

Summary

Ethyl 2-methoxymethylene-3-ethoxypropionate (III) undergoes condensation with urea, and N-substituted urea in ethanol solution in the presence of hydrochloric acid. With urea, III gave ethyl 2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (V), with N-methylurea a mixture of ethyl 2-oxo-3-methyl-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (XIII) and its isomeric 1-methyl compound (XIV), which was separated into each isomer, and with N-phenylurea the 1-phenyl compound (XV) was exclusively obtained. Conversion into pyrimidines was achieved by dehydrogenation and subsequent chlorination of V.

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115. Terumi Aoki, Hiroko Yamamura, Kyoko Takei,*¹ and Hiromu Mori*² : Synthesis of 16-Oxygenated Androst-5-ene-3 β -ol Derivatives.

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Androst-5-ene-3 β ,16 α ,17 β -triol,^{1~3)} androst-5-ene-3 β ,16 β ,17 β -triol,⁴⁾ and 3 β ,16 α -dihydroxyandrost-5-ene-17-one⁵⁾ are all steroid metabolites isolated from human urine. In our course of study on steroid metabolism, these compounds became necessary as standard samples. Androst-5-ene 3 β ,16 α ,17 β -triol was first prepared by Huffman and Lott,⁶⁾ from 3 β -hydroxyandrost-5-ene-17-one through nine steps, but much more convenient method seems not to be reported. This paper describes much more convenient method of synthesis of androst-5-ene-3 β ,16 α ,17 β -triol and related compounds.

In Huffman's method of synthesis, key steps for introduction of oxygen at C-16 contain three reactions (I $\rightarrow$ II $\rightarrow$ III $\rightarrow$ IV); the condensation of 17-oxo steroid (I) with isomyl nitrite to 16-oximino-17-oxo compound (II), reductive hydrolysis of II with zinc dust in aqueous acetic acid to 17 β -hydroxy-16-oxo compound (III) and reduction of III with sodium amalgam to 16 α ,17 β -glycol (IV). The last step (III $\rightarrow$ IV) is not stereospecific reaction, so that considerable amount of 16 β ,17 β -glycol is also produced⁷⁾. On the other hand, Gallagher and his coworkers⁸⁾ developed another method of synthesis of 16 α ,17 β -glycol from 17-oxo steroid which is more stereospecific; I is transformed into 17-enol acetate (V), which on oxidation with peracid gave the oxide (VI), followed by reduction with lithium aluminum hydride to 16 α ,17 β -glycol (IV). This elegant method could be applied for synthesis of androst-5-ene-3 β ,16 α ,17 β -triol.

