March, 1985] © *1985 The Chemical Society of Japan* *Bull. Chem. Soc. Jpn., 58, 981—986 (1985)*

The Syntheses of the Corticoid Side Chain. III. A New Synthesis of 17α,21-Dihydroxypregna-1,4-diene-3,20-dione 17,21-Diacetate from Androsta-1,4-diene-3,17-dione

Issei Nitta,* Shinichiro Fujimori, Toshio Haruyama, Shinya Inoue,
and Hiroaki Ueno
Biosciences Laboratory, Research Center, Mitsubishi Chemical Industries Limited,
1000 Kamoshida-cho, Midori-ku, Yokohama, Kanagawa 227

(Received August 9, 1984)

An efficient synthesis of 17α,21-dihydroxypregna-1,4-diene-3,20-dione 17,21-diacetate (**10**) from androsta-1,4-diene-3,17-dione (**1**), a biodegradation product of cholesterol, is described, which involves the ethynylation of the 17-ketone, the epimerization of the 17α-ethynyl group and conversion of the ethynyl group to the 20-keto pregnane. Overall yield is relatively high (about 54%) and **10** will be a potential intermediate for prednisolone.

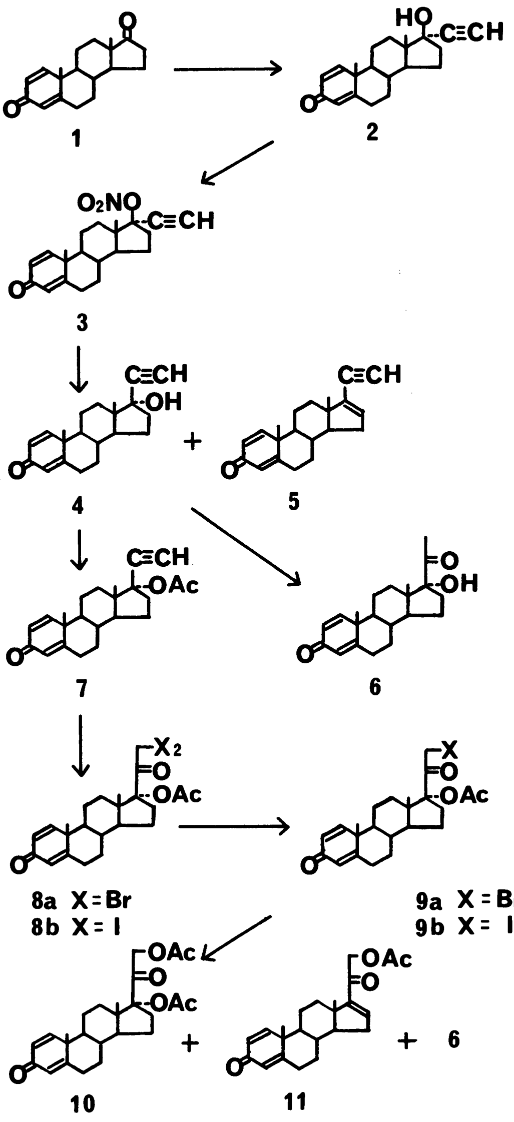
Corticosteroids are produced commercially from deoxycholic acid *via* a chemical process comprising many steps or from diosgenin and stigmasterol *via* a process involving a microbiological oxidation step at C-11.[1] Recent advances in the microbial degradation of cholesterol and abundant soya sterols allowed the production of androst-4-ene-3,17-dione and androsta-1,4-diene-3,17-dione,[2] from which various steroidal drugs such as estrone, testosterone, spironolactone, *etc.* have been produced. These 17-oxo steroids may be potentially useful starting materials for the synthesis of progestins and corticoids. Especially, androsta-1,4-diene-3,17-dione may be a useful starting material for prednisolone because the A ring is fully functionalized as 1,4-dien-3-one system and the 17-ketone provides a handle to elaborate the corticoid side chain.

Recently, efficient methods for partial synthesis of dihydroxyacetone side chain from 17-oxo steroids were published,[3] but most of them need protection of the 3-oxo group on ring A. Then they can not be simply applied for androsta-1,4-diene-3,17-dione because the protection of 3-carbonyl group of 1,4-diene-3,17-dione system is difficult. We present here an improved conversion of androsta-1,4-diene-3,17-dione into 17α, 21-dihydroxypregna-1,4-diene-3,20-dione 17,21-diacetate, an intermediate of artificial corticoids, especially prednisolone.

The methods employed in this conversion are summarized in Scheme 1.

