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

(*Chemical Research Laboratories, Research & Development Division, Takeda Chemical Industries, Ltd.**2)

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.

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*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.Y$_E$. Limanov, V.N. Leonov, V.N. Rzheznikov, I.V. Torgov: Tetrahedron, **18**, 1355 (1962).

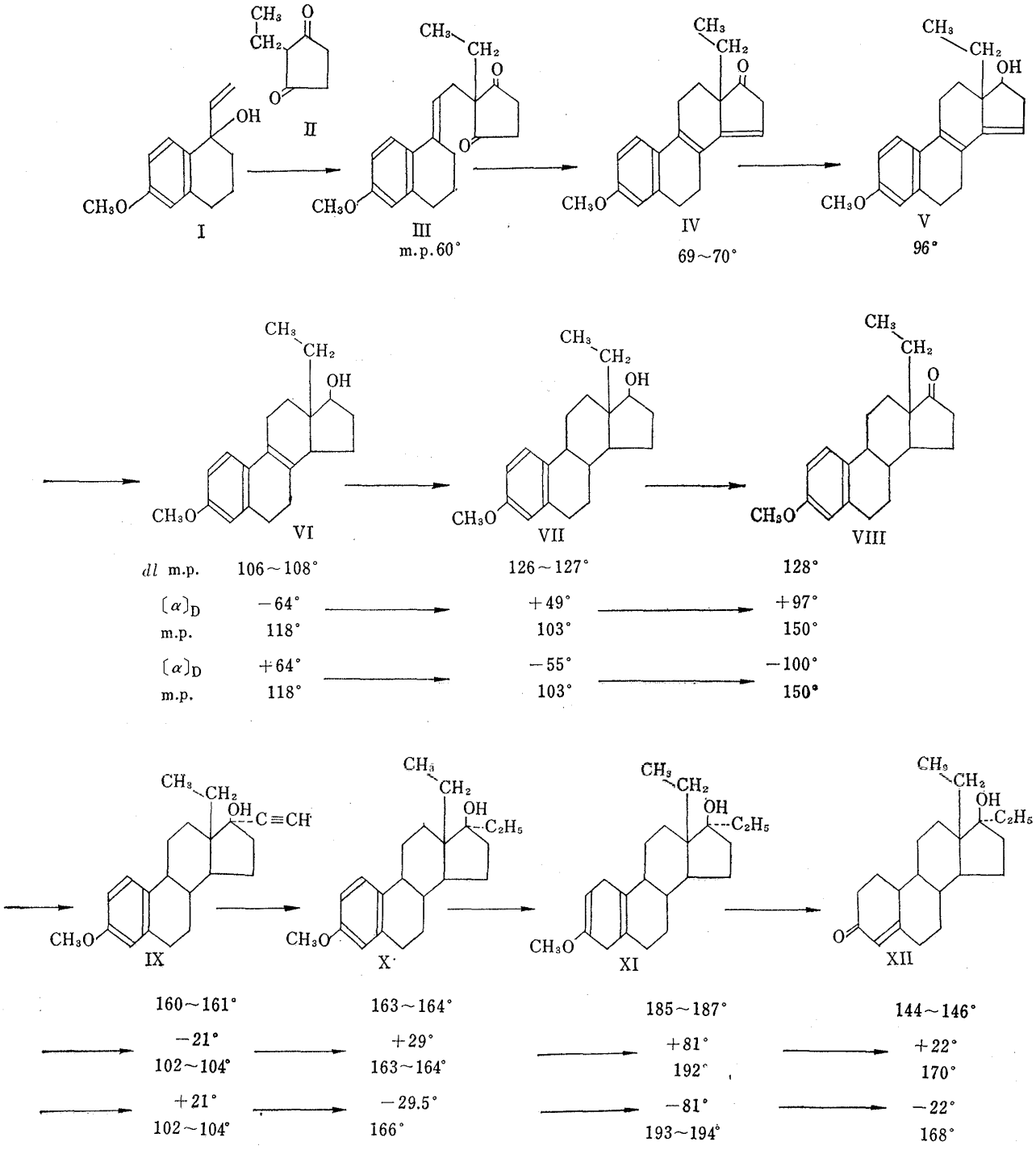

Chart 1.

