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

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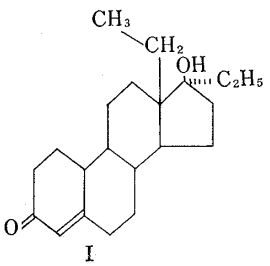
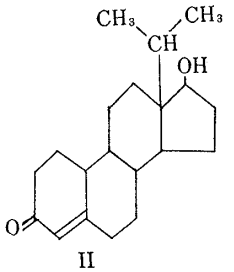
Recent report[1] on the strong anabolic activity of 17α-ethyl-18-methyl-19-nortestosterone (I) prompted us to introduce one more methyl group at 18-position of I for examination of the biological activities.



I



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

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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.

in methanol at 10°. While the 17-ketones of 13β-methyl and 13β-ethyl analogs were easily reduced to 17β-ol at −10°, it was necessary to elevate the reaction temperature for the reduction of the 17-ketone of VI probably because of the steric hindrance of 13β-isopropyl group over 17-ketone.

The pentaenol (VII) was partially hydrogenated over Raney nickel in dioxane to afford a tetraenol (VIII), which was further reduced with lithium in liquid ammonia and tetrahydrofuran to *dl*-3-methoxy-13β-isoprogylgona-1,3,5(10)-trien-17β-ol (XII).