The first step in the present conversion is the selective addition of a two-carbon fragment to the 17-keto function in androsta-1,4-diene-3,17-dione (**1**), *via* reaction with acetylene. Thus, by treating **1** with potassium acetylide in THF, 17α-ethynyl-17β-hydroxyandrosta-1,4-dien-3-one (**2**) was obtained in a quantitative yield, but this ethynyl compound **2** had the opposite configuration at C-17 to that required for the corticosteroids. Recently, a novel epimerization for converting 17α-ethynyl group into 17β-ethynyl group was reported,[4] which can be accomplished by the Ag$^+$-catalyzed hydrolysis of 17β-mesylate of 17α-ethynyl steroids.

However, the 17β-mesylate of **2** is extremely unstable and can be synthesized only in a very poor yield by limited procedure. Therefore, we examined various 17β-esters of **2** and selected 17α-ethynyl-17β-(nitro-



Scheme 1.

oxy)androsta-1,4-dien-3-one as the preferable one. Treatment of **2** with fuming nitric acid in acetic anhydride at −20 °C afforded 17*α*-ethynyl-17*β*-(nitrooxy) androsta-1,4-dien-3-one (**3**) in a high yield. The advantages of **3** were that the preparation was easy and the yield was very high.

Subsequently, **3** was stirred with $AgNO_3$ (0.2 mol equiv based on **3**) in a mixture of THF and distilled water for 72 h at 20 °C. The resulting reaction mixture was then poured into an aqueous NH_4Cl solution containing NaCN. The desired epimer **4** was obtained in an excellent yield (88.9%), together with a small amount of the enyne **5** (6.5%). Compound **4** could be easily purified from **5** by recrystallization from heptane–dichloromethane. The assignment of the configuration of **4** was conducted as follows. The desired epimer **4** was treated with mercury(II) chloride in benzene-water in the presence of aniline at 60 °C for 13 h to give 17*α*-hydroxypregna-1,4-diene-3,20-dione which was identified with the authentic sample prepared from 17*α*-hydroxypregn-4-ene-3,20-dione by treatment with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone. NMR signals of the 13-CH_3 proton in **4** showed an upfield shift and that of the ethynylic proton showed a downfield shift when compared with **2**. Similar shifts of the signals have already been observed for the epimeric 17-ethynyl-17-hydroxy steroids.[5] Under the conditions in the absence of silver nitrate, the nitrate **3** was recovered quantitatively. Besides silver nitrate, copper(I) chloride also catalyzed the hydrolysis of **3** to give **4** in about 63% yield and **5** in about 30% yield. Then, many additives were examined in order to increase the yield of **4** and it became apparent that the addition of thiourea improved it to about 74%. (Table 1.)

In order to elucidate the mechanism of these silver ion and copper(I) ion-catalyzed solvolyses, we examined the solvolysis of the epimeric nitrate, 17*β*-ethynyl-17*α*-(nitrooxy)androsta-1,4-dien-3-one in the presence of copper(I) chloride. Main product was 17*β*-ethynyl compound **4** and 17*α*-ethynyl compound **2** was less than 2%. (Table 2.) That is to say, the substitution reaction of epimer of **3** proceeded with retention of configuration compared with the reaction of **3** proceeded with inversion of configuration. Hofmeister *et al.* reported the formation of 17*β*-ethynyl-17*α*-formyloxyandrost-4-en-3-one (yield 15%) in Ag-catalyzed solvolysis of 17*α*-ethynyl-17*β*-(nitrooxy)androst-4-en-3-one in the mixture of formic acid and hexamethylphosphoramide and proposed the mechanism which involve the S_N2 type attack of nucleophile to the intermediate (I), in which the silver ion that makes a bridged ion structure between metal ion and acetylenic bond electrons, can interact with the oxygen atom of nitrooxy group and weaken the bond between C-17 and the leaving nitrooxy group. However, this mechanism can not be applied to our reaction because the reaction of epimer of **3** dose not proceed with inversion.

Hence, we are forced to suggest the formation of a carbonium ion stabilized by the silver or copper(I) ion (II) (S_N1 mechanism). That is , if we assume that the hydroxide ion or water attacks the carbonium ion (II) derived from both epimeric nitrates and that

Table 1. Effects of additives on the copper(I) chloride-catalyzed solvolysis of the nitrate **3**[a)]

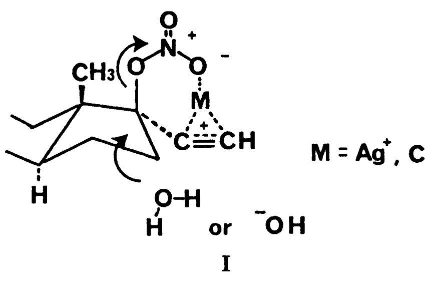
Additive	Reaction condition			Product (%)	
	Molar ratio		Solvent		
	Additive /CuCl	CuCl/**3**	H_2O vol%	**4**	**5**
None		0.7	15	63.2	28.2
Pyridine	1.2	0.7	15	26.2	65.8
Ethylene-diamine	1.2	0.7	15	58.5	35.5
Acetonitrile	1.0	0.6	30	61.4	24.6
Acetone-oxime	1.5	0.8	30	55.3	18.5
None		0.8	30	65.4	18.5
Thiourea	0.2	0.8	30	70.1	16.5
Thiourea	0.4	0.8	30	74.0	18.4
Thiourea	0.7	0.8	30	70.5	15.8

a) The reaction was carried out at 60 °C in THF-H_2O.

