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## **Suminori Umio and Kazuma Nishitsuji**: Studies on the Synthesis of 17β-Hydroxyandrostan-3-one.

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Since Kochakin found the anabolic activity of androgens in 1937, a number of investigations have been carried out on various steroids which have such activity. Among them, 17β-hydroxyandrostan-3-one (XI) has a marked anabolic activity and some male-hormone properties. The syntheses of (XI) were already reported by Butenandt, *et al.*1) and by Ruzicka, *et al.*2) almost at the same time, in which they obtained (XI) from 3β-acetoxy-5-androsten-17-one (I). However, these methods do not seem to be suitable for the manufacture of (XI), as large amounts of expensive reagents were used. In this paper will be described industrially profitable synthesis of (XI) from (I), as shown in Chart 1.

Reduction of 17-keto group (I) to 17β-hydroxyl in several different ways was previously reported, such as sodium and propanol,1,3) a large amount of aluminium amalgam,4) and catalytic reduction over Raney nickel.4) In the present series of experiments, sodium borohydride was used and (I) was refluxed with a large excess of sodium borohydride in ethanol, from which the main product was clearly different from 3β-acetoxy-17β-hydroxy-5-androstene (IV) in melting point, and was identified as 3β,17β-dihydroxy-5-androstene (II) from its infrared absorption spectrum ($\lambda_{\max}^{\text{Nujol}}$ μ: 2.89, 2.98, 3.12 (hydroxyl), no absorption of ester) and its acetate which agreed with Ruzicka's diacetate3)(IIIa) in melting point. On the other hand, when about two reducing equivalents of sodium borohydride were used, favorable intermediate (IV) was obtained almost quantitatively.

Ruzicka5) reported that the most favorable reducing material was 3β-acetoxy-17β-benzoyloxy-5-androstene (V), because, after protecting the 17β-hydroxyl and hydrogenation of 5-ene, 3-ester of 3β,17β-dihexahydrobenzoyloxyandrostane, which was obtained by the catalytic reduction of 3β,17β-dibenzoyloxy-5-androstene (IIIb), had a strong resistance to hydrolysis, while the diacetoxyl compound did not give a pure product. Consequently, it was very favorable for the following process that (IV) was obtained quantitatively by means of proper amounts of sodium borohydride.

Subsequently, it was recognized that, in preparation of 3β-acetoxy-17β-benzoyloxy-5-androstene (V) from (IV) with benzoyl chloride in pyridine, the reaction proceeds in better yield at room temperature than when strongly cooled. As to the saturation of 5-ene, Ruzicka5) carried it out with Adams platinum oxide in anhydrous ethanol-acetic acid, while Djerassi6) effected it in acetic acid with improvement. At first, this reduction was carried out with a mixture of 5% rhodium on alumina and Adams platinum oxide in acetic acid, which enabled saving the amount of platinum. When platinum oxide only is applied, 10% of the catalyst is required on the basis of the material, but when a mixture of rhodium and platinum oxide is used, about 6.4% of rhodium and 3.6% of platinum oxide are sufficient. Attempt was also made on the use of Raney nickel in dioxane and 3β-acetoxy-17β-hexahydrobenzoyloxyandrostane (VIII) was obtained

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1) A. Butenandt, *et al.*: Ber., **68**, 2097(1935).

2) L. Ruzicka, *et al.*: Helv. Chim. Acta, **18**, 1487(1935).

3) L. Ruzicka, A. Wettstein: *Ibid.*, **18**, 1264(1935).

4) Brit. Pat. 455,020 (C. A., **31**, 1557(1937)).

5) L. Ruzicka, H. Kägi: Helv. Chim. Acta, **20**, 1557(1937).

6) A. L. Wilds, C. Djerassi: J. Am. Chem. Soc., **68**, 2125(1946).