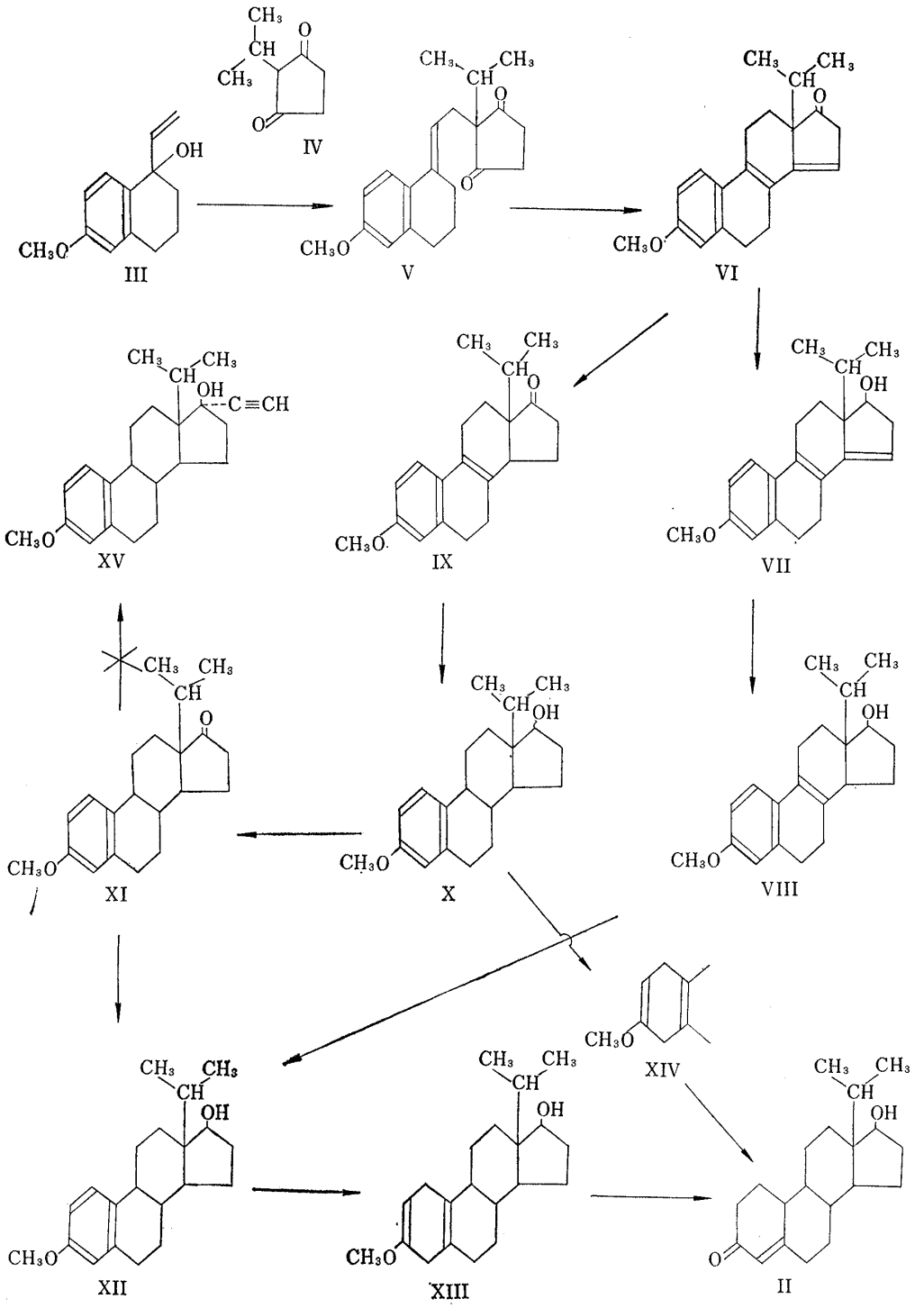

Chart 2.

An alternative route of reduction was studied. *dl*-3-Methoxy-13β-isopropylgona-1,3,5(10),8,14-pentaen-17-one (VI) was first subjected to the catalytic hydrogenation, and the treatment of the tetraenone (IX) thus obtained with lithium in liquid ammonia gave a trienol substance (X), which showed two adjacent spots in the thin-layer chromatography.

The substance was found to be a mixture of the isomers due to the difference of the configuration at 17, since it was oxidized with Jones' reagent to *dl*-3-methoxy-13β-isopropylgona-1,3,5(10)-trien-17-one (XI) in good yield, and then reduced to the pure 17β-ol (XII). For the reduction of the 17-ketone of XI, it was necessary to use a large excess of sodium borohydride or lithium aluminum hydride in boiling ether. This shows the steric hindrance of the 13β-isopropyl group over the 17-ketone of the trienone is much more severe than that of the pentaenone (VI), owing to the additional interaction between the isopropyl group and 8β-hydrogen in the former.

Reduction of the trienol (XII) with lithium and ethanol in liquid ammonia and tetrahydrofuran, followed by hydrolysis with hydrochloric acid in tetrahydrofuran gave *dl*-18,18-dimethyl-19-nortestosterone (II).

Steric hindrance of the 13β-isopropyl group was again observed on the ethynylation reaction at 17-ketone of XI. As reported in the preceding paper,[1b] ethylenediamine was proved to be the effective solvent for the ethynylation reaction in 13β-ethyl series, whereas the reaction did not occur when liquid ammonia was used as a solvent.

Here, an attempt to introduce an ethynyl group at the 17α-position of XI was unsuccessful even in ethylenediamine and at an elevated temperature (50°). The steric