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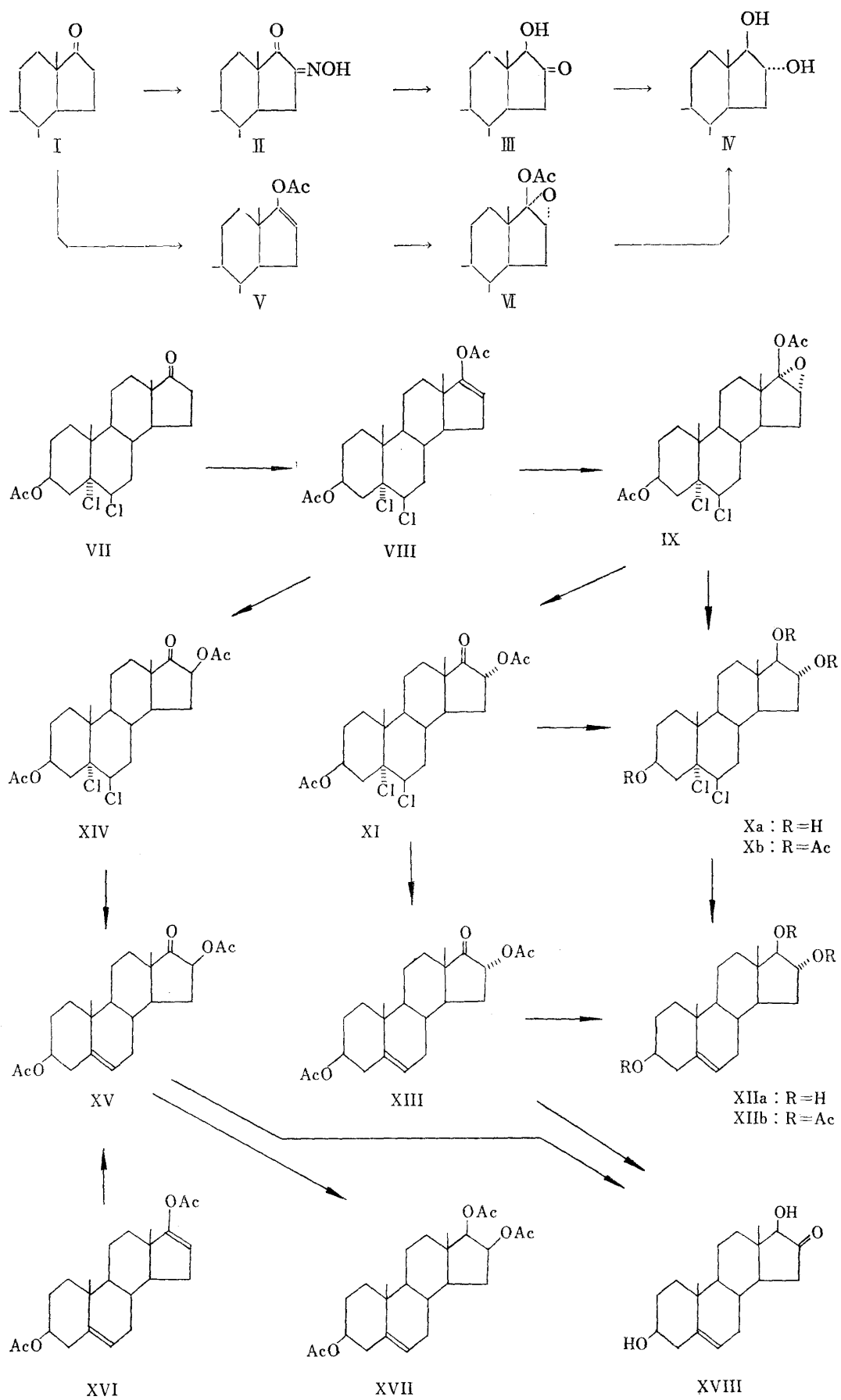
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3 β -Acetoxy-5 α ,6 β -dichloroandrostan-17-one (VII)⁹⁾ was used as a starting material, and was converted to enol acetate (VIII) without any trouble by refluxing with isopropenyl acetate in the presence of catalytic amount of sulfuric acid. When enol acetate (VIII) was oxidized with perphthalic acid, oxide (IX) was given, but recrystallization was not effective for purification. The crude oxide (IX) was reduced with sodium borohydride*³ and then hydrolized by alkali to give 5 α ,6 β -dichloroandrostan-3 β ,16 α ,17 β -triol (Xa), the structure of which was proved by introduction of Xa to androst-5-ene-3 β ,16 α ,17 β -triol triacetate (XIIb). Treatment of Xa with zinc dust in acetic acid afforded halogen free triol (XIIa), which on acetylation with acetic anhydride in pyridine gave triacetate (XIIb). The infrared spectrum of XIIb was identical with that for an authentic sample.¹⁰⁾

When the oxide (IX) was treated with perchloric acid, a rearrangement product, 3 β ,16 α -diacetoxy-5 α ,6 β -dichloroandrostan-17-one (XI) was obtained.⁹⁾ Reduction of XI with sodium borohydride and acetylation of the reduction product gave triacetate (Xb), which was identical with acetylation product of Xa. Dechlorination of XI with zinc dust gave 3 β ,16 α -diacetoxyandrost-5-ene-17-one (XIII), which could be transformed into triacetate (XIIb) by reduction and acetylation.