Hydrogenation of *dl*-3-methoxy-13β-ethylgona-1,3,5(10),8,14-pentaen-17β-ol (V), derived from IV with sodium borohydride, proved to be more stereospecific than that of IV itself[1] giving rise to tetraenol (VI). The yield at each step from III to VI was 90%.

The reduction of VI with lithium in liquid ammonia gave *dl*-3-methoxy-13β-ethylgona-1,3,5(10)-trien-17β-ol (VII) in 60% yield, which was then oxidized smoothly with Jones' reagent*[3] to yield *dl*-3-methoxy-13β-ethylgona-1,3,5(10)-trien-17-one (VIII) in 95% yield.

*[3] 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.

An attempt to introduce a 17α-alkyl group to Ⅷ with ethylmagnesium bromide caused the reduction to 17β-hydroxy compound (Ⅶ) together with the recovery of the original compound (Ⅷ). The difficulty of 17α-alkylation by means of Grignard reagent was already observed in the ordinary 17-ketosteroids.[3] The ethynylation of 17-ketone (Ⅷ) in liquid ammonia afforded *dl*-3-methoxy-13β-ethyl-17-ethynylgona-1,3,5(10)-trien-17β-ol (Ⅸ) in poor yield. On the other hand, as Smith, *et al.* described, smooth ethynylation of *dl*-3-methoxy-13β-ethylgona-1,3,5(10),8-tetraen-17-one (XIII) occurred in the same conditions. The difference between the two cases in ethynylation reaction can be explained with the concept of steric hindrance as shown in Chart 2.

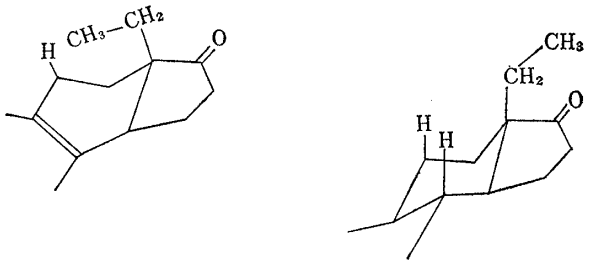

Chart 2.

Ethylenediamine was found to be an effective solvent for ethynylation of 17-ketone (Ⅷ) giving ethynyl compound (Ⅸ) in a dramatically good yield.

The reduction of ethynyl compound (Ⅸ) on palladium charcoal to the corresponding diethyl compound (X), followed by the Birch's reduction to *dl*-3-methoxy-13β,17α-diethylgona-2,5(10)-dien-17β-ol (XI), and the hydrolysis of the product proceeded smoothly to give *dl*-17β-hydroxy-13β,17α-diethylgon-4-en-3-one (XII).

For pharmaceutical purpose, the optically active compound may be preferred rather than racemic form. Moreover, it was interesting for the author to know which of the optically active compounds will have the biological activity. The author's route, containing 17β-hydroxy compounds as intermediates, is favorable over Smith's for optical resolution.

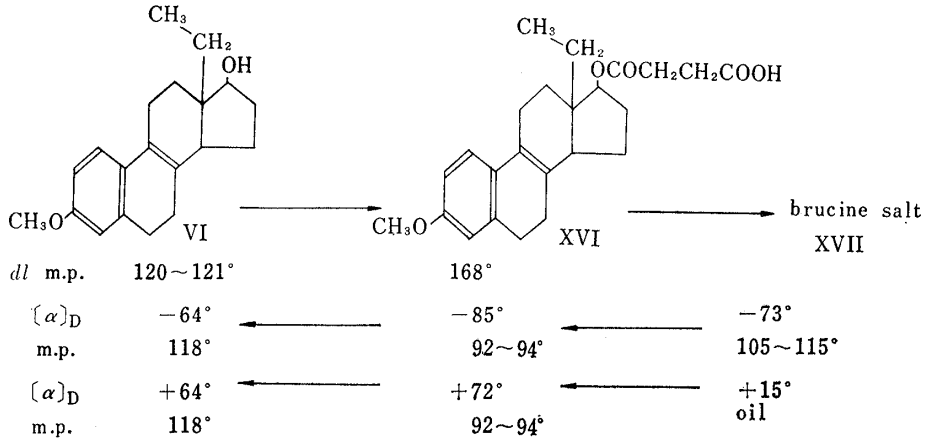

Chart 3.

