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163. Takuichi Miki, Kentaro Hiraga, and Tsunehiko Asako : An Improved Synthesis of Estrogens.[*1,2]

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Recently, Ananchenko and Torgov1) reported an excellent synthesis of D-homosteroid using a new reaction found by themselves. This prompted us to apply their method to the synthesis of estrogens. Around the time when our short communication2) was published, the similar synthetic studies were reported by several groups3) independently.

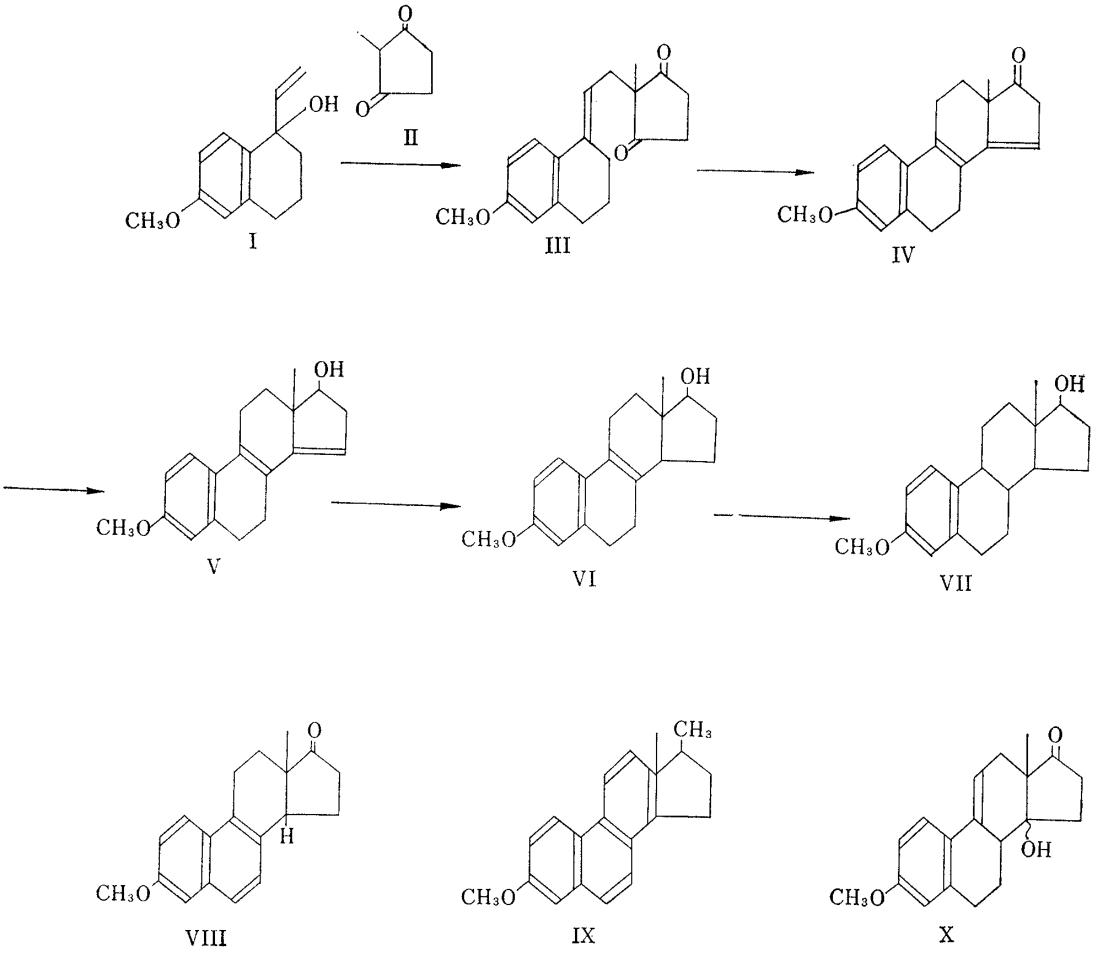

Chart 1.

[*1] This paper constitutes Part XXXIV of Takeda Laboratories' series entitled "Steroids"; Part XXXIII : This Bulletin, 12, 1189 (1964).

[*2] Preliminary communication, T. Miki, K. Hiraga, T. Asako : Proc. Chem. Soc., **1963**, 139.

[*3] Juso-nishino-cho, Higashiyodogawa-ku, Osaka (三木卓一, 平賀謙太郎, 朝子典彦).