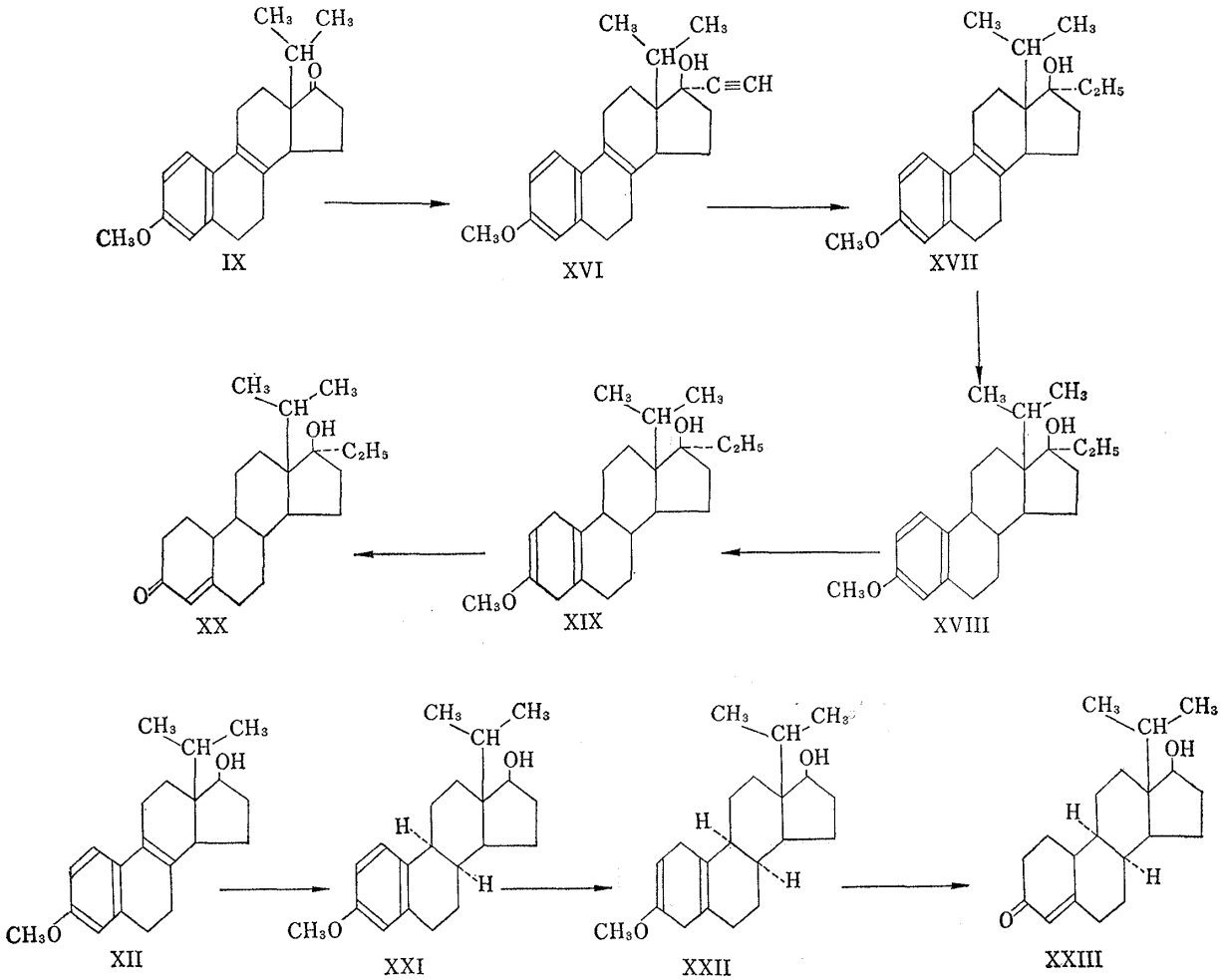

Chart 3.

hindrance of the 13β-isopropyl group over 17-ketone must be much more severe than that of 13β-ethyl group.

The ethynylation reaction of *dl*-3-methoxy-13β-isopropylgona-1,3,5(10),8-tetraen-17-one (IX), however, proceeded smoothly at room temperature, yielding 17α-ethynyl derivative (XVI) in 60% yield, which was hydrogenated over Raney nickel in dioxane to give *dl*-3-methoxy-13β-isopropyl-17α-ethylgona-1,3,5(10),8-tetraen-17β-ol (XVII).

Since reduction of XVII with lithium in liquid ammonia and tetrahydrofuran resulted in a mixture of *dl*-3-methoxy-13β-isopropyl-17α-ethylgona-1,3,5(10)-trien-17β-ol (XVIII) and *dl*-3-methoxy-13β-isopropyl-17α-ethylgona-2,5(10)-dien-17β-ol (XIX), this mixture was treated with additional lithium and ethanol in the same solvent to give pure gonadien (XIX), which was hydrolyzed with 6*N* hydrochloric acid in tetrahydrofuran to *dl*-17α-ethyl-18,18-dimethyl-19-nortestosterone (XX).

The nuclear magnetic resonance spectrum and the elemental analysis showed the crystals of XX contain benzene as a solvent of crystallization.

The steric hindrance of 13β-isopropyl group over 17-ketone has already been shown by the results described so far. It is possible, therefore, that during the course of reduction at 8-double bond with lithium-ammonia, hydrogen might come from α side to give 8α-compound. In order to examine the configuration at 8-position, VIII was subjected to catalytic hydrogenation to give *dl*-18,18-dimethyl-8α-estradiol 3-methyl ether (XXI). This was converted *via* XXII to *dl*-18,18-dimethyl-19-nor-8α-testosterone (XXIII), which was different from II in melting point and infrared spectrum, thus the configuration in II must be 8β, similarly to natural steroid.

