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Added in Proof (March 15, 1976) Recently several reports appeared, describing LAH-$TiCl_4$ as a characteristic reducing reagent: P. W Chun and S. T. Wilson, *Tetrahedron Letters*, **1976**, 15; Y. Watanabe, M. Shono and T. Mukaiyama, *Chem. Lett.*, **1975**, 871; T. Mukaiyama, M. Hayashi and K. Narasaka, *ibid.*, **1973**, 291.

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Chemical Modifications of Androsta-1,4-diene-3,17-dione. III.[1] The Synthesis of (20*R*)-17α,20,21-Trihydroxypregna-1,4-dien-3-one and Its Derivatives

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The partial synthesis of (20*R*)-17α,20,21-trihydroxypregna-1,4-dien-3-one (its D-ring moiety is identical with that of cortisone) from androsta-1,4-diene-3,17-dione is described. This conforms a model experiment for the synthesis of adrenal steroid compounds from the latter compound without affecting its A-ring moiety.

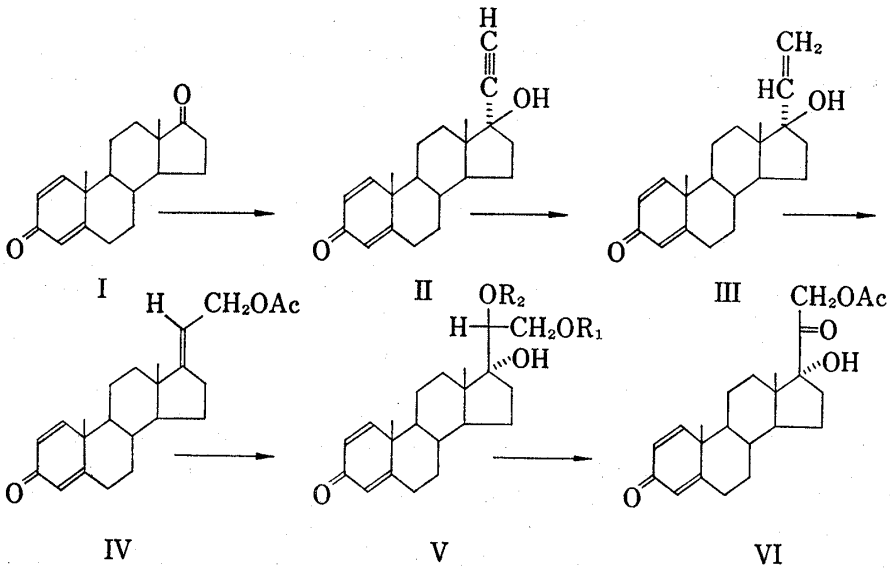
The conversion of androstanes to pregnanes has been one of the most thoroughly examine projects for synthetic chemists in the steroid field.[3] In order to show the wide synthetic applicability of androsta-1,4-diene-3,17-dione (I) readily obtainable from cholesterol by microbiological oxidation using *Arthrobactor Simplex*, we have converted this dione to pregnane-type steroids having the dihydroxyacetone side chain characteristic of cortisone and dihydrocortisone.

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

In the present scheme, we have attempted to preserve the 1,4-dien-3-one function in the starting material throughout, because it could serve for further chemical modifications (especially at A and B rings) of both the final and the intermediate compound obtainable in the conversion.[4]

The first step in the present conversion is the addition of a two carbon fragment selectively to the 17-keto function in I, *via* the reaction with acetylene. Thus, by treatment of I with

1) Part II: H. Sakamoto, A. Sugimoto, C. Kaneko, T. Suda, and S. Sasaki, *Chem. Pharm. Bull.* (Tokyo), **23**, 1733, (1975).
2) Location: *9-500-1, Nagareyama-shi, 270-01, Chiba.*
3) The fundamental methods for the conversion of androstanes to pregnanes were summarized recently by E.P. Oliveto, "Organic Reactions in Steroid Chemistry," edited by J. Fried and J.A. Edwards, Vol. 2, van Nostrand, Reinhold Co., 1972, pp. 129—140.
4) The successful modification of I at both A and B rings for the synthesis of androcalciferol derivatives having a hydroxyl group at either 1α- or 2β-positions was reported in the part I of this series; H. Sakamoto, A. Sugimoto, and C. Kaneko, *Chem. Pharm. Bull.* (Tokyo), **22**, 2903 (1974).



a : $R_1=R_2=H$
b : $R_2=Ac$, $R_1=H$
c : $R_1=R_2=Ac$

Chart 1

potassium acetylide in liquid ammonia, 17α-ethynyl-17β-hydroxyandrosta-1,4-dien-3-one (II) was obtained in a satisfactory yield. The ethynyl compound (II) was then hydrogenated to the vinyl compound (III) in presence of 10% palladium charcoal under an atmospheric pressure.