1) *a*) S.N. Ananchenko, V.N. Leonov, A.V. Platonova, I.V. Torgov: Doklady Akad. Nauk S.S.S.R., **153**, 73 (1960). *b*) S.N. Ananchenko, V.Ye. Limanov, V.N. Leonov, V.N. Rzheznikov, I.V. Torgov : Tetrahedron, **18**, 1355 (1962).

2) T. Miki, K. Hiraga, T. Asako : Proc. Chem. Soc., **1963**, 139.

3) *a*) D.J. Crispin, J.S. Whitehurst : Proc. Chem. Soc., **1963**, 22. *b*) H. Smith, *et al.* : Experientia, **19**, 394 (1963). *c*) T.B. Windholz, J.H. Fried, A.A. Patchett : J. Org. Chem., **28**, 1092 (1963). *d*) S.N. Ananchenko, I.V. Torgov : Tetrahedron Letter, **1963**, 1553.

Here will be described on what characterizes our work : the stereospecific reduction and the optical resolution mainly.

Instead of 2-methyl-1,3-cyclohexanedione which was used for the synthesis of D-homosteroids,[1] we treated 2-methyl-1,3-cyclopentanedione (II) with 1-vinyl-6-methoxy-1-tetralol (I).

This reaction proceeded smoothly in the presence of base such as Triton B or triethylenediamine, and the resulting product, *dl*-3-methoxy-8,14-secoestra-1,3,5(10),9-tetraene-14,17-dione (III) was then converted by heating at 120° with phosphorus pentoxide or by warming in methanolic hydrochloric acid to the known *dl*-3-methoxyestra-1,3,5(10),8,14-pentaen-17-one (IV).

When the secodione (III) was heated with phosphorus pentoxide at a temperature higher than 140° or with a large excess of phosphorus pentoxide at 120°, *dl*-isoequilenin 3-methyl ether (VIII) was obtained together with a small amount of the unknown compound melting at 132°. The latter was assigned to 1-methyl-7-methoxy-2,3-dihydro-1*H*-cyclopenta[*a*]phenanthrene (IX), since it showed no carbonyl absorption in infrared spectrum and an ultraviolet absorption curve similar to that of cyclopentenophenanthrene.[4]

On the other hand, when the secodione (III) was treated with silica gel or with dilute hydrochloric acid solution, there was obtained *dl*-3-methoxy-14-hydroxyestra-1,3,5(10),9-tetraen-17-one (X), which was found to be the intermediate compound in the reaction from III to IV. The stereochemistry of the hydroxyketone (X) will be discussed in the separate paper.

In our synthesis, the pentaenone (IV) was, first of all, reduced with sodium borohydride in methanol at a low temperature (0∼−30°) to yield *dl*-3-methoxyestra-1,3,5(10),8,14-pentaen-17*β*-ol (V). When the reaction was carried out at the higher temperature, an oily substance was produced.

Catalytic hydrogenation of the double bond at C-14 of the pentaenol (V) over Raney nickel or palladium charcoal proved to be more stereospecific than the same reaction on pentaenone (IV),[5] yielding *dl*-3-methoxyestra-1,3,5(10),8-tetraen-17*β*-ol (VI)

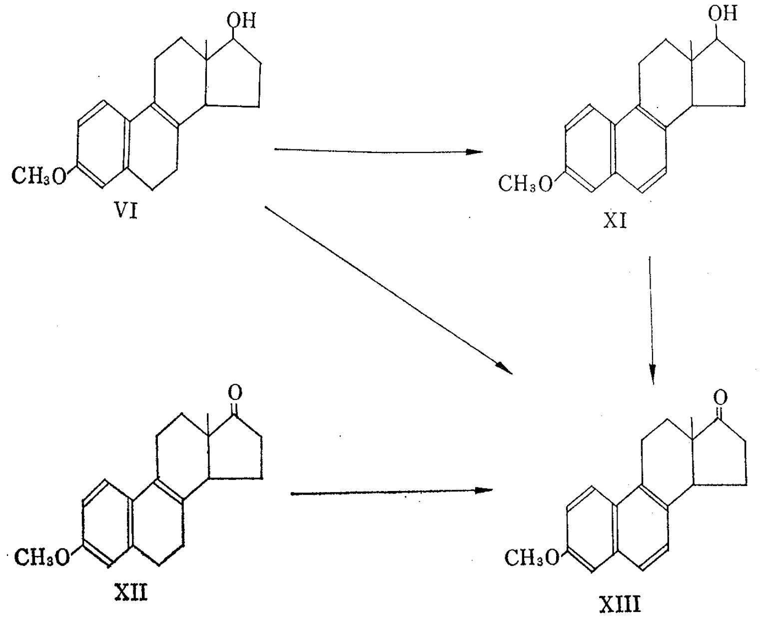

Chart 2.