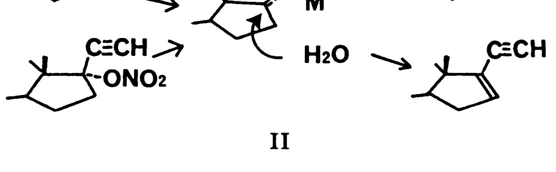
Table 2. Copper(I) chloride-catalyzed solvolysis of the nitrate **3** and its epimer[a)]

Substrate	Molar ratio CuCl/Substrate	Product (Yield/%)		
		2	**4**	**5**
3	0.7	1	63	28
Epimer of **3**[b)]	0.7	2	43	36

a) The reaction was carried out at 60 °C for 3 h in THF containing 15% water. In the absence of copper(I) chloride, the nitrate **3** was recovered quantitatively.
b) 17*β*-Ethynyl-17*α*-(nitrooxy)androsta-1,4-dien-3-one.



I



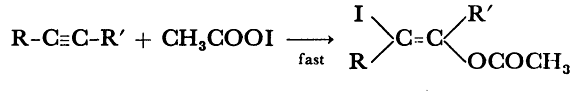
II

the attack occurs only from the least hindered side, opposite to the C-18 methyl group, formation of 17β-ethynyl compound **4** as the main product could be interpreted. As examples of metal-stabilized carbonium ions, cationic propargyl complexes ($(RC{\equiv}CCR_2)Co_2(CO)_6^+$) were reported.[6] But further study is required to elucidate a precise mechanism for these silver or copper(I) ion-catalyzed solvolysis.

The conversion of **4** into dihydroxyacetone side chain was accomplished as follows. Reaction of **4** with acetic anhydride in the presence of triethylamine and a catalytic amount of 4-(dimethylamino)pyridine in toluene gave the 17-acetate **7** in 96.7% yield. Treatment of 17-acetate **7** with *N*-bromoacetamide in buffered aqueous acetic acid furnished the dibromo ketone **8a**. This was converted to monobromo ketone **9a** in high yield (about 90% from **7**) on treatment with trimethyl phosphite in nitromethane at room temperature according to the "Perkow reaction."[7] According to conventional procedures for the acetoxylation of 21-bromo-17-hydroxy- or 21,21-dibromo-17-hydroxypregnane derivatives, the dibromide **8a** and monobromide **9a** were treated with potassium acetate in the presence or the absence of sodium iodide[8] in refluxing acetone, or with triethylammonium acetate in acetone.[9] But only unreacted **8a** or **9b** was recovered. Then, some dipolar aprotic solvents such as *N,N*-dimethylformamide, *N,N*-dimethylacetamide, dimethyl sulfoxide or acetonitrile were examined and it was found that on treatment with potassium acetate in *N,N*-dimethylformamide at around 60 °C the corresponding 21-acetate **10** was given from **9a** in moderate yield (50—70%). The major by-product was unsaturated product **11** and its amount increased when heating time or temperature was increased.

Next, the preparation of monoiodide **9b** was examined. Ogata and Urasaki reported the iodoacetoxylation of acetylenic compounds with a mixture of iodine and peracetic acid at 50 °C and suggested a mechanism involving slow formation of acetyl hypoiodite followed by its rapid addition to the triple bond to give α-iodo enol acetate[10] which may be converted to α-iodo ketone by hydrolysis.