Johnson and his coworkers¹¹⁾ have reported that oxidation of 5 α -androst-16-ene-3 β ,17-diol diacetate with lead tetraacetate affords 3 β ,16 β -diacetoxy-5 α -androstan-17-one, and this reaction was extended to estrogen series by Biggerstaff and Gallagher.¹²⁾ The oxidation of enol acetate (VIII) with lead tetraacetate gave the expected product, 3 β ,16 β -diacetoxy-5 α ,6 β -dichloroandrostan-17-one (XIV). Dechlorination of XIV with zinc dust afforded 3 β ,16 β -diacetoxyandrost-5-en-17-one (XV), which on reduction with sodium borohydride followed by acetylation gave androst-5-ene-3 β ,16 β ,17 β -triol triacetate (XVII) identical with an authentic sample. XV was also obtained from enol acetate (XVI) by lead tetraacetate oxidation. Both XV and XIII were transformed into 3 β ,17 β -dihydroxyandrost-5-en-16-one (XVIII) on treatment with alkali. It is generally accepted that the most stable 16,17-ketol is 17 β -hydroxy-16-oxo compound in C/D trans steroid.^{11,13)}

Experimental*⁴

3 β -Acetoxy-5 α ,6 β -dichloroandrostan-17-one 17-Enol Acetate (VIII)—A solution of 3 β -acetoxy-5 α ,6 β -dichloroandrostan-17-one (VII, 4.0 g.) in isopropenyl acetate (23 ml.) containing a catalyst solution (2.5 ml.)*⁵ was stirred at 90~95° for 2 hr., and then distilled slowly until 7 ml. of isopropenyl acetate was removed. Isopropenyl acetate (16 ml.) and catalyst solution (0.8 ml.) were added and the resulting solution was refluxed for 1 hr. After 20 ml. of isopropenyl acetate were removed by distillation, Et₂O was added and Et₂O solution was washed well with H₂O and dried over Na₂SO₄. Et₂O solution was passed through alumina (100 g.) column, and the column was eluted with another portion of Et₂O. The combined Et₂O solution was condensed to dryness, and the residue was recrystallized from Me₂CO-hexane to give enol acetate (VIII, 2.9 g.) m.p. 140~146°. Further recrystallization from the same solvent afforded an analytical sample as colorless cubes, m.p. 146~150°, [α]_D²⁷ -22° (c=1.05), IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1757 (C=O at 17-OAc), 1734 (C=O at 3-OAc). Anal. Calcd. for C₂₃H₃₂O₄Cl₂: C, 62.44; H, 7.29. Found: C, 62.51; H, 7.37.

5 α ,6 β -Dichloro-16 α ,17 α -epoxyandrostan-3 β ,17 β -diol Diacetate (IX)—A solution of perphthalic acid in Et₂O (2 g. in 32 ml.) was added dropwise to an ice cold solution of the enol acetate (VIII, 2.0 g.) in CHCl₃,

*³ Gallagher, *et al.* used LiAlH₄ for this type of reaction, but NaBH₄ was also a satisfactory reagent for reduction.

*⁴ All melting points are uncorrected and optical rotations are measured in CHCl₃ solution unless otherwise stated.

*⁵ Catalyst solution was a mixture of isopropenyl acetate (5 ml.) and H₂SO₄ (0.1 ml.).

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(10 ml.). The resulting solution was stored overnight in an ice box. Et₂O (150 ml.) was added and the Et₂O solution was washed with 5% Na₂CO₃ and H₂O, and dried over Na₂SO₄. Solvent was evaporated *in vacuo* to give white solid (2.0 g.), m.p. 158~161°, which was used for further transformation without purification.

5 α ,6 β -Dichloroandrostand-3 β ,16 α ,17 β -triol (Xa)—A solution of the crude epoxide obtained above (K, 2.0 g.) and NaBH₄ (2.0 g.) in MeOH (100 ml.) was refluxed for 1 hr., and 4% NaOH (4 ml.) was added. The solution was refluxed for additional half an hour and poured into 10% H₂SO₄ (600 ml.). Precipitates were collected by filtration and washed well with H₂O. Recrystallization from Me₂CO-hexane gave 5 α ,6 β -dichloroandrostand-3 β ,16 α ,17 β -triol (Xa, 970 mg.), m.p. 170~175°. Further recrystallization from MeOH gave an analytical sample as colorless plates, m.p. 170~172°, $[\alpha]_D^{27}$ -65° (c=1.06, dioxane), IR: $\nu_{\text{max}}^{\text{KBr}}$ 3300~3480 cm⁻¹ (-OH). Anal. Calcd. for C₁₉H₃₀O₃Cl₂·H₂O: C, 57.72; H, 8.14. Found: C, 57.99; H, 8.24.