In estrogen series,[4] *l*-menthoxyacetate of 3-methoxyestra-1,3,5(10),8,14-pentaen-17β-ol was found suitable for resolution. But in 13β-ethylgonane series, the corresponding ester was not obtained as pure crystals. Finally the resolution was performed through the brucine salt of hydrogen succinate of tetraenol (Ⅵ). From the salt (m.p. 105~115°, $[\alpha]_D$ −73° ($CHCl_3$)) that crystallized from methanol-acetone solution was

3) *a*) L. B. Fieser, M. Fieser: "Steroids," 520 (1959), Reinhold, N. Y. *b*) A. Butenandt, J. Schmidt-Thomé, H. Paul: Ber., **71**, 1313 (1938). *c*) L. Ruzicka, K. Hofmann, H. F. Meldahl: Helv. Chim. Acta, **21**, 597 (1938).

4) T. Miki, K. Hiraga, T. Asako: This Bulletin, **13**, 1285 (1965).

obtained levorotatory hydrogen succinate (XVI, m.p. 92~94°, $[\alpha]_D$ −85° ($CHCl_3$)), and from the filtrate of the crystalline salt was obtained dextrorotatory hydrogen succinate (XVI, m.p. 92~94°, $[\alpha]_D$ +72° ($CHCl_3$)).

The hydrolysis of hydrogen succinate (XVI) in methanolic potassium hydroxide at room temperature gave tetraenol (VI), which was subjected to the same series of reactions as those in racemic form. The melting points and rotations of the resulting compounds are shown in Chart 1.

According to the report from the pharmacological section, the dextrorotatory diethylgonenone as well as the corresponding racemic diethylgonenone showed strong anabolic effects, whereas the levorotatory compound had absolutely no effect.

Considering molecular rotation differences, the dextrorotatory diethylgonenone possesses absolute configuration corresponding to that of natural steroid, and these facts suggest that biological activity in this series is confined to the compounds with the "natural" configuration.

Most recently, Smith, *et al.*[5] reported the biological activity of the optically active diethylgonenone, and the result was completely the same as the author's. They mentioned that the resolution was achieved by microbial action on *dl*-17β-hydroxy-13β-ethylgon-4-en-3-one, but the details have not been reported yet.

Experimental*4

***dl*-3-Methoxy-13-ethyl-8,14-secogona-1,3,5(10),9-tetraene-14,17-dione (III)**——To a solution of 15 g. of 2-ethyl-1,3-cyclopentanedione (II) and 8 g. of triethylenediamine in 120 ml. of xylene was added dropwise a solution of 25 g. of 1-vinyl-6-methoxy-1-tetralol (I) in 30 ml. of xylene during 40 min. at the refluxing temperature.

After stirring for additional 2 hr. at the temperature, the reaction mixture was concentrated to the half volume, cooled, worked up with ether, and the ether solution was washed with 5% KOH and H_2O, dried over Na_2SO_4, and concentrated to yield 10 g. of crude crystals of III. Recrystallization from EtOH gave colorless needles, m.p. 64~65°. UV λ_{max}^{EtOH} mμ (ε): 266 (17000). IR ν_{max}^{Nujol} cm^{-1}: 1760, 1710. *Anal.* Calcd. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.69; H, 7.75.

***dl*-3-Methoxy-13β-ethylgona-1,3,5(10),8,14-pentaen-17-one (IV)**——A solution of 5 g. of III and 10 ml. of 2*N* HCl in 90 ml. of MeOH was warmed at 40~45° for 1 hr. The solution was diluted with 500 ml. of H_2O, shaken with ether, and the ether layer was washed with H_2O, dried over Na_2SO_4, and concentrated to give 4.5 g. of IV, which was recrystallized from EtOH to give colorless prisms, m.p. 70~72°. UV λ_{max}^{EtOH} mμ (ε): 314 (25400). *Anal.* Calcd. for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.84; H, 7.59.