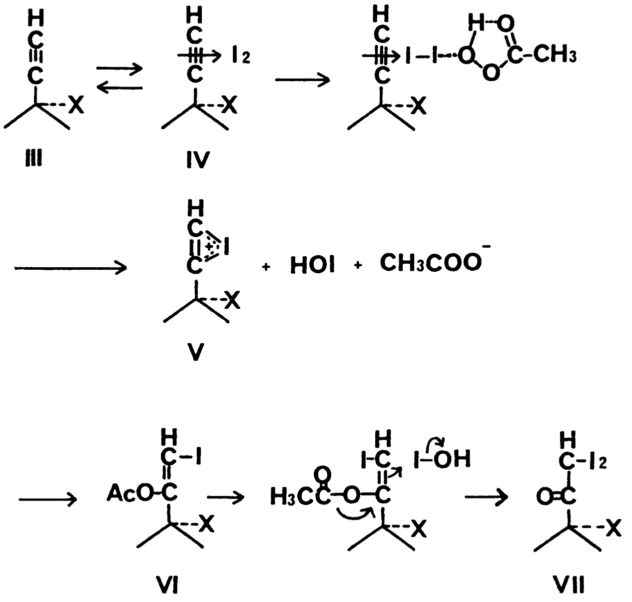
$$I_2 + CH_3CO_3H + CH_3CO_2H \xrightarrow[\text{slow}]{\text{rate-determining step}} 2CH_3COOI + H_2O$$



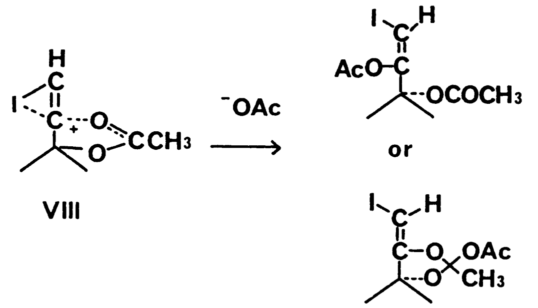
$$R\text{-}C{\equiv}C\text{-}R' + CH_3COOI \xrightarrow[\text{fast}]{} \overset{I}{\underset{R}{>}}C{=}C\overset{R'}{\underset{OCOCH_3}{<}}$$

17-Acetate **7** was treated with a mixture of iodine and peracetic acid in 10% aqueous acetic acid at room temperature (mole ratio; **7**:I_2:CH_3CO_3H=1:1:1). This reaction was completed in 2 h at room temperature. In contrast, the rate of formation of acetyl hypoiodite was very slow, the second-order rate constant for the consumption of iodine k_2 being *ca.* $2\times10^{-5}\,M^{-1}\,s^{-1}$ at 25 °C, and the consumption of iodine was less than 2% in the reaction of iodine and peracetic acid alone in the absence of 17-acetate **7** in 2 h at room temperature. The product was not enol acetate but diiodo ketone **8b** which was afforded in quantitative yield. When the molar ratio of iodine and peracetic acid to **7** was reduced to one-half, **8b** and unreacted **7** yielded at about 50% each, instead of the enol acetate. Here we could say that the reaction of **7** with a mixture of iodine and peracetic acid did not involve the formation of acetyl hypoiodite, because the rate of the whole reaction was faster than that of the rate-determining acetyl hypoiodite formation.

These observations lead to a hypothetical mechanism involving a rapid complex formation between the triple bond and iodine followed by a rate-determining attack of peracetic acid on the π-complex (IV), which was discussed as an alternative mechanism of iodoacetoxylation by Ogata and Urasaki.[10] The initially formed π-complex (IV) can be converted to cyclic iodonium ion (V) by peracetic acid. Carbonium ion (V) reacts with acetate ion to form enol acetate (VI) and is successively attacked by hypoiodous acid to give diiodo ketone (VII).



When the acetoxyl group at C-17 position in **7** was replaced with a hydroxyl group, the reaction was significantly slow and many products were formed. (When X=OAc, conversion after 1 h at room temperature 100%. When X=OH, conversion after 2 h was 20%.) These observations also indicate that the present reaction involves a carbonium ion as an intermediate. That is, the neighboring acetoxyl group can delocalize the positive charge of the carbonium ion center, stabilize the carbonium ion and accelerate the reaction involving the carbonium ion. The proposed carbonium ion is (VIII).



VIII

Diiodo ketone **8b** could be converted to monoiodo ketone **9b** on treatment with sodium acetate or triethylammonium acetate in refluxing acetone in 94.4% yield from **7**. Moreover, **8b** was treated with pyridine *p*-toluenesulfonate in refluxing acetone to give 17*α*-hydroxypregna-1,4-diene-3,20-dione 17-acetate (**6**) in about 90% yield.

Monoiodo ketone **9b** resisted acetoxylation to give a diacetate **10** and gave large amounts of **11** and **6** by conventional methods. The use of tetramethylammonium acetate afforded **10** in 79% yield under optimum conditions (in *N*-methylpyrrolidone at 21 °C for 7 h). Crude **10** of 80% purity was obtained in 60% overall yield from **1** and was subsequently recrystallized from acetone–water to give practically pure **10** (94% purity) in 91% yield. (54% yield from **1**).