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[4] *a*) J. W. Cook, C. L. Hewett : J. Chem. Soc., **1933**, 1098. *b*) H. Hilemann : Ber., **69**, 2610 (1936).

[5] G. A. Hughes, H. Smith : Chem. & Ind. (London), **1960**, 1022.

in good yield. The tetraenol (Ⅵ) was further reduced with potassium in liquid ammonia to give *dl*-estradiol 3-methyl ether which was identical with the material from natural origin in infrared[*4] and ultraviolet spectrum.

The optical resolution was performed by means of the ester formation of 17β-hydroxyl group with *l*-menthoxyacetyl chloride. The crystals of *l*-menthoxyacetate (Ⅺ) of the pentaenol (V) which precipitated from benzene-methanol were mainly levorotatory isomer. Hydrolysis of this ester should be carried out at room temperature in methanolic potassium hydroxide solution, since the pentaenol was unstable in hot alkaline solution. The *l*-pentaenol (V), $[\alpha]_D$ −126° ($CHCl_3$) thus obtained, was reduced, through the *l*-tetraenol (Ⅵ), $[\alpha]_D$ −3° ($CHCl_3$), to *d*-estradiol 3-methyl ether (Ⅶ) $[\alpha]_D$ +80° ($CHCl_3$), which was identical with the material of natural origin in all respects.

Dehydrogenation reaction of tetraenol (Ⅵ) with selenium dioxide in acetic acid or *tert*-butyl alcohol preceeded smoothly to yield *dl*-dihydroequilenin 3-methyl ether (Ⅺ),[6)] which was then converted to *dl*-equilenin 3-methyl ether (XⅢ) by chromic acid oxidation.

Another route investigated was to oxidize 17β-hydroxyl group of Ⅵ with chromic acid. The product obtained was found to be *dl*-equilenin 3-methyl ether (XⅢ), indicating that chromic acid caused dehydrogenation at 6,7-position, unexpectedly, in addition to oxidation of 17β-hydroxyl group. The dehydrogenation reaction by chromic acid was observed at 6,7-position of tetraenone (Ⅻ) to afford *dl*-equilenin 3-methyl ether.

Experimental[*5]

***dl*-3-Methoxy-8,14-secoestra-1,3,5(10),9-tetraene-14,17-dione (III)**——A solution of 0.5 g. of 1-vinyl-6-methoxy-1-tetralol (I) in 15 ml. of xylene was added to a stirred solution of 0.27 g. of 2-methyl-1,3-cyclopentanedione (Ⅱ) and 0.05 g. of triethylenediamine in 30 ml. of xylene at the refluxing temperature. After stirring for 1 hr. at the refluxing temperature, the reaction mixture was concentrated to the half volume, cooled, worked up with ether. Some unchanged 2-methyl-1,3-cyclopentanedione (Ⅱ) was separated by filtration and washed with ether. The combined ether solutions were washed with 5% KOH solution and H_2O, dried over Na_2SO_4 and concentrated. The oily residue deposited 0.25 g. of a crystalline material which was recrystallized from EtOH to yield 0.2 g. of V, m.p. 79~80°. UV λ_{max}^{EtOH} mμ (ε): 266 (13000). *Anal.* Calcd. for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.58; H, 7.48.

***dl*-3-Methoxyestra-1,3,5(10),8,14-pentaen-17-one (IV)**——a) A mixture of 0.3 g. of Ⅲ and 0.3 g. of P_2O_5 was heated at 120° for 7 min. under reduced pressure. After cooling, the mixture was shaken with ether. The ether solution was washed with saturated $NaHCO_3$ solution and H_2O, dried over Na_2SO_4 and concentrated to yield 0.25 g. of a crystalline material. Recrystallization from EtOH afforded an analytical sample, m.p. 108°. UV λ_{max}^{EtOH} mμ (ε): 310 (22700). *Anal.* Calcd. for $C_{19}H_{20}O_2$: C, 81.43; H, 7.14. Found: C, 81.55; H, 7.08.

b) To a hot solution of 1 g. of Ⅲ in 30 ml. of MeOH was added 1 ml. of 4*N* HCl and the solution was allowed to stand at room temperature overnight to deposit a crystalline substance. Filtration and recrystallization from EtOH yielded 0.8 g. of Ⅳ.

