The Syntheses of the Corticoid Side Chain. I. An Improved Method for the Preparation of 17α-Hydroxyprogesterone from Androst-4-ene-3,17-dione

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The 17β-cyano-17α-hydroxyandrost-4-en-3-one can be prepared from androst-4-ene-3,17-dione in an excellent yield. This derivative can be converted into 17α-hydroxyprogesterone, an intermediate of corticosteroids.

Since the microbial degradation of the side chain of cholesterol or sitosterol had been developed,[1] the transformation of androstan-17-one derivatives into corticoids became very important and recently, several efficient methods for partial synthesis of corticoid side chain from 17-oxo steroids have been published.[2]

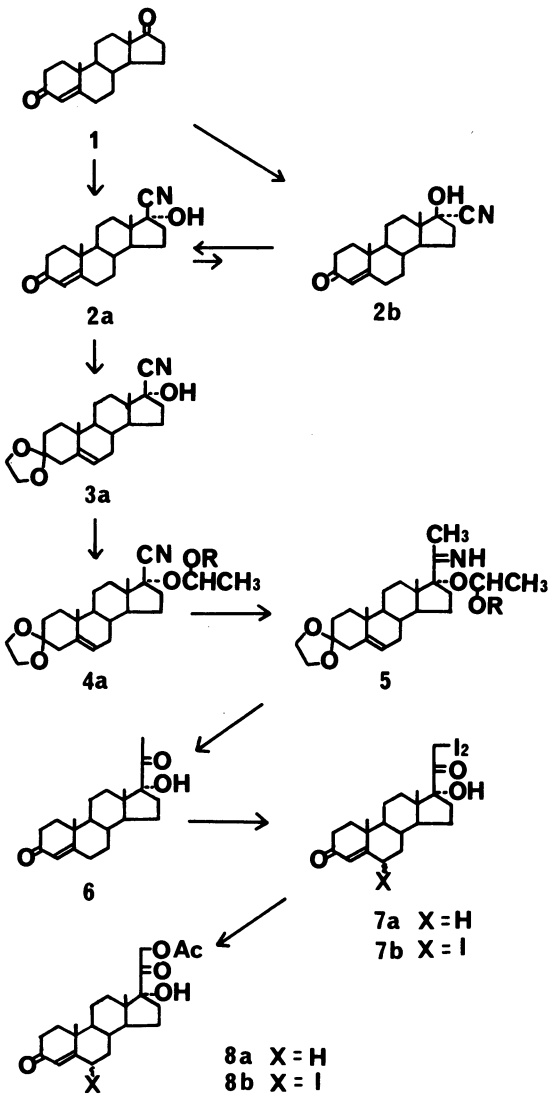
We present here an improved method for converting androst-4-ene-3,17-dione (**1**) into 17α-hydroxyprogesterone (**6**), an intermediate of corticoids, featuring a stereoselective one-step formation of 17β-cyano-17α-hydroxy group at the C-17 position of **1**.[3]

Results and Discussion

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

The first step is the regio- and stereoselective addition of hydrogen cyanide to 17-keto function of **1**. According to the conventional procedure, the dione **1** was treated with alcoholic hydrogen cyanide.[4a] Many products were formed and it was expected that 17α-cyano and 17β-cyano compounds were formed in addition to 3,17-bis(cyanohydrin)s. The use of acetone cyanohydrin (in an exchange reaction in acetone cyanohydrin in the presence of a small amount of amine) afforded 17-monocyanohydrin **2b** quantitatively. In order to determine the configuration of the cyano group of **2b**, 3,3-ethylene acetal 17-silyl ether of **2b** was treated with excess methylmagnesium chloride at 70 °C, followed by deprotection of the 3-acetal. The isolated product was 17α-acetyl-17β-hydroxyandrost-4-en-3-one. This result indicated that the configuration of the cyano group at C-17 was α-configuration, which meant that an undesirable epimer was formed.

On the other hand, when acetic acid (5 equiv of **1**) was added to a suspension of **1** and KCN (10 equiv of **1**) in methanol at 25 °C, the poorly soluble isomer **2a** crystallized out. The HPLC analysis of the crystal showed that **2a**, having a retention time of 9.1 min, was formed as almost the sole product (the retention time of **2b** is 8.4 min). By means of NMR and IR, **2a** was identified as 17β-cyano-17α-hydroxyandrost-4-en-3-one. This process gives the required cyanohydrin **2a** in pure form yielding about 95%. This may be attributed to the fact that the 17α-cyanohydrin **2b** which was formed by the cyanide anion attack on C-17 from the least hindered side was converted to **2a** under equilibrium conditions (in the presence of KCN) and the poorly soluble **2a** crystallized out preferentially. We have also found that this procedure could be applica-



Scheme 1.

ble to the preparation of 17β-cyanohydrins of various androstanes. (see Experimental)

For the following step of the synthesis, it is necessary to protect the carbonyl and hydroxyl functions of **2a**. Treatment of **2a** in ethylene glycol with trimethyl orthoformate in the presence of TsOH led to the expected acetal **3a**. Without further purification, **3a** was treated with butyl vinyl ether in THF containing a small amount of TsOH to give **4a**. Without isolation, **4a** was treated with a 1 M† solution of methyllithium (1.2 equiv of **2a**). Aqueous acetic acid was added and the solution was heated to 110 °C for 1 h. 17α-hydroxyprogesterone, a versatile intermediate for the synthesis of corticoids, was obtained from **2a** with an overall yield of about 70%.