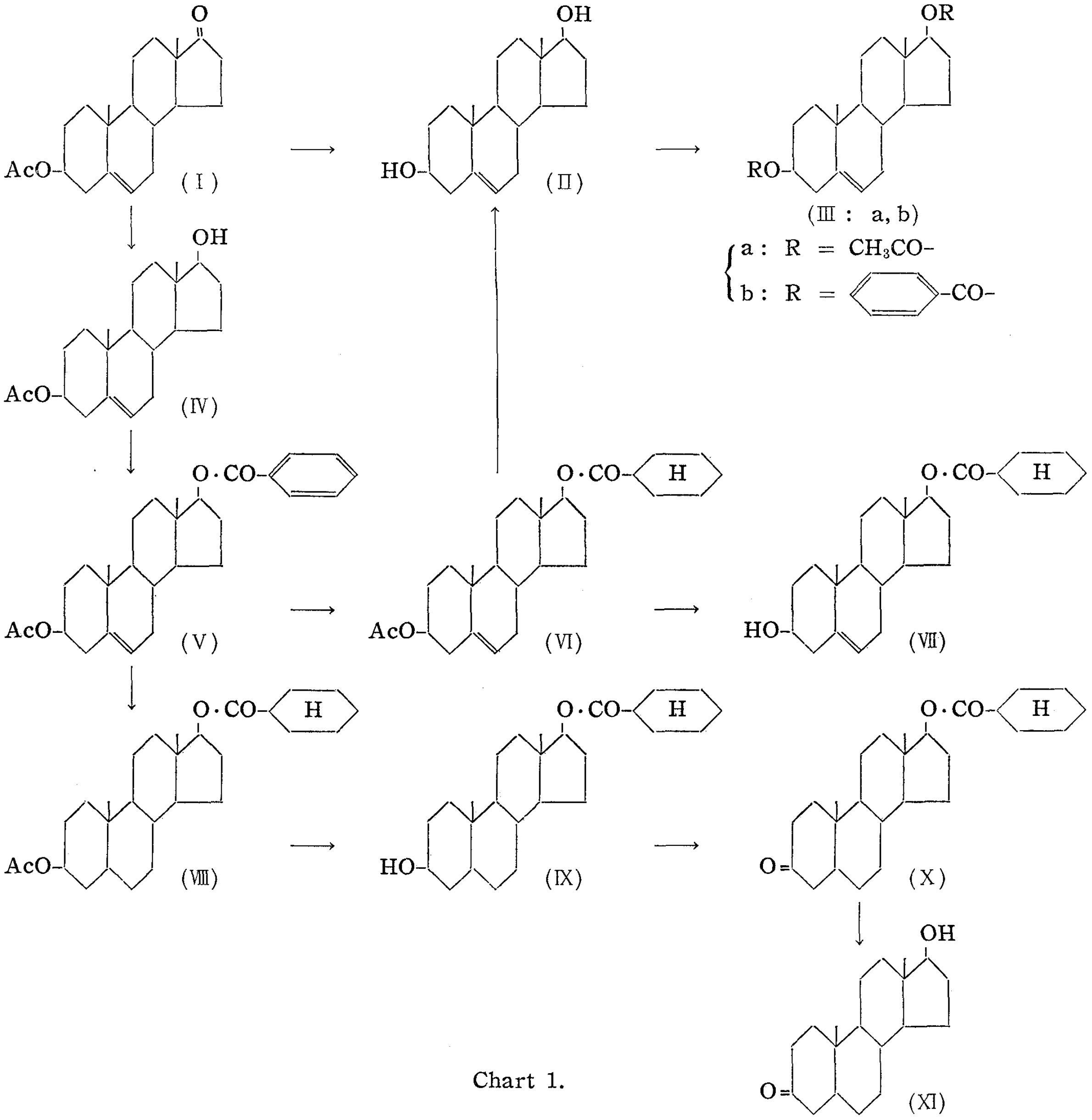

Chart 1.

in about 75% yield by the use of 40% of the Raney nickel against the material. However, when 20% of the Raney nickel on the basis of material was used, the product was obtained as leaflets (m.p. 148~149°), which differed clearly from (VIII) (needles, m.p. 126~129°). Infrared spectrum of this product, which indicated a double-bond ($\lambda_{\max}^{\text{Nujol}}$ : 6.04 μ) and an ester-carbonyl absorptions, agreed with that of (VIII) ($\lambda_{\max}^{\text{Nujol}}$ : 5.79 μ). A partial hydrolysis of this reduction product gave 3β-hydroxy-17β-hexahydrobenzoyloxy-5-androstene (VII) and a complete hydrolysis gave a substance of m.p. 180°, which agreed with 3β,17β-dihydroxy-5-androstene in infrared spectrum. From these evidences, it was concluded that this reduction product is 3β-acetoxy-17β-hexahydrobenzoyloxy-5-androstene and its analytical result agreed with (VI). This result indicates an interesting fact that, in the catalytic hydrogenation, aromatic ring is the first to be reduced, followed by the double bond of steroidal 5-ene.

Oxidation of 3-hydroxyl of 3β-hydroxy-17β-hexahydrobenzoyloxyandrostane (IX), obtained by partial hydrolysis of (VIII), had been effected by chromium trioxide but Ruzicka and Kägi[5)] reported difficulty in the purification of 17β-hexahydrobenzoyloxyandrostan-3-one (X), failing to obtain an analytically pure sample, and Djerassi[6] recognized the presence of an acid substances in his reëxperiment. Hence it seems that over-oxidation occurred partially with the use of chromium trioxide. In the present work, a mild oxidation[7] was used by heating with activated alumina and cyclohexanone in non-polar solvent, and the compound (IX) was oxidized to the 3-keto compound (X) in a good yield.