Transformation of **10** into a typical corticoid, prednisolone, was followed by microbiological C-11 hydroxylation process. In such a process, **10** was a more suitable substrate than 17*α*,21-dihydroxypregna-1,4-diene-3,20-dione or 17*α*,21-dihydroxypregna-1,4-diene-3,20-dione 21-acetate, because introduction of the acetoxyl group into C-17 prevented the hydroxylation at C-14 and could bring a higher yield of prednisolone.

From the above, we concluded that the overall yield was relatively high and this sequence could be applied to other 17-keto steroids to provide useful pregnane steroids such as 17*α*,21-dihydroxypregn-4-en-3-one 17,21-diacetate, possible intermediate of hydrocortisone, or 17*α*-hydroxyprogesterone acetate.

Experimental

Melting points were determined with a Mettler FP61. Preparative TLC was accomplished with silica gel 60 F-254 plates (2 mm thick, E. Merck). HPLC was performed with a Shimadzu LC-2 liquid chromatograph instrument equipped with a Shimadzu Zorbax-ODS column (4.6 mmX25 cm) and a UV detector, and operated at a flow rate of 2 ml/min by using a solvent consisting of MeOH-H_2O (8:2).

Optical rotations were determined with a Jasco model DTP-4 digital polarimeter. NMR spectra were determined with a JEOL JMN-PS-100 spectrometer, with TMS as the internal standard. GLC analyses were performed on a Shimadzu GC-6A gas chromatograph equipped with a flame-ionization detector, using column packed with 1% Silicone DC-QF-1 on Gaschrom Q (3 mmX0.5 m; column temp 220 °C; carrier gas, N_2 60 ml/min; injector temp 250 °C).

17α-Ethynyl-17β-hydroxyandrosta-1,4-dien-3-one (*2*). In a three-necked flask, 95% potassium hydroxide (200 g), tetrahydrofuran (1000 ml) and ethanol (120 ml) were stirred at 50 °C for 1 h under a nitrogen atmosphere and then cooled to 3 °C. Into the mixture prepared as above, pure dry acetylene was passed at 3 °C for 2 h. A solution of androsta-1,4-diene-3,17-dione (**1**) (100 g) in 200 ml of dry tetrahydrofuran was added and stirred for 2 h. The mixture was acidified with 10% aqueous HCl solution, stirred under reflux for half an hour and diluted with water. The resulting precipitated product was collected by filtration, washed with water and dried to give 17*α*-ethynyl-17*β*-hydroxyandrosta-1,4-dien-3-one (**2**) (110.3 g, purity 92.9%, yield 96.6%), which was satisfactorily pure for the subsequent reaction. Recrystallization from acetone–hexane afforded the analytically pure sample, mp 218.9—219.1 °C; IR (KBr) cm^{-1}: 3330, 3250, 1660, 1615, 1605; NMR ($CDCl_3$) δ=0.92 (s, 3H), 1.23 (s, 3H), 2.54 (s, 1H), 6.05 (d, 1H), 6.20 (q, 1H), 7.03 (d, 1H).

Found: C, 81.48; H, 8.43%. Calcd for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44%.

17α-Ethynyl-17β-(nitrooxy)androsta-1,4-dien-3-one (*3*). To 17*α*-ethynyl-17*β*-hydroxyandrosta-1,4-dien-3-one (**2**) (8.00 g) was added acetic anhydride (64 ml) and the mixture was cooled to −20 °C. Thereafter, fuming nitric acid (6.4 ml) was added dropwise and stirred for 1 h at −20 °C. The reaction mixture was poured into 500 g of ice water and stirred. The resulting precipitated product was filtered off and then dissolved in ethyl acetate. The ethyl acetate solution was washed with water, dried and concentrated to give 17*α*-ethynyl-17*β*-(nitrooxy)androsta-1,4-dien-3-one (8.9 g, purity 98.1%, yield 96.1%). The product could be used as the starting material in the subsequent hydrolysis step without further purification. Recrystallization from benzene afforded the analytically pure sample, mp 137—139 °C; NMR ($CDCl_3$) δ=1.02 (s, 3H), 1.26 (s, 3H), 2.72 (s, 1H), 6.03 (s, 1H), 6.18 (q, 1H), 7.00 (d, 1H); IR (KBr) 1660, 1625, 1295 cm^{-1}; MS *m*/*z* 355 (M^+).

Found: C, 71.23; H, 7.06; N, 4.03%. Calcd for $C_{21}H_{25}O_4N$: C, 70.96; H, 7.09; 3.94%.