The 21-acetoxy introduction into **6** was accomplished by Stork's iodination procedure.[4b] Iodination of **6** in THF–methanol with excess iodine in the presence of calcium oxide gave the 21,21-diiodosteroid **7a**, which was converted directly to **8a** by treating it with potassium acetate in acetone. The HPLC analysis of the product showed that 17α,21-dihydroxypregn-4-ene-3,20-dione 21-acetate (about 60%) and a by-product (about 35%) were formed. The by-product was isolated by TLC on silica gel developed with ethyl acetate–benzene (1:2). From NMR spectra, it was assumed to be 17α,21-dihydroxy-6-iodopregn-4-ene-3,20-dione 21-acetate (**8b**), and **8a** was recovered from **8b** by treating it with zinc powder in acetic acid in a satisfactory yield.

Transformation of **8a** into hydrocortisone, a typical corticoid, was followed by microbilological process.

Experimental

Melting points were determined with a Mettler FP 61. 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 mm×25 cm) and a UV detector, and operated at flow rate of 2 ml min^{-1} by using a solvent consisting of MeOH–H_2O (8:2). Optical rotations were determined with a Jasco model DIP-digital polarimeter. NMR spectra were determined with a JEOL JNM-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 a column packed with 1% Silicone DC-QF-1 on Gaschrom Q (3 mm×0.5 m; column temp, 220 °C; carrier gas, N_2 60 ml/min; injector temp., 250 °C).

Materials. Androst-4-ene-3,17-dione (**1**) was obtained from Sigma. Androsta-4,9(11)-diene-3,17-dione was prepared according to the procedure in the literature[2f] from 9α-hydroxyandrost-4-ene-3,17-dione.

17β-Cyano-17α-hydroxyandrost-4-en-3-one (2a). Acetic acid (17.6 ml, 0.293 mol) was added over a period of 20 min at 25 °C to a stirred mixture of androst-4-ene-3,17-dione (**1**) (52.3 g, 0.182 mol) and potassium cyanide (50.0 g, 0.769 mol) in methanol (400 ml). The mixture was stirred at 25 °C. The starting material was completely dissolved within 1 h and product began to crystallize after reaction for 2 h. The mixture was kept overnight at room temp and then acetic acid (30 ml) was added. After dilution with water, the precipitated product was collected by filtration, washed with water and dried to give crude **2a** (57.5 g). The HPLC analysis indicated that the purity of **2a** (t_r: 9.1 min) was 95%, and 2% of **2b** and 2.5% of **1** were contained. Recrystallization from ethanol afforded the analytically pure sample: mp 169—172 °C dec.; $[\alpha]_D^{28}$ +120.3° (*c* 0.66, dioxane); IR (KBr) 3250 (OH), 2220 (C≡N) and 1640 cm^{-1} (C=O); NMR ($CDCl_3$) δ=0.98 (3H, s, 13-CH_3).

Found: C, 76.59; H, 8.72; N, 4.48%. Calcd for $C_{20}H_{27}O_2N$: C, 76.64; H, 8.68, N, 4.46%.

In a similar procedure, 17β-cyano-17α-hydroxyandrosta-4,9(11)-dien-3-one (**9a**), 3,3-ethylenedioxy-17β-cyanoandrosta-5,9(11)-dien-17α-ol (**10a**) were prepared.

(**9a**): Mp 199—201 °C dec.; $[\alpha]_D^{28}$ +95.6° (*c* 0.83, dioxane); NMR ($CDCl_3$) δ=0.95 (3H, s, 13-CH_3). Found: C, 77.17; H, 8.01; N, 4.45%. Calcd for $C_{20}H_{25}O_2N$: C, 77.13; H. 8.09: N, 4.50%.

(**10a**): Mp 202—205 °C; $[\alpha]_D^{28}$ +17.8° (*c* 0.53, dioxane); NMR ($CDCl_3$) δ=0.91 (3H, s, 13-CH_3). Found: C, 74.52; H, 8.28; N, 3.72%. Calcd for $C_{22}H_{29}O_3N$: C, 74.33; H, 8.23; N, 3.94%.