Treatment of III with tribromophosphate in chloroform in presence of pyridine at room temperature, followed by treatment with potassium acetate in acetone afforded 21-hydroxypregna-1,4,17(20)-trien-3-one 21-acetate (IV) again in a satisfactory yield. Based on a stereochemical consideration and by analogy from the related reactions,[3] the side chain configuration of IV was concluded as E (carbon atoms at 21 and 13 are *trans*). The oxidation of this vinyl compound (IV) with osmium tetraoxide resulted in the formation of the (20*R*)-17α,20-diol (Va) in very high yield. The stereochemistry at C_{20} of Va was assigned to be R, since the attack of the reagent to IV should occur from the back-side of the 18-methyl group.[5]

The attempted crystallization of Va was unsuccessful, though its purity was assured either thin-layer chromatography (TLC) or gass-liquid chromatography (GLC). Its diacetate, obtained by standing in excess of acetic anhydride and pyridine, crystallized as a colorless prism.

These five steps thus accomplished the synthesis of (20*R*)-17α,20,21-trihydroxypregna-1,4-dien-3-one starting from androsta-1,4-diene-3,17-dione without affecting its A ring.

Several derivatives shown in Chart 1 were then prepared from V, again without affecting its A ring.

Experimental

All melting points were determined in capillary tube and are uncorrected. Infrared (IR) spectra were recorded in KBr pellets or chloroform solution on a Hitachi Model EPI-G31 spectrometer. Ultraviolet (UV) spectra were determined on a Hitachi Model ESP-2U spectrophotometer. Optical rotations were measured in dioxane by JASCO ORD/UV-5 spectrophotometer.

5) The same kind of stereoselectivity by such oxidation reactions has been found for the related compounds: see for example; L.F. Fieser and M. Fieser, "Steroids," Reinhold Pub. Co., New York, 1959, pp. 337—340.

17β-Hydroxy-17α-pregna-1,4-dien-3-on-20-yne (II)——In a three-necked frask with dry ice–acetone condenser, pure dry acetylene was passed into a solution of potassium metal (0.9 g) in 100 ml of anhydrous liquid ammonia till the decoloration of the solution was completed. To the solution of potassium acetylide prepared as above, a solution of 3 g of androsta-1,4-diene-3,17-dione (I) in 30 ml of dry dioxane and 30 ml of absolute ether was added under stirring over 75 sec. The ammonia was then permitted to evaporate at room temperature, while 50 ml of absolute ether was added under stirring continuously. The mixture was then poured into water and the suspension acidified with dilute sulfuric acid and extracted with ethyl acetate. The organic layer was washed with aq. 5% sodium bicarbonate solution, then with water and concentrated *in vacuo* to dryness. The residue was chromatographed on alumina. Elution with hexane–benzene (1: 2 v/v) gave 1.7 g of II, which was satisfactorily pure for the subsequent reaction. Recrystallization from acetone–hexane afforded the analytically pure sample, mp 221—222.5°. $[\alpha]_D^{25}$ −27. UV λ_{max}^{EtOH} nm (log ε): 245 (4.18). IR ν_{max}^{KBr} cm^{-1}: 3330, 3250, 1660, 1615, 1605. *Anal.* Calcd. for $C_{21}H_{26}O_2$: C, 81.24; H, 8.44. Found: C, 81.58; H, 8.41.

17β-Hydroxy-17α-pregna-1,4,20-trien-3-one (III)——A suspension of 900 mg of 10% Pd/C catalyst in 400 ml of methanol was stirred under an atmospheric hydrogen until equilibrium was reached. To this suspension, 1.39 g of I was added and the whole was hydrogenated in an atmospheric pressure at room temperature until 72.3 ml of hydrogen was absorbed. The catalyst was filtered off and the filtrate was evaporated *in vacuo*. Recrystallization from acetone–hexane gave 1.03 g of III, mp 155—159°. $[\alpha]_D^{25}$ +16°. UV λ_{max}^{EtOH} nm (log ε): 245 (4.19). IR ν_{max}^{KBr} cm^{-1}: 3400, 1660, 1620, 1600. *Anal.* Calcd. for $C_{21}H_{28}O_2$: C, 80.71; H, 9.04. Found: C, 80.72; H, 9.03.

21-Hydroxypregna-1,4,17(20)-trien-3-one 21-Acetate (IV)——To the solution of 300 mg of phosphorous tribromide in 1.85 ml of dry chroloform, refrigerated in a dry ice–methanol bath, was added dropwise a solution of 1 g of III in 1.4 ml of absolute chloroform containing 5 drops of pyridine. The solution was allowed to stand at room temperature overnight. After addition of a small amount of water, the whole was concentrad *in vacuo* at room temperature. The residue was dissolved in 40 ml of dry acetone and refluxed for 5 hr in presence of 3.2 g of potassium acetate. The solution was filtered and the filtrate was evaporated to dryness *in vacuo*. The yellow gummy residue (1.06 g) was chromatographed on alumina. Elution with hexane–benzene (2: 1 v/v) gave 690 mg of colorless non-crystalline residue, which was sufficiently pure for subsequent reactions. UV λ_{max}^{EtOH} 245 nm. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730, 1660, 1620, 1600.