17β-Ethynyl-17α-hydroxyandrosta-1,4-dien-3-one (*4*). (*A*) *Silver Nitrate-catalyzed Hydrolysis*. 17*α*-Ethynyl-17*β*-(nitrooxy)androsta-1,4-dien-3-one (**3**) (2.50 g) was dissolved in tetrahydrofuran (17 ml). Subsequently distilled water (3.0 ml) and silver nitrate (9.55 g) were added and the mixture was stirred for 24 h at 25 °C. The reaction mixture was poured into saturated ammonium chloride solution (70 ml) containing sodium cyanide (0.7 g). After stirring for 15 min, the reaction mixture was extracted with dichloromethane and the separated organic layer was washed with water and dried to give 2.40 g of white crystals. The crude crystals thus obtained were recrystallized from a mixture of tetrahydrofuran (20 ml) and hexane (140 ml) to give 17*β*-ethynyl-17*α*-hydroxyandrosta-1,4-dien-3-one (**4**) (1.10 g). Recrystallization from ethyl acetate twice afforded the analytically pure sample, mp 218—219 °C; $[\alpha]_D^{24}$ +90.9° (c: 1.02, tetrahydrofuran); IR (KBr) 1660, 1620 cm^{-1}; NMR ($CDCl_3$) δ=0.96 (s, 3H), 1.26 (s, 3H), 2.52 (s, 1H), 6.09 (s, 1H), 6.25 (q, 1H), 7.08 (d, 1H); MS *m*/*z* 310 (M^+).

Found: C, 81.79; H, 8.33%. Calcd for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44%.

To 17*α*-ethynyl-17*β*-hydroxyandrosta-1,4-dien-3-one (**2**)

(100.2 g, purity 94.1%) was added acetic anhydride (250 ml) and cooled to −20 °C. Fuming nitric acid (55 ml) was added and stirred for 1 h at −20 °C. The reaction mixture was poured into ice water and the resulting precipitated product was filtered off. The wet product (153.5 g) was dissolved in tetrahydrofuran (3000 ml). Distilled water (2960 ml) and silver nitrate (11.6 g) were added and stirred for 72 h at room temperature. After tetrahydrofuran was distilled off, 150 ml of 60% nitric acid was added, and the mixture was extracted with dichloromethane, washed with water and concentrated to give crude 17β-ethynyl-17α-hydroxyandrosta-1,4-dien-3-one (100.7 g, purity 81.2%, yield 86.7% from **2**). The crude crystals were recrystallized from a mixture of dichloromethane and heptane to give 17β-ethynyl-17α-hydroxyandrosta-1,4-dien-3-one (84.2 g, purity 92.0%, yield 95.0%). *(B) Copper(I) Chloride-catalyzed Hydrolysis.* To a mixture prepared by adding tetrahydrofuran (6.2 ml) and water (15.8 ml) to 17α-ethynyl-17β-(nitrooxy)androsta-1,4-dien-3-one (**3**) (2.50 g) was added copper(I) chloride (0.2 g), and the resulting mixture was stirred for 4 h at 65 °C in a nitrogen atmosphere. Benzene and saturated saline were added to the reaction mixture to extract the product into benzene. The separated benzene layer was further washed three times with saturated saline, dried over anhydrous sodium sulfate and concentrated to get crystals. HPLC analysis of the crystals showed that 17β-ethynyl-17α-hydroxyandrosta-1,4-dien-3-one (**4**) and 17-ethynylandrosta-1,4,16-trien-3-one (**5**) were formed in yields of 63 mole% and 32 mole%, respectively.

17α-Hydroxypregna-1,4-diene-3,20-dione (6). To 17β-ethynyl-17α-hydroxyandrosta-1,4-dien-3-one (**4**) (0.680 g) were added benzene (40 ml), distilled water (8 ml), mercury(II) chloride (1.12 g), and aniline (0.2 ml). The mixture was stirred at 60 °C for 13 h. The insoluble matters were filtered off and they were thoroughly washed with chloroform. The chloroform washings were combined with the filtrate (reaction mixture) and the aqueous layer was separated. The organic layer was washed successively with 5% hydrochloric acid and saturated sodium hydrogencarbonate solution and then dried over sodium sulfate. The solvent was then distilled off to give 17α-hydroxypregna-1,4-diene-3,20-dione (**6**) (0.616 g). Recrystallization from a mixture of tetrahydrofuran (40 ml) and octane (10 ml) gave analytically pure 17α-hydroxypregna-1,4-diene-3,20-dione (**6**) (0.499 g). High speed liquid chromatogram, thin layer chromatogram and infrared absorption, NMR and mass spectra of the product were all in agreement with those of an authentic sample, mp 258.0—258.7 °C; NMR ($CDCl_3$) δ=0.8 (s, 3H), 1.26 (s, 3H), 2.28 (s, 3H), 2.96 (s, 1H), 6.08 (s, 1H), 6.22 (d, 1H, J=10 Hz), 7.06 (d, 1H, J=10 Hz).