17α-Cyano-17β-hydroxyandrost-4-en-3-one (2b). Androst-4-ene-3,17-dione (**1**) (20.0 g) was dissolved by gentle warming in 30 ml of acetone cyanohydrin. Stirring was continued for 8 h at room temp, but the crystallization did not begin. Two drops of DBU was added. After five minutes crystallization began and was completed within 1 h at room temp. The resulting precipitated product was collected by filtration, washed with ether and dried to give 17-cyanohydrin **2** (23.0 g). The HPLC analysis showed that 17α-cyano-17β-hydroxyandrost-4-en-3-one (**2b**) (t_R: 8.4 min) formed as an almost sole product and no 17β-cyano-17α-hydroxyandrost-4-en-3-one (**2a**) (t_R: 9.1 min) was detected. Recrystallization from ethanol afforded the analytically pure sample, mp 153—155 °C (pre-melting point), 171—172 °C dec.; $[\alpha]_D^{28}$ +45.5° (*c* 0.72, dioxane); IR (KBr) 3250 (OH), 2230 (C≡N), and 1640 cm^{-1} (C=O); NMR ($CDCl_3$) δ=0.91 (3H, s, 13-CH_3).

Found: C, 76.87; H, 8.52; N, 4.43%. Calcd for $C_{20}H_{27}O_2N$: C, 76.64; H, 8.68: N, 4.46%.

According to the previous procedure,[5] 3,3-ethylenedioxy-17α-cyanoandrost-5-en-17β-ol (**3b**), 17α-cyano-17β-hydroxyandrosta-4,9(11)-dien-3-one (**9b**), 3,3-ethylenedioxy-17α-cyanoandrosta-5,9(11)-dien-17β-ol (**10b**) were also prepared.

(**3b**): Mp 194—195 °C dec.; $[\alpha]_D^{28}$ −71.4° (*c* 0.95, dioxane); NMR ($CDCl_3$) δ=0.83 (3H, s, 13-CH_3). Found: C, 73.72; H, 8.63; N, 3.82%. Calcd for $C_{22}H_{31}O_3N$: C, 73.91; H, 8.74; N, 3.92%.

(**9b**): Mp 201—204 °C dec.; $[\alpha]_D^{28}$ +20.8° (*c* 0.76, dioxane); NMR ($CDCl_3$) δ=0.88 (3H, s, 13-CH_3). Found: C, 77.07; H, 7.99; N, 4.31%. Calcd for $C_{20}H_{25}O_2N$: C, 77.13; H, 8.09; N, 4.50%.

(**10b**): Mp 185—186 °C; $[\alpha]_D^{28}$ −44.7° (*c* 0.49, dioxane); NMR ($CDCl_3$) δ=0.85 (3H, s, 13-CH_3). Found: C, 74.50; H,

† 1 M=1 mol dm^{-3}.

8.14; N, 3.95%. Calcd for $C_{22}H_{29}O_3N$: C, 74.33; H, 8.23; N, 3.94%.

*3,3-Ethylenedioxy-17β-cyanoandrost-5-en-17α-ol (**3a**).* *p*-Toluenesulfonic acid (1.5 g) was added to a suspension of **2a** (57.5 g) in trimethyl orthoformate (50 ml) and ethylene glycol (350 ml) and the mixture was stirred at 40 °C for 6 h. The solution was poured into water containing pyridine (1.5 ml). The resulting precipitated product was collected by filtration, washed with water and dried to give 3,3-ethylenedioxy-17β-cyanoandrost-5-en-17α-ol (**3a**) containing about 10% of 3,3-ethylenedioxy-17β-cyanoandrost-4-en-17α-ol (60.3 g). Without further purification, crude **3a** was used in the next step. Recrystallization from methanol afforded the analytically pure sample; mp 227—229 °C dec.; $[\alpha]_D^{28}$ −15.3 °C (*c* 1.00, dioxane); IR (KBr) 3450 (OH) and 2240 cm^{-1} (C≡N); NMR ($CDCl_3$) δ=0.94 (s, 3H, 13-CH_3).

Found: C, 73.90; H, 8.51; N, 3.88%. Calcd. for $C_{22}H_{31}O_3N$: C, 73.91; H, 8.74; N, 3.92%.

*17α-Hydroxyprogesterone (**6**).* To the crude **3a** (2.00 g), butyl vinyl ether (1.27 ml) and *p*-toluenesulfonic acid soln. (0.2% in THF, 3.0 ml) were added. After stirring for 20 min at room temp, methyllithium (1 M solution in ether, 10 ml) was added and stirred for 2 h at room temp. Acetic acid (8.0 ml) and water (4.0 ml) were added and heated at 110 °C for 1 h. After dilution with water containing sodium carbonate, the precipitated product was collected by filtration, washed with water and dried to give 17α-hydroxyprogesterone (**6**) (1.77 g, purity 72% which was determined by HPLC analysis, yield 69%). Recrystallization from ethyl acetate afforded the analytically pure sample. The NMR and IR spectrum were identical to that of an authentic specimen of 17α-hydroxyprogesterone and the melting point was undepressed on admixture with authentic specimen.

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