Cyclization of Ⅲ at 150°——A mixture of 2 g. of Ⅲ and 2 g. of P_2O_5 was heated at 150° for 7 min. under reduced pressure. After cooling, the mixture was worked up with ether and the ether solution was washed with saturated $NaHCO_3$ solution and H_2O, dried over Na_2SO_4, and concentrated to yield 1.3 g. of an oily material, which was chromatographed on florisil. Elution with benzene-petr. ether (1:4) gave 0.1 g. of colorless crystals, m.p. 132°. UV λ_{max}^{EtOH} mμ (ε): 262 (22500), 284 (shoulder), 292 (4500), 302 (2300). *Anal.* Calcd. for $C_{19}H_{18}O$: C, 86.98; H, 6.91. Found: C, 86.71; H, 6.98.

The portion eluted with benzene-petr. ether (1:1) gave 0.32 g. of *dl*-isoequilenin methyl ether, m.p. 130°. UV λ_{max}^{EtOH} mμ (ε): 230 (23600), 265 (2800), 320 (480), 335 (630).

***dl*-3-Methoxy-14-hydroxyestra-1,3,5(10),9-tetraen-17-one (X)**——To a solution of 0.5 g. of Ⅲ in 40 ml. of tetrahydrofuran was added 1 ml. of 2*N* HCl and the solution was allowed to stand at room temperature for 20 hr. The solution was poured into H_2O, shaken with AcOEt, and the AcOEt layer was washed with $NaHCO_3$ solution and H_2O, dried over Na_2SO_4, and concentrated to yield 0.45 g. of an oily residue,

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[*4] Measured in $CHCl_3$.

[*5] All melting points are uncorrected.

6) D.K. Banerjee, S. Chatterjee, C.N. Pillai, M.V. Bhatt: J. Am. Chem. Soc., 78, 3769 (1956).

which was chromatographed on alumina. Elution with ether gave 0.02 g. of X, m.p. 165°. UV λ_{max}^{EtOH} mμ (ε): 267 (18000). IR ν_{max}^{Nujol} cm^{-1}: 3450, 1740. *Anal.* Calcd. for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.53; H, 7.33.

***dl*-3-Methoxyestra-1,3,5(10),8,14-pentaen-17β-ol (V)**——To a solution of 1.6 g. of IV in 100 ml. of MeOH was added 0.3 g. of $NaBH_4$ at −30°. After stirring for 1 hr., the excess $NaBH_4$ was destroyed with 3 drops of AcOH and 500 ml. of H_2O. The mixture was shaken with ether and the ether solution was washed with saturated $NaHCO_3$ solution and H_2O, dried over Na_2SO_4, and concentrated to yield 1.5 g. of a crystalline material. Recrystallization from benzene–hexane afforded 1.3 g. of V, m.p. 113°. UV λ_{max}^{EtOH} mμ (ε): 310 (22200). IR ν_{max}^{Nujol} cm^{-1}: 3300. *Anal.* Calcd. for $C_{19}H_{22}O_2$: C, 80.85; H, 7.80. Found: C, 81.16; H, 7.88.

***dl*-3-Methoxyestra-1,3,5(10),8-tetraen-17β-ol (VI)**——A solution of 0.5 g. of VII in 50 ml. of dioxane was hydrogenated over 0.5 g. of Raney Ni at room temperature and atmospheric pressure. The mixture was filtered and solvent was evaporated to afford 0.4 g. of a crystalline material, which was recrystallized from EtOH–H_2O to give colorless prisms, m.p. 126°. UV λ_{max}^{EtOH} mμ (ε): 278 (14100). *Anal.* Calcd. for $C_{19}H_{24}O_2 \cdot \frac{1}{3}H_2O$: C, 78.65; H, 8.51. Found: C, 78.51; H, 8.66.