***dl*-3-Methoxy-13β-ethylgona-1,3,5(10),8,14-pentaen-17β-ol (V)**——To a solution of 0.65 g. of IV in 35 ml. of MeOH was added 0.16 g. of $NaBH_4$ at −5° under stirring. After stirring for 1 hr., the reaction mixture was diluted with 0.5 ml. of AcOH and 300 ml. of H_2O, and extracted with ether. The extract was washed with H_2O, dried over Na_2SO_4 and concentrated to yield 0.6 g. of an oily material, which was crystallized by trituration with benzene. Recrystallization from benzene afforded colorless needles, m.p. 96°. UV λ_{max}^{EtOH} mμ (ε): 311 (30800). IR ν_{max}^{Nujol} cm^{-1}: 3456. NMR δ (p.p.m.)^{CCl_4} 5.5 (15-H). *Anal.* Calcd. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.25; H, 8.19.

***dl*-3-Methoxy-13β-ethylgona-1,3,5(10),8-tetraen-17β-ol (VI)**——In the presence of 6 g. of Raney Ni, 2.2 g. of V in 150 ml. of dioxane was hydrogenated. The mixture was filtered and the residue obtained on evaporation of the filtrate afforded a crystalline material, which was recrystallized from EtOH to give 2 g. of VI as colorless needles, m.p. 106~108°. UV λ_{max}^{EtOH} mμ (ε): 280 (14200). *Anal.* Calcd. for $C_{20}H_{26}O_2$: C, 80.24; H, 8.78. Found: C, 80.34; H, 8.78.

***dl*-3-Methoxy-13β-ethylgona-1,3,5(10)-trien-17β-ol (VII)**——To a solution of 2.5 g. of VI in 75 ml. of dioxane, 150 ml. of ether and 400 ml. of liq. NH_3 was added 0.7 g. of Li at −50°. After stirring for 2 hr., the reaction mixture was neutralized with NH_4Cl, then NH_3 was evaporated. To the residue was added 1 L. of H_2O and the mixture was extracted with ether. The extract was washed with H_2O, dried over Na_2SO_4 and concentrated to yield an oily substance, which was crystallized on addition of EtOH. Recrystallization from EtOH afforded 1.7 g. of VII, m.p. 126~127°. *Anal.* Calcd. for $C_{20}H_{28}O_2$: C, 80.00; H, 9.3. Found: C, 80.01; H, 9.37.

*4 All melting points are uncorrected.

5) R. A. Edgren, H. Smith, G. A. Hughes, L. L. Smith, G. Greenspan: Steroids, 2, 731 (1963).

***dl*-3-Methoxy-13β-ethylgona-1,3,5(10)-trien-17-one (VIII)**——To a solution of 1.5 g. of VII in 50 ml. of acetone was added 2.5 ml. of Jones' reagent. After agitation for 5 min. at room temperature, the reaction mixture was diluted with 10 ml. of MeOH and 300 ml. of H_2O. The resulting precipitate was filtered and recrystallized from MeOH to afford 1.4 g. of VIII, m.p. 128°. IR ν_{max}^{Nujol} cm^{-1} : 1738.

***dl*-3-Methoxy-13β-ethyl-17α-ethynylgona-1,3,5(10)-trien-17β-ol (IX)**——Acetylene was passed through a solution of 0.5 g. of Li in 100 ml. of ethylenediamine for 1 hr., and 1 g. of VIII in 30 ml. of tetrahydrofuran was added to the lithium acetylide solution during 30 min. with stirring at room temperature. After acetylene was passed through the solution for additional 2 hr., the mixture was neutralized with 5 g. of NH_4Cl, diluted with 500 ml. of H_2O, and the mixture was extracted with ether. The ether extract was washed with 10% H_2SO_4, saturated $NaHCO_3$ solution and H_2O successively, dried over Na_2SO_4 and concentrated to yield a crystalline material, which was recrystallized from MeOH to afford 0.95 g. of IX as colorless needles, m.p. 161°. IR ν_{max}^{Nujol} cm^{-1} : 3250, 3400. *Anal.* Calcd. for $C_{22}H_{36}O_2$: C, 81.48; H, 8.64. Found : C, 81.32; H, 8.54.