3 β ,16 α -Diacetoxy-5 α ,6 β -dichloroandrostand-17-one (XI)—The crude epoxide obtained above (K, 2.0 g.) was dissolved in AcOH (120 ml.). After addition of 70% HClO₄ (0.4 ml.), the solution was stored in a dark place for 1.5 hr. Et₂O (500 ml.) was added and Et₂O solution was washed with 5% NaHCO₃ and 4% NaCl, and dried over Na₂SO₄. After evaporation of the solvent, the residue was dissolved in dry pyridine (40 ml.) and Ac₂O (40 ml.) and the solution was allowed to stand overnight and poured into H₂O. The product was extracted with Et₂O, and the ethereal solution was washed with 10% H₂SO₄, 5% Na₂CO₃ and H₂O, and dried over Na₂SO₄. Evaporation of the solvent gave colorless solid, which on recrystallization from MeOH afforded 3 β ,16 α -diacetoxy-5 α ,6 β -dichloroandrostand-17-one (XI, 1.57 g.), m.p. 155~156°. Further recrystallization from MeOH gave an analytical sample as colorless cubes, m.p. 155~156°, $[\alpha]_D^{27}$ +4° (c=1.02), IR $\nu_{\text{max}}^{\text{CS}_2}$ cm⁻¹: 1765, 1750. Anal. Calcd. for C₂₃H₃₂O₅Cl₂: C, 60.13; H, 7.02. Found: C, 60.34; H, 7.11.

5 α ,6 β -Dichloroandrostand-3 β ,16 α ,17 α -triol Triacetate (Xb). a) From 5 α ,6 β -Dichloroandrostand-3 β ,16 α ,17 β -triol (Xa)—A solution of 5 α ,6 β -dichloroandrostand-3 β ,16 α ,17 β -triol (Xa, 500 mg.) in dry pyridine (10 ml.) and Ac₂O (10 ml.) was allowed to stand overnight at room temperature, and poured into H₂O. The product was extracted with Et₂O, and the Et₂O solution was washed with 10% H₂SO₄, 5% Na₂CO₃ and H₂O, and dried over Na₂SO₄. The solvent was removed by distillation, and the residue was recrystallized from MeOH to give 5 α ,6 β -dichloroandrostand-3 β ,16 α ,17 β -triol triacetate (Xb, 350 mg.), m.p. 202~204°. $[\alpha]_D^{27}$ -91° (c=0.98), IR: $\nu_{\text{max}}^{\text{KBr}}$ 1730 cm⁻¹ (-OAc). Anal. Calcd. for C₂₅H₃₆O₆Cl₂: C, 59.64; H, 7.21. Found: C, 59.84; H, 7.38.

b) From 3 β ,16 α -Diacetoxy-5 α ,6 β -dichloroandrostand-17-one (XI)—A solution of 3 β ,16 α -diacetoxy-5 α ,6 β -dichloroandrostand-17-one (XI, 100 mg.) and NaBH₄ (50 mg.) in MeOH (10 ml.) was stirred at room temperature for 3 hr. After decomposition of excess NaBH₄ by one drop of AcOH, the solution was poured into H₂O, and the product was extracted with Et₂O. The Et₂O solution was washed with 10% H₂SO₄, 5% Na₂CO₃ and H₂O, and dried over Na₂SO₄. After evaporation of the solvent, the residue was dissolved in dry pyridine (5 ml.) and Ac₂O (5 ml.) and the solution was stored at room temperature overnight, and poured into H₂O. The product was extracted with Et₂O, and the Et₂O solution washed with 10% H₂SO₄, 5% Na₂CO₃ and H₂O, and dried over Na₂SO₄. After evaporation of the solvent, the residue was recrystallized from MeOH to give triacetate (Xb, 70 mg.). Further recrystallization from MeOH afforded an analytical sample as colorless needles, m.p. 200~202°, which was identical with the sample obtained above.

Androst-5-ene-3 β ,16 α ,17 β -triol (XIIa)—Zn dust (300 mg.) was added portionwise to a solution of 5 α ,6 β -dichloroandrostand-5-ene-3 β ,16 α ,17 β -triol (Xa, 290 mg.) in AcOH (12 ml.) and the resulting suspension was stirred at room temperature for 2 hr. Zn cake was removed by filtration and washed with MeOH. The combined solution was poured into H₂O, and precipitates were collected by filtration and washed with H₂O. Recrystallization from MeOH afforded androst-5-ene-3 β ,16 α ,17 β -triol (XIIa, 80 mg.), m.p. 257~258°. An analytical sample was obtained by further recrystallization from MeOH as colorless plates, m.p. 263~265°, $[\alpha]_D^{27}$ -67° (c=0.6, AcOH). (reported, m.p. 267~270°, $[\alpha]_D^{28}$ -75.7° (90% AcOH)). IR: $\nu_{\text{max}}^{\text{KBr}}$ 3260~3320 cm⁻¹ (-OH).