***dl*-3-Methoxyestra-1,3,5(10)-trien-17β-ol (VII)**——To a solution of 1 g. of VI in 50 ml. of dioxane, 90 ml. of ether and 150 ml. of liq. NH_3 was added 1.5 g. of K at −50°. After stirring for 2 hr., the reaction mixture was neutralized with NH_4Cl, and NH_3 was evaporated. The residue was shaken with 500 ml. of H_2O and 300 ml. of ether, and the ether layer was washed with H_2O, dried over Na_2SO_4, and concentrated to yield 0.8 g. of a crystalline material, which was recrystallized from EtOH–H_2O to afford 0.5 g. of VII, m.p. 130°. *Anal.* Calcd. for $C_{19}H_{20}O_2$: C, 79.72; H, 9.09. Found: C, 80.22; H, 9.18.

***l*-3-Methoxyestra-1,3,5(10),8,14-pentaen-17β-ol *l*-Menthoxyacetate (XI)**——To a solution of 1.7 g. of V in 8.5 ml. of pyridine and 12 ml. of dioxane was added dropwise 4.8 g. of *l*-menthoxyacetyl chloride, then the reaction mixture was allowed to stand at room temperature overnight. The mixture was poured into ice water and extracted with ether. The ether solution, after washing with dil. HCl, saturated $NaHCO_3$ solution, and H_2O successively, was dried over Na_2SO_4 and concentrated to yield 4 g. of an oily residue, which deposited 1 g. of crystalline *l*-menthoxyacetate (XI). Filtration and recrystallization from MeOH–ether afforded 0.9 g. of pure XI, m.p. 61°. $[\alpha]_D^{24}$ −142° (c=1, $CHCl_3$). UV λ_{max}^{EtOH} mμ (ε): 310 (34000). *Anal.* Calcd. for $C_{31}H_{42}O_4$: C, 77.82; H, 8.76. Found: C, 78.46; H, 8.43.

***l*-3-Methoxyestra-1,3,5(10),8,14-pentaen-17β-ol (V)**——Under cooling with ice, 20 ml. of 1*N* ethanolic KOH was added to a solution of 0.65 g. of XI in 30 ml. of EtOH, then the solution was stirred for 40 min. at room temperature. To the mixture was added 100 ml. of H_2O and the mixture was shaken with ether. The ether solution was washed with H_2O, dried over Na_2SO_4, and concentrated to yield 0.2 g. of *l*-VII, m.p. 55°. $[\alpha]_D^{24}$ −126° (c=1, $CHCl_3$).

***l*-3-Methoxyestra-1,3,5(10),8-tetraen-17β-ol (VI)**——Catalytic reduction at the 14 double bond of *l*-V was carried out in the same manner as in the case of racemic one, giving *l*-VI, m.p. 125°. $[\alpha]_D^{24}$ −3° (c=0.78, $CHCl_3$).

***d*-3-Methoxyestra-1,3,5(10)-trien-17β-ol (VII)**——Reduction of *l*-VI with K in liq. NH_3 gave *d*-estradiol 3-methyl ether (VII), m.p. 98°. $[\alpha]_D^{24}$ +80° (c=1, $CHCl_3$).

***dl*-3-Methoxyestra-1,3,5(10),6,8-pentaen-17β-ol (XI)**——A solution of 0.1 g. of *dl*-3-methoxyestra-1,3,5(10),8-tetraen-17β-ol (VI), 0.05 g. of SeO_2 and 0.02 ml. of pyridine in 10 ml. of *t*-BuOH was heated at refluxing temperature for 18 hr. The Se deposited was filtered off and the filtrate was concentrated *in vacuo* to yield an oily material, which was chromatographed on alumina. The fraction eluted with benzene afforded 0.02 g. of a colorless material melting at 132°, the structure of which is not investigated yet and the fraction eluted with benzene–ether (7:3) afforded 0.03 g. of crude crystals of IV, which were recrystallized from acetone–MeOH to give colorless plates, m.p. 178°. UV λ_{max}^{EtOH} mμ (ε): 233 (20140), 255 (6800), 265 (7100), 279 (3835), 291 (3770), 306 (3350).