According to the report from the pharmacological section, both II and XX showed almost no anabolic and androgenic activity.

The reduction of the biological activity may be explained by the steric hindrance of the isopropyl group over 17β-hydroxyl group.

Experimental*3

***dl*-3-Methoxy-13-isopropyl-8,14-secogona-1,3,5(10),9-tetraene-14,17-dione (V)**——To a stirred solution of 15 g. of 2-isopropyl-1,3-cyclopentanedione (IV) and 8 g. of triethylenediamine in 150 ml. of xylene was added dropwise a solution of 20 g. of 1-vinyl-6-methoxy-1-tetralol in 30 ml. of xylene during 40 min. at the refluxing temperature. The reaction was continued for additional 1.5 hr. using a water separator, and the solution was concentrated to the half volume and then cooled. The concentrate was diluted with ether, washed with 5% KOH solution and H_2O, dried over Na_2SO_4. Evaporation of the solvent yielded 14 g. of crude crystals of V, which were recrystallized from EtOH to give colorless prisms, m.p. 70~71°. IR ν_{max}^{Nujol} cm^{-1} : 1712, 1606, 1500. UV λ_{max}^{EtOH} mμ (ε) : 266 (18000). *Anal.* Calcd. for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found : C, 76.76; H, 7.84.

***dl*-3-Methoxy-13β-isopropylgona-1,3,5(10),8,14-pentaen-17-one (VI)**——To a solution of 2 g. of V in 22 ml. of MeOH was added 5 ml. of 2*N* HCl and the solution was heated at the refluxing temperature. After heating for 30 min., the solution was allowed to stand at room temperature to deposit a crystalline precipitate, which was filtered. The mother liquor was diluted with H_2O and shaken with ether. The ether layer was washed with saturated $NaHCO_3$ solution and H_2O, dried over Na_2SO_4, and concentrated *in vacuo* to yield a further quantity of crystals. Recrystallization from EtOH afforded 0.9 g. of colorless prisms, m.p. 105~108°. IR ν_{max}^{Nujol} cm^{-1} : 1733. UV λ_{max}^{EtOH} mμ (ε) : 314 (28300). *Anal.* Calcd. for $C_{21}H_{24}O_2$: C, 81.78; H, 7.84. Found : C, 81.80; H, 7.80.

***dl*-3-Methoxy-13β-isopropylgona-1,3,5(10),8,14-pentaen-17β-ol (VII)**——a) To a solution of 1.85 g. of VI in 90 ml. of MeOH was added 0.45 g. of $NaBH_4$, and the solution was stirred for 45 min. at 10°. After addition of a few drops of AcOH to decompose the excess $NaBH_4$, the solution was poured into H_2O, and the mixture was extracted with ether. The extract was washed with H_2O, dried over Na_2SO_4, and concentrated *in vacuo* to yield 1.7 g. of an oily material, which was crystallized from ether-hexane, m.p. 109~110°. IR ν_{max}^{Nujol} cm^{-1} : 3400. UV λ_{max}^{EtOH} mμ (ε) : 312 (31000). *Anal.* Calcd. for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found : C, 80.62; H, 8.27.

b) To a solution of 1.2 g. of $LiAlH_4$ in 30 ml. of ether was added a solution of 9.2 g. of VI in 150 ml. of ether, and the solution was stirred at room temperature for 30 min. The excess $LiAlH_4$ was

*3 All melting points are uncorrected.

decomposed by addition of AcOEt, and the solution was washed with dil. HCl, and H_2O successively. After drying with Na_2SO_4, the solvent was evaporated and the residue was recrystallized from EtOH–petr. ether to give 4.1 g. of colorless needles, m.p. 112~113°. *Anal.* Calcd. for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found : C, 81.25; H, 8.47.