Found: C, 76.95; H, 8.48%. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59%.

17β-Ethynyl-17α-hydroxyandrosta-1,4-dien-3-one 17-Acetate (7). To 17β-ethynyl-17α-hydroxyandrosta-1,4-dien-3-one (**4**) (2.00 g) were added acetic anhydride (2.0 ml), triethylamine (2.0 ml), 4-(dimethylamino)pyridine (0.114 g) and toluene (5.0 ml) and the mixture was heated at 80—90 °C for 11 h. Upon cooling, the reaction product was extracted into dichloromethane. The organic layer was washed successively with 5% hydrochloric acid and 5% sodium hydrogencarbonate solution and the separated organic layer was dried over anhydrous sodium sulfate and concentrated. The liquid chromatograph analysis of the extract showed that 17β-ethynyl-17α-hydroxyandrosta-1,4-dien-3-one 17-acetate was formed in 96.7% yield. The concentrate was passed through a column filled with 250 g of alumina and eluted with 500 ml of a mixture of benzene and ethyl acetate (9:1) to give 2.3 g of crystals. Recrystallization of the crystals from octane–tetrahydrofuran (20:1), heptane–ethanol (5:1) and octane–tetrahydrofuran (30:7) gave 17β-ethynyl-17α-hydroxyandrosta-1,4-dien-3-one 17-acetate (**7**), mp 171.8—172.6 °C; NMR ($CDCl_3$) δ=1.00 (s, 3H), 1.26 (s, 3H), 2.02 (s, 3H), 2.56 (s, 1H), 6.04 (d, 1H), 6.15 (q, 1H), 6.98 (d, 1H).

Found: C, 79.02; H, 8.01%. Calcd for $C_{23}H_{28}O_3$: C, 78.38; H, 8.01%.

21-Bromo-17α-hydroxypregna-1,4-diene-3,20-dione 17-Acetate (9a). A mixture of 17β-ethynyl-17α-hydroxyandrosta-1,4-dien-3-one 17-acetate (**7**) (0.786 g), *N*-bromoacetamide (0.644 g), anhydrous sodium acetate (0.735 g), water (1.3 ml) and acetic acid (13 ml) was left at 0 °C for 1 h, then poured into ice–water and the resulting precipitate was collected by filtration, washed with water and dried to give crude 21,21-dibromo-17α-hydroxypregna-1,4-diene-3,20-dione 17-acetate (**8a**) (1.158 g). To this crude dibromide **8a** (0.134 g) in nitromethane (2.5 ml), trimethyl phosphite (0.2 ml) was added and stirred at room temp for 50 min. The reaction mixture was diluted with ether and washed with water. The separated organic layer was dried over anhydrous sodium sulfate and concentrated to give crude 21-bromo-17α-hydroxypregna-1,4-diene-3,20-dione (**9a**) (0.112 g). Recrystallization from octane–tetrahydrofuran gave an analytically pure sample (0.083 g). MS m/z 448, 450 (M^+).

Found: C, 61.59; H, 6.61; Br, 17.77%. Calcd for $C_{23}H_{29}O_4Br$; C, 61.47; H, 6.50; Br, 17.78%.

17α-Hydroxy-21-iodopregna-1,4-diene-3,20-dione 17-Acetate (9b). To a mixture prepared by adding iodine (0.408 g), acetic acid (4.5 ml), and water (0.5 ml) to 17β-ethynyl-17α-hydroxyandrosta-1,4-dien-3-one 17-acetate (**7**) (0.571 g), a mixture of 40% peracetic acid (0.26 ml), acetic acid (16 ml) and water (2 ml) was added dropwise and stirred at room temp for 2 h. The reaction mixture was poured into water (150 ml) and the resulting precipitate was collected with filtration, washed with water and dissolved in dichloromethane. The solution was washed successively with 7% aqueous KI solution, 10% aqueous sodium thiosulfate solution and water, dried over anhydrous sodium sulfate and concentrated to give crude 21,21-diiodo-17α-hydroxypregna-1,4-diene-3,20-dione 17-acetate (**8b**) (0.961 g), NMR ($CDCl_3$) δ=0.89 (s, 3H), 1.24 (s, 3H), 2.09 (s, 3H), 5.52 (s, 1H), 6.11 (d, 1H), 6.26 (q, 1H), 7.10 (d, 1H); MS m/z 496 (M^+).

