil (wt. 175 mg.), which was dissolved in methanol and the methanolic solution was concentrated to give 16α,17-epoxy-4-ethylthiopregn-4-ene-3,20-dione (IV) as pale yellow needles, m.p. 146~146.5° (wt. 94 mg., 11.9%). A further crop of IV, m.p. 134~136° (wt. 43 mg., 5.4%), was obtained from the methanolic mother liquor. The total yield of IV then reached 17.3%. Recrystallization of the crystals from methanol gave colorless needles, m.p. 146.5~147°. *Anal.* Calcd. for $C_{23}H_{32}O_3S$: C, 71.09; H, 8.30; S, 8.25. Found : C, 70.91; H, 8.51; S, 7.96. $[\alpha]_D^{20}$ +146° (c=1.24); UV λ_{max} mμ (ε) : 247 (10600), 314 (1800); IR ν_{max} cm^{-1} : 1698 (s), 1676 (s), 1560 (w); NMR τ : 6.22 (one proton, doublet, J=14.5 c.p.s.) ($C_6\alpha$–H),[8] 6.29 (one proton, singlet) ($C_{16}\beta$–H), 7.25~7.61 (multiplet*9) (–S–CH_2–), 7.97 (three protons, singlet) ($C_{17}\beta$–$COCH_3$), 8.77 (three protons, singlet) (19–CH_3), 8.91 (three protons, singlet) (18–CH_3).

Polyphosphoric Acid-catalyzed Ring Opening of IIb with Ethanedithiol : Formation of 16α,17-epoxy-20-oxopregna-3,5-dieno[3,4-*b*]dithiane (VI)——A solution IIb (1.0 g.), ethanedithiol (4.0 ml.), and PPA (4.0 g.) in dioxane (80 ml.) was kept at room temperature for 54.5 hr. when the reaction was complete (TLC). The reaction mixture was poured into ice-water depositing colorless crystals (wt. 642 mg.). They were chromatographed on silica gel (Merck Co.) (20 g.) and elution with benzene (500 ml.) afforded colorless crystals (wt. 490 mg.). Recrystallization from ether gave 16α,17-epoxy-20-oxopregna-3,5-dieno [3,4-*b*]-dithiane (VI) as colorless needles, m.p. 242~244° (wt. 435 mg., 36%). *Anal.* Calcd. for $C_{23}H_{30}O_2S_2$: C, 68.61; H, 7.51; S, 15.92. Found : C, 68.60; H, 7.77; S, 16.29. $[\alpha]_D^{22}$ −77°(c=0.96); UV λ_{max} mμ (ε) : 239 (10800), 293 (12700); IR ν_{max} cm^{-1} : 1695 (s), 1580 (w); NMR τ : 4.11 (one proton, broad) (C_6–H), 6.31 (one proton, singlet) ($C_{16}\beta$–H), 6.83 (four protons, singlet) (–S–CH_2CH_2–S–), 7.97 (three protons, singlet) ($C_{17}\beta$–$COCH_3$), 8.93 (three protons, singlet) (19–CH_3), 9.00 (three protons, singlet) (18–CH_3).

Further elution of the chromatogram with 1:1 benzene–ether (200 ml.) afforded an unidentified oil (wt. 84 mg.).

Polyphosphoric Acid-catalyzed Ring Opening of IIb with 2-Mercatoethanol : Formation of 16α,17-Epoxy-20-oxopregna-3,5-dieno[3,4-*b*]oxathiane (VII)——A solution of IIb (400 mg.), 2-mercaptoethanol (1.6 ml.), and PPA (1.6 g.) in dioxane (32 ml.) was kept at room temperature for 70 hr. when the reaction was complete (TLC). The reaction mixture was poured into ice-water depositing a colorless solid, m.p. 253~264° (wt. 430 mg.). This was chromatographed on silica gel (Davison Co.) (13 g.) and elution with benzene (600 ml.) afforded colorless crystals (wt. 425 mg.). They were recrystallized from acetone to give 16α,17-epoxy-20-oxopregna-3,5-dieno[3,4-*b*]oxathiane (VII) as colorless needles, m.p. 268~271°(wt. 206 mg., 45.6%). A further crop of VII was obtained from the recrystallization mother liquor, m.p. 267~271° (wt. 21 mg., 4.5%). The total yield of VII then reached 50.1%. Further recrystallization from the same solvent gave material, m.p. 272.5~273.5°. *Anal.* Calcd. for $C_{23}H_{30}O_3S$: C, 71.46; H, 7.82; S, 8.29. Found : C, 71.79; H, 7.90; S 8.55. $[\alpha]_D^{19}$ −79° (c=1.03); UV λ_{max} mμ (ε) : 216~219 (9900), 271 (8700); IR ν_{max} cm^{-1} : 1696 (s), 1642 (w), 1618 (m); NMR τ: 4.46 (one proton, broad) (C_6–H), 5.55~5.92 (multiplet, two protons) (–O–CH_2–), 6.31 (one proton, singlet) ($C_{16}\beta$–H), 6.90~7.07 (two protons, multiplet) (–S–CH_2–), 7.97 (three protons, singlet) ($C_{17}\beta$–$COCH_3$), 8.93 (three protons, singlet) (19–CH_3), 8.98 (three protons, singlet) (18–CH_3).