***dl*-Equilenin 3-Methyl Ether (XIII)**——a) From XI. To a solution of 0.02 g. of IV in 50 ml. of acetone was added 0.05 ml. of Jones' reagent.[*6] After 2 min., the excess CrO_3 was destroyed with 10 ml. of MeOH. The mixture was diluted with 50 ml. of H_2O, and the resulting precipitate was filtered and recrystallized from acetone–MeOH to yield 0.01 g. of II, m.p. 187°. UV λ_{max}^{EtOH} mμ (ε): 230 (33600), 268 (3400), 278 (3400), 289 (2400), 323 (1400), 338 (1700).

b) From VI. To a solution of 0.1 g. of III in 10 ml. of acetone was added 0.3 ml. of Jones' reagent. After 2 min., this reaction mixture was worked up as above to give 0.036 g. of IV as yellow scales, m.p. 184∼187°.

c) From XII. To a solution of 0.02 g. of I in 2 ml. of acetone was added 0.08 ml. of Jones' reagent. The reaction mixture was worked up as above to give 0.006 g. of IV melting at 183∼184°.

[*6] A solution of 26.72 g. of CrO_3 in 23 ml. of H_2SO_4 was diluted with H_2O to 100 ml. and it was used as a standard reagent.

The authors express their deep gratitude to Takeda Chemical Industries, Ltd. for permission to publish this report, to Dr. Y. Abe for his kind guidance. Thanks are also due to Mr. H. Kamio and his associates for spectral determinations and Mr. M. Kan and his associates for elemental analysis.

Summary

A short step synthesis of estradiol was presented. 1-Vinyl-6-methoxy-1-tetralol (I) was condensed with 2-methyl-1,3-cyclopentanedione (Ⅱ) in the presence of Triton B to give *dl*-3-methoxy-8,14-secoestra-1,3,5(10),9-tetraene-14,17-dione (Ⅲ) which was converted by phosphorus pentoxide into the known *dl*-3-methoxyestra-1,3,5(10),8,14-pentaen-17-one (Ⅳ). The ketone (Ⅳ) was treated with sodium borohydride in methanol, yielding *dl*-3-methoxyestra-1,3,5(10),8,14-pentaen-17β-ol (V). Catalytic hydrogenation of this compound over Raney nickel was found to be stereospecific, yielding *dl*-3-methoxyestra-1,3,5(10), 8-tetraen-17β-ol(Ⅵ). This compound was subjected to K-NH$_3$ reduction to give *dl*-estradiol 3-methyl ether (Ⅶ).

Racemic V was resolved through its 17 *l*-menthoxyacetate and *d*-estradiol 3-methyl ether obtained by the above series of reactions was identical with the material of natural origin.

dl-Equilenin 3-methyl ether was prepared from *dl*-3-methoxyestra-1,3,5(10),8-tetraen-17β-ol (Ⅵ) by oxidation with Jones' reagent at one step.

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164. Kentaro Hiraga : Syntheses of Racemic and Optically Active 13β-Ethylgonanes.[*1]

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Recently, Smith, *et al.*[1] reported that *dl*-17β-hydroxy-13β,17α-diethylgon-4-en-3-one has an excellent anabolic activity. Quite independently, the author also synthesized the compound, and applied for patents already.

The synthetic route is similar to that of Smith, *et al.*, but different in many steps, and this paper deals with the synthesis and the resolution of the 13β-ethylgonane series (Chart 1).

Condensation[2] of 1-vinyl-6-methoxy-1-tetralol (I) and 2-ethyl-1,3-cyclopentanedione (Ⅱ) in boiling xylene without catalyst or in the presence of basic catalyst gave *dl*-3-methoxy-13-ethyl-8,14-secogona-1,3,5(10),9-tetraene-14,17-dione (Ⅲ) in 40% yield.

The seco-compound (Ⅲ) in methanolic hydrogen chloride solution cyclized easily to yield *dl*-3-methoxy-13β-ethylgona-1,3,5(10),8,14-pentaen-17-one (Ⅳ). As an intermediate compound of this reaction was obtained *dl*-3-methoxy-13β-ethyl-14ξ-hydroxygona-1,3,5(10),9-tetraen-17-one, on which will be described separately.

[*1] This paper constitutes Part XXXV of Takeda Laboratories' series entitled "Steroids"; Part XXXIV: This Bulletin, 13, 1285 (1965).

[*2] Juso-nishino-cho, Higashiyodogawa-ku, Osaka (平賀謙太郎).

1) H. Smith, *et al.*: Experientia, **19**, 394 (1963); J. Chem. Soc., **1964**, 4472.

2) S.N. Ananchenko, V.Ye. Limanov, V.N. Leonov, V.N. Rzheznikov, I.V. Torgov: Tetrahedron, **18**, 1355 (1962).