To this crude iodide **8b** (0.200 g), triethylamine (0.83 ml), acetic acid (0.53 ml), and acetone (5 ml) were added and stirred under reflux for 1 h. The reaction mixture was poured into water (100 ml) and the resulting precipitate was collected by filtration and dried to give 17α-hydroxy-21-iodopregna-1,4-diene-3,20-dione 17-acetate (**9b**) (0.142 g). Without further purification, crude iodide was used for the next step. Recrystallization from acetone–heptane afforded the analytically pure sample, mp 156.9—157.2 °C, NMR ($CDCl_3$) δ=0.78 (s, 3H), 1.26 (s, 3H), 2.12 (s, 3H), 3.92 (d, 2H), 6.10 (d, 1H), 6.26 (q, 1H), 7.09 (d, 1H); MS m/z 496 (M^+).

Found: C, 55.74; H, 5.92; I, 25.45%. Calcd for $C_{23}H_{29}O_4I$: C, 55.65; H, 5.89; I, 25.57%.

17α,21-Dihydroxypregna-1,4-diene-3,20-dione 17,21-Diacetate (10). To 17α-hydroxy-21-iodopregna-1,4-diene-3,20-dione 17-acetate (**9b**) (2.01 g), *N*-methylpyrrolidone (6.0 ml), and tetramethylammonium acetate (0.80 g) were added and stirred at 21 °C for 7 h. Thereafter, 60 ml of water was slowly dropped while agitating. The resulting crystal was filtered off, washed with water, and dried to obtain 1.64 g of crystals. Recrystallization from ethanol (16 ml) yielded 17α,21-dihydroxypregna-1,4-diene-3,20-dione 17,21-diacetate (**10**), mp 207.7—208.0 °C; NMR ($CDCl_3$) δ=0.80 (s, 3H), 1.26 (s, 3H), 2.08 (s, 3H), 2.16 (s, 1H), 4.74 (q, 2H), 6.04 (broad, 1H), 6.18 (q, 1H), 7.02 (d, 1H), MS m/z 428 (M^+).

Found: C, 70.14; H, 7.56%. Calcd for $C_{25}H_{32}O_6$: C, 70.07; H, 7.53%.

References

1) a) A. Applezweig, "Steroid Drugs," McGraw-Hill, New York (1962), pp 41—86; b) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York (1959), Chapter 19.

2) a) M. Nagasawa, H. Hashiba, N. Watanabe, M. Bae, G. Tamura, and K. Arima, *Agric. Biol. Chem.*, **34**, 801 (1970); b) Y. Imada and I. Nitta, *Hakko To Kogyo*, **38**, 1117 (1980).

3) a) D. H. R. Barton, W. B. Motherwell, and S. Z. Zard, *Bull. Soc. Chim. Fr.*, **1983**, 61; b) A. R. Daniewski and W. Wojciechowska, *J. Org. Chem.*, **47**, 2993 (1982); c) D. H. R. Barton, W. B. Motherwell, and S. Z. Zard, *J. Chem. Soc., Chem. Commun.*, **1981**, 774; d) R. M. Moriarty, L. S. John, and P. C. Du, *J. Chem. Soc., Chem. Commun.*, **1981**, 641; e) G. Neef, U. Eder, A. Seeger, and R. Wiechert, *Chem. Ber.*, **113**, 1184 (1980); f) V. V. Rheenen and K. P. Shephard, *J. Org. Chem.*, **44**. 1582 (1979); g) R. W. Freerksen, M. L. Raggio, C. A. Thoms, and D. S. Watt, *ibid.*, **44**, 702 (1979); h) H. Hofmeister, K. Annen, H. Laurent, and R. Wiechert, *Chem. Ber.*, **111**, 3086 (1978); i) M. Biollaz, W. Haefliger, E. Velarde, P. Crabbe, and J. H. Fried, *J. Chem. Soc., Chem. Commun.*, **1971**, 1322.

4) H. Westmijze, H. Kleijn, P. Vermeer, and L. A. Van Dijck, *Tetrahedron Lett.*, **1980**, 2665.

5) L. A. Van Dijck, B. J. Lankwerden, and J. G. C. M. Vermeer, *Recl. Trav. Chim. Pays-Bas*, **96**, 200 (1977).

6) K. M. Nicholas and R. Pettit, *Tetrahedron Lett.*, **1971**, 3475; H. D. Hodes and K. M. Nicholas, *ibid.*, **1978**, 4349.

7) F. W. Lichtenthaler, *Chem. Rev.*, **61**, 607 (1961).

8) F. A. Cuther, Jr., L. Mandell, J. F. Fisher, D. Shew, and J. M. Chermerda, *J. Org. Chem,*, **24**, 1629 (1959).

9) W. T. Moreland, Jr., *J. Org. Chem.*, **21** 820 (1956).

10) Y. Ogata and I. Urasaki, *J. Org. Chem.*, **36**, 2164 (1971).