Further elution of the chromatogram with 1:1 benzene–ether (400 ml.) afforded an unidentified oil (wt. 65 mg.).

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Summary

An example of the mild and selective catalytic action of PPA for the ring opening

*9 The correct proton number for the multiplet could not be identified because of the presence of signals by cyclic methylene protons of the compound as back ground in the same region.

reaction of α,β-epoxy ketone systems under different steric environment in the steroid nucleus was described. A remarkably inert character of the 16α,17-epoxy-20-oxo system in the pregnane series for the ring opening under PPA catalysis with such nucleophile as alkylmercaptans was observed. The efficient catalytic action of PPA for normal ring opening at C-4 of 4β,5:16α,17-diepoxy-5β-pregnane-3,20-dione (Ⅱb) was reported. Ethanethiol reacted with the diepoxide (Ⅱb) in PPA-dioxane affording 16α,17-epoxy-4-ethylthiopregn-4-ene-3,20-dione (Ⅳ) and a further product, 3,4-bis(ethylthio)-16α,17-epoxypregna-3,5-dien-20-one (Ⅴ). Ethanedithiol and 2-mercaptoethanol reacted with Ⅱb, as expected, affording 16α,17-epoxy-20-oxopregna-3,5-dieno[3,4-*b*]dithiane (Ⅵ) and its oxathiane derivative (Ⅶ) respectively.

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142. Shinsaku Minami, Masatsugu Tomita, Hideji Takamatsu,*1 and Shojiro Uyeo*2 : The Schmidt Reaction with Some Tetralone and Indanone Derivatives.*3

(*Research Laboratory, Dainippon Pharmaceutical Co., Ltd.*[*1] *and Faculty of Pharmaceutical Sciences, Kyoto University*[*2])

In the previous paper[1] we have reported a synthesis of demethyldeoxylycoramine (Ⅰ), the seven-membered heterocyclic ring of which was elaborated by the use of Bischler-Napieralski reaction. Since, however, the yield of the desired product was not satisfactory and an alternative effective pathway to this ring system still remained to be worked out.*4

Towards the end of this synthetic study, we noted that Ichii[2] had shown that the Schmidt reaction on 1,2-dihydro-3*H*-pyrido[3,2,1-*kl*]phenothiazin-3-one (Ⅱ) afforded, contrary to his initial expectation, compound (Ⅲ) in which the nitrogen atom introduced was not adjacent to a benzene ring. This result led us to believe that the formation of a homodihydroisocarbostyril was possible with a substituted tetralone possessing an electron releasing group (*e.g.* alkoxyl) in the position ortho or para to the carbonyl group, though it had been reported[3] that the Schmidt reaction with tetralone itself gave exclusively homodihydrocarbostyril.

In order to confirm this idea, we undertook several experiments using the tetralone (Ⅸ) and the indanones (XIX and XX). For the synthesis of the tetralone (Ⅸ), 1-(*m*-methoxyphenyl)cyclohexaneacetic acid (Ⅳ)[4,5] was converted into its homologous acid (Ⅷ)

*1 Ebie, Kami-2-chôme, Fukushima-ku, Osaka (南 新作, 富田真次, 高松秀二).
*2 Shimoadachi-cho, Sakyo-ku, Kyoto (上尾庄次郎).
*3 Presented at the Kinki Branch Meeting of the Pharmaceutical Society of Japan, Kyoto, May, 1963.
*4 Very recently Professor Ban of Hokkaido University reported that the Bischler-Napieralski cyclization to a seven-membered heterocyclic ring could effectively be achieved by using polyphosphoric ester as a condensing agent (19th Annual Meeting of Pharmaceutical Society of Japan (1964)).

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