***dl*-3-Methoxy-13β-isopropylgona-1,3,5(10),8-tetraen-17β-ol (VIII)**——Ⅶ (4 g.) was hydrogenated in 150 ml. of dioxane in the presence of Raney Ni until 1 mole of H_2 had been absorbed. When the catalyst and the solvent were removed, there was obtained a crystalline material, which was recrystallized from EtOH to give 3 g. of colorless needles, m.p. 74~76°. UV λ_{max}^{EtOH} mμ (ε) : 281 (13400). NMR δ (p.p.m.)^{CCl_4} : 3.62 ($CH_3C\underline{H}_2OH$). *Anal.* Calcd. for $C_{21}H_{28}O_2 \cdot C_2H_5OH$: C, 77.09; H, 9.49. Found : C, 76.51; H, 9.36.

***dl*-3-Methoxy-13β-isopropylgona-1,3,5(10),8-tetraen-17-one (IX)**——Ⅵ (1 g.) was hydrogenated in 100 ml. of dioxane in the presence of Raney Ni until 1 mole of H_2 had been absorbed. The mixture was filtered and, on evaporation of the solvent there was obtained an oily material, which was chromatographed on 100 g. of silica gel. Elution with benzene gave 0.5 g. of colorless needles, m.p. 95~99°. IR ν_{max}^{Nujol} cm^{-1} : 1722. UV λ_{max}^{EtOH} mμ (ε) : 282 (16200). *Anal.* Calcd. for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found : C, 81.19; H, 8.33.

The mixture of two isomers :

***dl*-3-Methoxy-13β-isopropylgona-1,3,5(10)-trien-17α- and β-ol (X)**——To a solution of 1.4 g. of Ⅸ in 30 ml. of dioxane, 70 ml. of ether and 400 ml. of liq. NH_3 was added 1 g. of Li at −50°. After stirring for 4 hr., 5 g. of NH_4Cl was added to the reaction mixture, then NH_3 was evaporated. The residue was shaken with 1 L. of H_2O and the organic layer was washed with H_2O, dried over Na_2SO_4 and concentrated to yield an oily residue, which was dissolved in benzene and chromatographed on 100 g. of silica gel. Elution with benzene gave 0.7 g. of colorless crystals, m.p. 79~84°. IR ν_{max}^{Nujol} cm^{-1} : 3330, 1605, 1580, 1495. UV λ_{max}^{EtOH} mμ (ε) : 278.5 (2090), 287 (1990). NMR δ (p.p.m.)^{CCl_4} : 3.47 ($C\underline{H}_3OH$). *Anal.* Calcd. for $C_{21}H_{30}O_2 \cdot \frac{2}{3}CH_3OH$: C, 77.53; H, 9.74. Found : C, 77.57; H, 9.69.

***dl*-3-Methoxy-13β-isopropylgona-1,3,5(10)-trien-17-one (XI)**——To a solution of 0.2 g. of X in 30 ml. of acetone was added 0.5 ml. of Jones' reagent and the mixture was stirred at room temperature for 10 min. After addition of MeOH to decompose the excess CrO_3, the reaction mixture was shaken with 500 ml. of H_2O, and 200 ml. of ether, and the ether solution was washed with H_2O and dried over Na_2SO_4. Evaporation of the solvent yielded an oily material, which was dissolved in benzene and chromatographed on 30 g. of silica gel. Elution with benzene gave 0.1 g. of colorless needles, m.p. 97~100°. IR ν_{max}^{Nujol} cm^{-1} : 1729. UV λ_{max}^{EtOH} mμ (ε) : 279.5 (2000), 288 (1900). *Anal.* Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found : C, 80.41; H, 9.25.

***dl*-3-Methoxy-13β-isopropylgona-1,3,5(10)-trien-17β-ol (XII)**——To a solution of 0.3 g. of Ⅺ in 20 ml. of MeOH was added 0.8 g. of $NaBH_4$ and the mixture was stirred at room temperature for 3 hr. and then allowed to stand overnight. The excess $NaBH_4$ was decomposed with 300 ml. 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 afford 0.3 g. of a pale yellow paste. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3580.

***dl*-3-Methoxy-13β-isopropylgona-2,5(10)-dien-17β-ol (XIII)**——To a solution of 1.2 g. of Ⅻ in 100 ml. of tetrahydrofuran and 400 ml. of liq. NH_3 was added 3.5 g. of Li at −50°. After stirring for 30 min., 30 ml. of EtOH was added dropwise to the mixture, then NH_3 was evaporated. To the residue was added a large amount of H_2O and the resulting precipitate was recrystallized from MeOH to yield 0.55 g. of colorless prisms, m.p. 115°.