(20*R*)-17α,20,21-Trihydroxypregna-1,4-dien-3-one (Va)——A solution of 516 mg of IV in 5 ml of dry ether was allowed to stand in presence of 310 mg of osmium tetraoxide and 170 mg of pyridine. The ether was removed in nitrogen atmosphere *in vacuo*. The residue was refluxed for 3.5 hr in a mixture of 23.5 ml of ethanol, 16 ml of water, and 3.6 g of sodium sulfite. The whole was filtered off and the residue obtained was extracted three times with each 20 ml of ethanol. The combined ethanol fraction was concentrated *in vacuo* to dryness. The residue was taken up in excess of chloroform and washed with water. The chloroform layer was evaporated to dryness *in vacuo*, to give 468 mg of colorless non-crystalline residue, which showed a single spot in TLC. In order to obtain a more purified crystalline derivative, the triol was converted to the diacetate by dissolving it in an excess of mixture composed of equivalent volumes of pyridine and acetic anhydride. Recrystallization from acetone–hexane gave Vc in a quantitative yield, mp 176—178°. UV λ_{max}^{EtOH} nm (log ε): 245 (4.18). IR ν_{max}^{KBr} cm^{-1}: 3500, 1740, 1660, 1625, 1600. *Anal.* Calcd. for $C_{25}H_{35}O_6$: C, 69.57; H, 8.18. Found: C, 69.78; H, 7.98.

(20*R*)-17α,20,21-Trihydroxypregna-1,4-dien-3-one 21-Acetate (Vb)——A solution of 468 mg of triol (Va) obtained as above in 1 ml of dioxane containing 136 mg of pyridine and 152 mg of acetic anhydride was allowed to stand overnight. The solution was treated with a small amount of water, concentrated *in vacuo* to dryness, and extracted with chloroform. The chloroform layer was washed with water and evaporate *in vacuo* to dryness. The residue was chromatographed on alumina. Elution with benzene gave 292 mg of the monoacetate (Vb). Further elution with benzene containing 10% of methanol afforded 68 mg of the starting material (Va). The combined benzene fraction was recrystallized from acetone–hexane to give pure Vb, mp 178.5—180°. UV λ_{max}^{EtOH} nm (log ε): 245 (4.21). IR ν_{max}^{KBr} cm^{-1}: 3450, 3330, 1740, 1670, 1620. *Anal.* Calcd. for $C_{23}H_{33}O_5$: C, 70.91; H, 8.55. Found: C, 71.45; H, 8.40.

17α,21-Dihydroxypregna-1,4-diene-3,20-dione 21-Acetate (VI)——A solution of 49 mg of the monoacetate (Vb) in 2.9 ml of glacial acetic acid was cooled to 11° and to this solution was added dropwise over 10 min a solution of 22 ml of chromic oxide in 0.46 ml of water. The whole was kept at 11° for 1 hr and the excess chromic oxide was destroyed by the addition of a small volume of dilute sulfuric acid. The whole was then poured into water and extracted with chloroform. The chloroform layer was washed with dilute aq. sodium bicarbonate solution and then with water. After dryness over $MgSO_4$, the solvent was evaporated *in vacuo* and the residue was chromatographed on alumina. Elution with hexane–benzene (1: 1 v/v) gave 10 mg of the crystalline material, which after recrystallization by acetone–hexane afforded androsta-1,4-diene-3,17-dione (I), mp 140—142.

Elution with benzene followed by recrystallization from acetone–hexane gave 10 mg of the dione (VI) as colorless crystals, mp 216—220°. $[\alpha]_D^{25}$ +90. UV λ_{max}^{EtOH} nm (log ε): 245 (4.37). IR ν_{max}^{KBr} cm^{-1} 3400, 1750, 1660, 1620, 1600. *Anal.* Calcd. for $C_{23}H_{31}O_5$: C, 71.28; H, 8.07. Found: C, 71.73; H, 8.02.

Nineteen mg of the unreacted starting material (Va) was eluted with benzene–ether (4: 1 v/v).

17α,21-Dihydroxypregna-1,4-diene-3,20-dione 21-Acetate (VI) from Reichstain Substance S.——A solution of 50 mg of 17,21-dihydroxypregn-4-ene-3,20-dione (Reichstain substance S) in 3 ml of dioxane in presence of 4 ml of 2,3-dichloro-5,6-dicyanobenzoquinone was refluxed for 15.5 hr. The whole was poured into water and extracted with ether. Evaporation of the solvent afforded 45 mg of the residue. The residue was allowed to stand overnight in a mixture of 1 ml of pyridine and 0.5 ml of acetic anhydride. The whole was poured into water and extracted with ether. The ether layer was washed with 5% aq. sodium bicarbonate and then with water several times. Evaporation of the solvent gave 47 mg of the residue, which after recrystallization from acetone–hexane afforded 11 mg of the analytically pure diketone (VI), mp 212—218°.

The mixed melting point determination with the sample obtained as above assured an identity of both samples.

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