3 β ,16 α -Diacetoxyandrostand-5-en-17-one (XIII)—Zn dust (1.6 g.) was added portionwise to a solution of 3 β ,16 α -diacetoxy-5 α ,6 β -dichloroandrostand-17-one (XI, 1.57 g.) in AcOH (64 ml.) and the resulting suspension was stirred for 2 hr. at room temperature. Zn cake was removed by filtration and washed with MeOH. The combined filtrate was poured into H₂O and precipitates were collected by filtration and washed with H₂O. Recrystallization from MeOH afforded 3 β ,16 α -diacetoxyandrostand-5-en-17-one (XIII, 1.0 g.) m.p. 153~165°. Further recrystallization from MeOH gave an analytical sample as colorless needles, m.p. 166~168°, $[\alpha]_D^{27}$ -15° (c=1.00), IR $\nu_{\text{max}}^{\text{CS}_2}$ cm⁻¹: 1763, 1748 (-OAc, C=O). Anal. Calcd. for C₂₃H₃₂O₅: C, 71.01; H, 8.30. Found: C, 71.02; H, 8.32.

Androst-5-ene-3 β ,16 α ,17 β -triol Triacetate (XIIb). a) From Androst-5-ene-3 β ,16 α ,17 β -triol (XIIa)—A solution of androst-5-ene-3 β ,16 α ,17 β -triol (XIIa, 80 mg.) in pyridine (8 ml.) and Ac₂O (8 ml.) was allowed to stand overnight at room temperature, and poured into H₂O. The product was extracted with Et₂O, and the Et₂O solution was washed with 10% H₂SO₄, 5% Na₂CO₃ and H₂O, and dried over Na₂SO₄.

After evaporation of the solvent, the residue was recrystallized from MeOH to give androst-5-ene-3 β ,16 α ,17 β -triol triacetate (XIIb). An analytical sample was obtained by further recrystallization from MeOH as colorless plates, m.p. 186~187°, $[\alpha]_D^{27} -91^\circ$ (c=1.05). IR: $\nu_{\max}^{CS_2}$ 1742 cm⁻¹ (-OAc). (reported, m.p. 184~185°, $[\alpha]_D^{28} -102^\circ$ (95% EtOH)). The IR spectrum of XIIb was the same as that for an authentic sample.

b) From 3 β ,16 α -Diacetoxyandrost-5-en-17-one (XIII)—A solution of 3 β ,16 α -diacetoxyandrost-5-en-17-one (XIII, 300 mg.) and NaBH₄ (150 mg.) in MeOH (20 ml.) was stirred at room temperature for 3 hr. After decomposition of excess NaBH₄ by one drop of AcOH, the solution was poured into H₂O and the product was extracted with Et₂O. The ethereal solution was washed with 10% H₂SO₄, 5% Na₂CO₃ and H₂O, and dried over Na₂SO₄. After evaporation of the solvent, the residue was dissolved in dry pyridine (10 ml.) and Ac₂O (10 ml.). The solution was stored at room temperature overnight, and poured into H₂O. The product was extracted with Et₂O and the Et₂O solution was washed with 10% H₂SO₄, 5% Na₂CO₃ and H₂O, and dried over Na₂SO₄. After evaporation of the solvent, the residue was recrystallized twice from MeOH to give pure XIIb as colorless plates, which was identical with the sample obtained above in all respects.