***dl*-3-Methoxy-13β,17α-diethylgona-1,3,5(10)-trien-17β-ol (X)**——An amount of 0.75 g. of IX in 30 ml. of tetrahydrofuran and 40 ml. of EtOH was hydrogenated over Pd-C at room temperature and atmospheric pressure. After separation of the catalyst, the solution was concentrated to yield a solid material, which was recrystallized from MeOH to afford 0.7 g. of X as colorless needles, m.p. 163~164°. *Anal.* Calcd. for $C_{22}H_{32}O_2$: C, 80.49; H, 9.75. Found : C, 80.68; H, 9.64.

***dl*-3-Methoxy-13β,17α-diethylgona-2,5(10)-dien-17β-ol (XI)**——To a solution of 0.55 g. of X in 200 ml. of tetrahydrofuran and 400 ml. of liq. NH_3 was added 4 g. of Li at −60°. After stirring for 30 min., 50 ml. of EtOH was added dropwise to the solution and the reaction mixture was allowed to stand at room temperature to evaporate NH_3. To the residue was added H_2O and the resulting precipitate was collected on a filter and recrystallized from MeOH to yield 0.5 g. of XI, m.p. 185~187°. *Anal.* Calcd. for $C_{22}H_{34}O_2$: C, 79.87; H, 10.36. Found : C, 79.90; H, 10.21.

***dl*-17β-Hydroxy-13β,17α-diethylgon-4-en-3-one (XII)**——To a solution of 0.4 g. of XI in 10 ml. of tetrahydrofuran and 6 ml. of MeOH was added 15 ml. of 6*N* HCl with stirring at room temperature. After stirring for 45 min., the reaction mixture was poured into H_2O and the resulting precipitate was collected on a filter and recrystallized from acetone-petr. ether to yield 0.25 g. of XII, m.p. 144~146°. The melting point was the same as that reported by Wyeth group. UV λ_{max}^{EtOH} mμ (ε) : 240 (16000). IR ν_{max}^{Nujol} cm^{-1} : 1660. NMR δ (p.p.m.)^{CCl_4} : 5.67 (4-H). *Anal.* Calcd. for $C_{21}H_{32}O_2$: C, 79.74; H, 10.12. Found : C, 79.44; H, 9.97.

Succinate (XVI) of VI——To a solution of 20 g. of VI in 200 ml. of pyridine was added 30 g. of succinic anhydride and the mixture was heated at 75~85° for 10 hr. The solution was concentrated to one-third volume, then 10% H_2SO_4 was added until it became fully acidic. The resulting precipitate was collected on a filter, washed with H_2O and recrystallized from AcOEt to yield 21 g. of XVI as colorless scales, m.p. 166~168°.

Brucine Salt (XVII) of XVI——To a solution of 20 g. of XVI in 200 ml. of acetone and 110 ml. of MeOH was added 21.6 g. of brucine and the mixture was allowed to stand at room temperature to deposit the brucine salt of XVI. The crystalline salt was collected on a filter and recrystallized from MeOH-acetone to afford 18 g. of levorotatory brucine salt of XVI as colorless needles, m.p. 105~115°. $[\alpha]_D^{21}$ −73° (c=1, $CHCl_3$). The dextrorotatory salt ($[\alpha]_D^{21}$ +69° (c=0.9, MeOH)) was obtained from the filtrate as a gelatinoid solid.

***l*-3-Methoxy-13β-ethylgona-1,3,5(10),8-tetraen-17β-ol 17-Hydrogen Succinate (XVI)**——A solution of 14.2 g. of *l*-XVII in $CHCl_3$ was shaken with 10% H_2SO_4. The $CHCl_3$ solution was separated and washed with H_2O, dried over Na_2SO_4 and concentrated to yield a crystalline material, which was recrystallized from AcOEt to afford 6 g. of levorotatory XVI (m.p. 92~94°, $[\alpha]_D^{20}$ −80° (c=0.8, $CHCl_3$)). Dextrorotatory XVI (m.p. 92~94°, $[\alpha]_D^{20}$ +72° (c=1.1, $CHCl_3$)) was obtained from the dextrorotatory brucine salt.