The mixture of the isomers :

***dl*-3-Methoxy-13β-isopropylgona-2,5(10)-dien-17α- and β-ol (XIV)**——To a solution of 0.2 g. of X in 80 ml. of tetrahydrofuran and 250 ml. of liq. NH_3 was added 2 g. of Li at −50°. After stirring for 30 min., 20 ml. of EtOH was added dropwise to the mixture, then NH_3 was evaporated. To the residue was added 1 L. of H_2O and the mixture was extracted with ether. The ether solution was washed with H_2O, dried over Na_2SO_4, and concentrated to yield 0.2 g. of a crystalline material. Recrystallization from MeOH afforded 0.14 g. of colorless scales, m.p. 104~113°, which showed two spots in the thin-layer chromatography. IR ν_{max}^{Nujol} cm^{-1} : 3350, 1695, 1664.

***dl*-18,18-Dimethyl-19-nortestosterone (II)**——a) To a solution of 0.7 g. of XIV in 25 ml. of MeOH and 15 ml. of tetrahydrofuran was added 14 ml. of 6*N* HCl. The mixture was stirred at room temperature for 3 hr., diluted with H_2O and shaken with ether. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated under reduced pressure. The oily residue was crystallized by the addition of ether. Three recrystallizations from acetone–petr. ether gave 0.2 g. of crystals, m.p. 148°.

b) To a solution of 0.3 g. of XIII in 20 ml. of tetrahydrofuran was added 6 ml. of 6*N* HCl and the solution was stirred at room temperature for 1.5 hr. The solution was poured into H_2O and extracted repeatedly with ether. The extracts were combined, washed with saturated $NaHCO_3$ solution and H_2O, dried over Na_2SO_4, and evaporated to dryness. The residue was dissolved in benzene and chromatographed on 15 g. of silica gel. Elution with benzene–ether (3:1) gave 0.1 g. of colorless crystals identical with those obtained in a), which were recrystallized from acetone–petr. ether, m.p. 148°. IR ν_{max}^{Nujol} cm^{-1} : 1660. UV λ_{max}^{EtOH} mμ (ε) : 240 (16100). *Anal.* Calcd. for $C_{20}H_{30}O_2$: C, 79.47; H, 9.93. Found : C, 79.13;

H, 10.04.

***dl*-3-Methoxy-13β-isopropyl-17α-ethynylgona-1, 3, 5 (10), 8-tetraen-17β-ol (XVI)**——Acetylene was passed through a solution of 0.5 g. of Li in 100 ml. of ethylenediamine for 1 hr. To this solution was added a solution of 1 g. of IX in 20 ml. of tetrahydrofuran with stirring at room temperature. After passing acetylene through the solution for additional 5 hr., 10 g. of NH_4Cl was added, then the mixture was poured onto ice and extracted with ether. The ether solution was washed with 10% H_2SO_4, saturated $NaHCO_3$ solution and H_2O, dried over Na_2SO_4, and concentrated *in vacuo* to yield 0.6 g. of a solid material. Recrystallization from MeOH gave colorless needles, m.p. 91~93°. IR ν_{max}^{Nujol} cm^{-1} : 3280. NMR δ (p.p.m.)^{CCl_4} : 3.43 ($C\underline{H}_3OH$). *Anal.* Calcd. for $C_{23}H_{28}O_2 \cdot \frac{1}{2}CH_3OH$: C, 80.00; H, 8.41. Found : C, 80.12; H, 8.56.

***dl*-3-Methoxy-13β-isopropyl-17α-ethylgona-1, 3, 5 (10), 8-tetraen-17β-ol (XVII)**——XVI (0.5 g.) was hydrogenated in 70 ml. of dioxane in the presence of Raney Ni. The catalyst was filtered off and the solvent was evaporated to dryness under reduced pressure. The residue was recrystallized from MeOH to give 0.5 g. of colorless crystals, m.p. 75~78°. *Anal.* Calcd. for $C_{23}H_{32}O_2$: C, 81.17; H, 9.41. Found : C, 80.63; H, 9.42.