3 β ,16 β -Diacetoxy-5 α ,6 β -dichloroandrostan-17-one (XIV)—The enol acetate (XIII, 2.0 g.) was dissolved in AcOH (32 ml.) and Ac₂O (3.2 ml.), and Pb(OAc)₄ (2.4 g.) was added to the solution. The solution was allowed to stand at room temperature for 18 hr. The solvent was distilled *in vacuo* and the product was dissolved in Et₂O. The Et₂O solution was washed with 5% NaHCO₃, and H₂O, and dried over Na₂SO₄. After evaporation of the solvent, the residue was recrystallized from Me₂CO-hexane to give 3 β ,16 β -diacetoxy-5 α ,6 β -dichloroandrostan-17-one (XIV, 1.7 g.), m.p. 191~193°. An analytical sample was obtained by further recrystallization from the same solvent, m.p. 195~196°, $[\alpha]_D^{27} 0^\circ$ (c=1.02). IR $\nu_{\max}^{KBr}$ cm⁻¹: 1730, 1745 (C=O, -OAc). Anal. Calcd. for C₂₃H₃₂O₅Cl₂: C, 60.13; H, 7.02. Found: C, 59.95; H, 7.20.

3 β ,16 β -Diacetoxyandrost-5-en-17-one (XV). a) From 3 β ,16 β -Diacetoxy-6 β -dichloroandrostan-17-one (XIV)—Zn dust (500 mg.) was added in portions to a solution of 3 β ,16 β -diacetoxy-5 α ,6 β -dichloroandrostan-17-one (XIV, 500 mg.) in AcOH (20 ml.) and the resulting suspension was stirred at room temperature for 2 hr. After removal of Zn cake by filtration, the filtrate was poured into H₂O. The product was extracted with Et₂O, and the Et₂O solution was washed with 5% Na₂CO₃ and H₂O, and dried over Na₂SO₄. The solvent was evaporated to dryness and the residue was recrystallized from Me₂CO-hexane to give 3 β ,16 β -diacetoxyandrost-5-en-17-one (XV, 210 mg.), m.p. 168~170°. Further recrystallization from the same solvent gave an analytical sample as colorless plates, m.p. 172~173°, $[\alpha]_D^{27} +9^\circ$ (c=1.00), IR $\nu_{\max}^{KBr}$ cm⁻¹: 1730, 1745 (-OAc, C=O). Anal. Calcd. for C₂₃H₃₂O₅: C, 71.10; H, 8.30. Found: C, 71.19; H, 8.39.

b) From 3 β -Acetoxyandrost-5-en-17-one 17-Enol Acetate (XVI)—The enol acetate (XVI, 1 g.) was treated with Pb(OAc)₄ (1.2 g.), AcOH (16 ml.), and Ac₂O (1.6 ml.) as described above. Recrystallization from MeOH gave 3 β ,16 β -diacetoxyandrost-5-en-17-one (XV, 620 mg.), m.p. 164~168°, the IR spectrum of which was identical with the product obtained above.

Androst-5-ene-3 β ,16 β ,17 β -triol Triacetate (XVII)—3 β ,16 β -Diacetoxyandrost-5-en-17-one (XV, 100 mg.) was treated with NaBH₄ (50 mg.) and the reduction product was acetylated with Ac₂O in pyridine as described above. Recrystallization from Me₂CO-hexane gave androst-5-ene-3 β ,16 β ,17 β -triol triacetate (XVII, 50 mg.) as colorless plates, m.p. 212~214°, $[\alpha]_D^{27} -30^\circ$ (c=1.02), the IR spectrum of which was identical with that for an authentic sample.

3 β ,17 β -Dihydroxyandrost-5-en-16-one (XVIII). a) From 3 β ,16 β -Diacetoxyandrost-5-en-17-one (XV)—A solution of 3 β ,16 β -diacetoxyandrost-5-en-17-one (XV, 100 mg.) and KOH (100 mg.) in MeOH (10 ml.) was refluxed for 2 hr., and poured into H₂O. The product was extracted with CHCl₃-MeOH (50:4) and organic layer was washed with 10% HCl, 5% Na₂CO₃ and H₂O and dried over Na₂SO₄. After evaporation of the solvent, the residue was recrystallized from MeOH to give 3 β ,17 β -dihydroxyandrost-5-en-16-one (XVIII, 50 mg.) as colorless plates, m.p. 207~211°, the IR spectrum of which was identical with that for an authentic sample.

b) From 3 β ,16 α -Diacetoxyandrost-5-en-17-one (XIII)—3 β ,16 α -Diacetoxyandrost-5-en-17-one (XIII, 100 mg.) was treated as the same way described above and the same product (XVIII) was obtained.

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Summary

Some 16-oxygenated androst-5-ene steroids, which are all steroid metabolites, were prepared from 3 β -acetoxy-5 α ,6 β -dichloroandrostan-17-one.

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