***l*-3-Methoxy-13β-ethylgona-1,3,5(10),8-tetraen-17β-ol (VI)**——To a stirred solution of 6 g. of *l*-XVI in 60 ml. of MeOH was added 30 ml. of 10% methanolic KOH with ice cooling. The solution was allowed to stand at room temperature for 24 hr., then extracted with ether. The ether extract was washed with H_2O, dried over Na_2SO_4 and concentrated to yield a crystalline material, which was recrystallized from dilute MeOH to afford 4 g. of *l*-VI as colorless plates, m.p. 118°. $[\alpha]_D^{21}$ −64° (c=1.0, $CHCl_3$).

d-VI (m.p. 116~118°, $[\alpha]_D^{21}$ +64 (c=1, $CHCl_3$)) was obtained from *d*-XVI by the same procedure.

The author wishes to express his deep gratitude to Takeda Chemical Industries, Ltd. for permission to publish this report, to Dr. Y. Abe and Dr. T. Miki for their guidance and encouragement throughout this work. He is also indebted to Dr. T. Masuda and Mr. S. Fujii for their help in preparation of 3-ethyl-1,2,4-cyclopentanetrione and to Mr. T. Asako and Mr. H. Masuya for their technical assistance. Thanks are also due to Mr. H. Kamio and his associates for physicochemical measurements and Mr. M. Kan and his associates for elemental analysis.

Summary

During the course of the synthesis of 18-methylestradiol 3-methyl ether, steric effect caused by the methyl group at 18-position was observed. It was found that ethylenediamine was a good solvent for the ethynylation reaction of the hindered ketone.

Racemic and optically active 17β-hydroxy-13β,17α-diethylgon-4-en-3-one were synthesized from 1-vinyl-6-methoxy-1-tetralol and 2-ethyl-1,3-cyclopentanedion. The dextrorotatory diethylgonenone as well as the corresponding racemic diethylgonenone showed strong anabolic activities, whereas the levorotatory compound had no biological activity.

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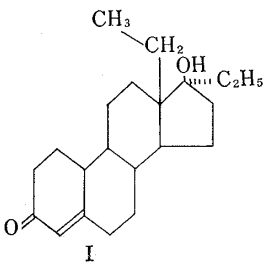
165. Kentaro Hiraga, Tsunehiko Asako, and Takuichi Miki : Syntheses and Steric Hindrances in 13β-Isopropylgonanes.*1

(*Chemical Research Laboratories, Research & Development Division, Takeda Chemical Industries, Ltd.**2)

Recent report[1] on the strong anabolic activity of 17α-ethyl-18-methyl-19-nortestosterone (I) prompted us to introduce one more methyl group at 18-position of I for examination of the biological activities.



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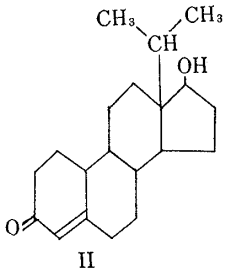

II

Chart 1.

The present paper deals with the syntheses of *dl*-18,18-dimethyl-19-nortestosterone (II) as well as its 17α-ethyl derivative (XX).

Condensation of 1-vinyl-6-methoxy-1-tetralol (III) with 2-isopropyl-1,3-cyclopentanedione (IV) in the presence of Triton B or triethylenediamine gave *dl*-3-methoxy-13β-isopropyl-8,14-secogona-1,3,5(10),9-tetraene-14,17-dione (V) in 40% yield.

The seco-compound (V) was cyclized to *dl*-3-methoxy-13β-isopropylgona-1,3,5(10),8,14-pentaen-17-one (VI)[3] by heating at 70° in a methanolic hydrogen chloride solution. It is to be noted that the cyclization reaction proceeded very slowly at room temperature which was sufficiently effective to cyclize 13β-methyl-[2] and 13β-ethyl-seco compound.[1b] Then the 17-ketone of VI was reduced to 17β-ol with sodium borohydride

*1 This paper constitutes Part XXXVI of Takeda Laboratories' series entitled "Steroid"; Part XXXV: This Bulletin, **13**, 1289 (1965).

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

1) *a*) R. A. Edgren, H. Smith, G. A. Hughes, L. L. Smith, G. Greenspan : Steroids, **2**, 731 (1963). *b*) K. Hiraga : This Bulletin, **13**, 1289 (1965).
2) T. Miki, K. Hiraga, T. Asako : This Bulletin, **13**, 1285 (1965).
3) H. Smith, *et al.* : J. Chem. Soc., **1964**, 4472.