***dl*-3-Methoxy-13β-isopropyl-17α-ethylgona-2,5(10)-dien-17β-ol (XIX)**——To a stirred solution of 0.7 g. of XVII in 70 ml. of tetrahydrofuran and 150 ml. of liq. NH_3 was added 2 g. of Li at −50°. After 30 min., 30 ml. of EtOH was added dropwise to the mixture, then NH_3 was evaporated. The residue was diluted with ether and the ether solution was washed with H_2O, dried over Na_2SO_4 and concentrated *in vacuo* to yield 0.7 g. of an oily material, which was crystallized from MeOH. Recrystallization from MeOH gave 0.3 g. of colorless crystals, m.p. 109~111°.

***dl*-17α-Ethyl-18,18-dimethyl-19-nortestosterone (XX)**——To a solution of 0.3 g. of XIX in 15 ml. of tetrahydrofuran was added 8 ml. of 4*N* HCl and the mixture was stirred for 3 hr. at room temperature. The solution was diluted with H_2O, shaken with ether, and the ether solution was washed with saturated $NaHCO_3$ solution and H_2O, dried over Na_2SO_4. Evaporation of the solvent afforded 0.3 g. of an oily material, which was crystallized by trituration with benzene. Recrystallization from benzene gave 0.2 g. of colorless crystals, m.p. 70~73°. IR ν_{max}^{Nujol} cm^{-1} : 3430, 1660. UV λ_{max}^{EtOH} mμ (ε) : 240 (12000). NMR δ (p.p.m.)^{CCl_4} : 7.27 (). *Anal.* Calcd. for $C_{22}H_{34}O_2 \cdot \frac{1}{2}C_6H_6$: C, 81.30; H, 10.03. Found : C, 81.19; H, 10.30.

***dl*-3-Methoxy-13β-isopropyl-8α-gona-1,3,5(10)-trien-17β-ol (XXI)**——VIII (0.35 g.) was hydrogenated in 100 ml. of MeOH in the presence of 1 g. of Pd-C (5%). After separation of the catalyst, the solvent was evaporated under reduced pressure. The residue was recrystallized from MeOH to yield 0.2 g. of colorless crystals, m.p. 63~65°. UV λ_{max}^{EtOH} mμ (ε) : 278 (1700), 286.5 (1600).

***dl*-13β-Isopropyl-17β-hydroxy-8α-gon-4-en-3-one (XXIII)**——To a solution of 0.15 g. of XXI in 15 ml. of tetrahydrofuran and 50 ml. of liq. NH_3 was added 0.5 g. of Li at −50°. After stirring for 30 min., 15 ml. of EtOH was added dropwise, then NH_3 was evaporated. The organic substance was taken in ether, and the ether solution was washed with H_2O, dried over Na_2SO_4, and concentrated to give 0.1 g. of a crystalline material, m.p. 102~104°. This material was dissolved in 10 ml. of tetrahydrofuran and 3 ml. of 6*N* HCl was added. After stirring at room temperature for 2 hr., the mixture was poured into H_2O and extracted with ether. The ether solution was washed with saturated $NaHCO_3$ solution and H_2O successively, dried over Na_2SO_4, the solvent was evaporated, and the residue was chromatographed on 15 g. of silica gel. Elution with benzene-ether (3:1) gave 0.02 g. of colorless crystals, m.p. 174~176°. IR ν_{max}^{Nujol} cm^{-1} : 1650. UV λ_{max}^{EtOH} mμ (ε) : 240 (12000). *Anal.* Calcd. for $C_{20}H_{30}O_2$: C, 79.47; H, 9.93. Found : C, 79.15; H, 9.64.

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Summary

dl-18,18-Dimethylestradiol 3-methyl ether (XII), *dl*-18,18-dimethyl-19-nortestosterone (II) and their derivatives were synthesized starting from 1-vinyl-6-methoxy-1-tetralol (III) and 2-isopropyl-1,3-crclopentanedione (IV).

The steric effect of the 13-isopropyl group over 17-position was observed in every kind of reactions in this series.

Both II and *dl*-17α-ethyl-18,18-dimethyl-19-nortestosterone (XX) showed almost no anabolic and androgenic activity.

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