Ruzicka and Kägi[5] carried out hydrolysis of 17-ester by refluxing with 0.01*N* sodium hydroxide in methanol for 2 hours but (XI) was not produced under this condition, the total amount of the starting material being recovered. However, a modification of hydrolysis of 17β-hydroxy-1,4-androstadien-3-one, which was carried out by Wilds and Djerassi[6] by refluxing in 5% potassium hydroxide in methanol, gave 17β-hydroxyandrostan-3-one (XI) in a high yield.

## Experimental*2

**3β,17β-Dihydroxy-5-androstene (II)**—To a solution of 0.5 g. of 3β-acetoxy-5-androsten-17-one (I) in 120 cc. of MeOH, a solution of 2.5 g. of $NaBH_4$ in 80 cc. of $H_2O$ was added dropwise and the mixture was refluxed for 3 hr. A solution of $NaBH_4$ was added further, refluxed for 3 hr. again, and allowed to stand overnight. Precipitated crystals were collected on a filter and recrystallized from MeOH. Yield, 0.45 g. (90%) of m.p. 181~182°. IR $\lambda_{\max}^{\text{Nujol}}$ μ: 2.89, 2.98, 3.12, 6.00, 6.04, 6.11.

**3β,17β-Dibenzoyloxy-5-androstene (IIIb)**—A solution of 0.35 g. of (II) in 3 cc. of pyridine was treated with 0.7 g. of BzCl. After standing overnight, the mixture was poured into cold dil. $H_2SO_4$, precipitated crystals were collected on a filter, and washed successively with water, 5% $Na_2CO_3$, water, and MeOH. Repeated recrystallizations of 0.38 g. of crude crystals from $CHCl_3$ or acetone gave needles, m.p. 211~212°. *Anal.* Calcd. for $C_{33}H_{38}O_4$: C, 79.48; H, 7.68. Found: C, 79.20; H, 7.66. IR $\lambda_{\max}^{\text{Nujol}}$ μ: 5.83, 6.22, 7.81.

**3β-Acetoxy-17β-hydroxy-5-androstene (IV)**—To a solution of 25 g. of (I) in 880 cc. of 99% EtOH, 1.6 g. of $NaBH_4$ was added at 10° and the mixture was left to stand for 4 hr. at the same temperature. The mixture was neutralized with AcOH, concentrated *in vacuo* to 1/3 the original volume, and poured into 1200 cc. of cold water. Precipitated product was collected on a filter, washed with water, and dried to 24.7 g. of crude product (98.3%), m.p. 138~142°. Two recrystallizations from hexane gave analytical sample of m.p. 147~148°. *Anal.* Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.29; H, 9.73.

**3β-Acetoxy-17β-hexahydrobenzoyloxy-5-androstene (VI)**—A mixture of 5 g. of 3-acetoxy-17-benzoyloxy-5-androstene (V), 120 cc. of dioxane, and 1 g. of Raney Ni was catalytically reduced in an autoclave at 120~130° for 6 hr. with initial $H_2$ pressure of 100 kg./cm$^2$. After the catalyst was filtered off, dioxane was evaporated *in vacuo* and the residue was recrystallized from EtOH. Yield, 3.9 g. (76.9%) of m.p. 128~130°. Repeated recrystallizations gave leaflets, m.p. 148~149°. *Anal.* Calcd. for $C_{28}H_{42}O_4$: C, 75.97; H, 9.56. Found: C, 76.10; H, 9.62. IR $\lambda_{\max}^{\text{Nujol}}$ μ: 5.79, 6.04, 8.00.

**3β-Hydroxy-17β-hexahydrobenzoyloxy-5-androstene (VII)**—A mixture of 1 g. of (VI) and 23 cc. of 0.1*N* MeOH-NaOH was shaken for 9 hr. at room temperature and poured into water. Precipitated product was collected on a filter, washed with water, and recrystallized three times from EtOH; m.p. 150~151°. *Anal.* Calcd. for $C_{26}H_{40}O_3$: C, 77.95; H, 10.07. Found: C, 77.41; H, 10.26.

**3β,17β-Dihydroxy-5-androstene (II) by Complete Hydrolysis of 3β-Acetoxy-17β-hexahydrobenzoyloxy-5-androstene (VI)**—A solution of 0.5 g. of (VI) in 15 cc. of 5% MeOH-KOH was refluxed for 2 hr. and poured into 50 cc. of water, precipitated product was collected, washed with water, and recrystallized from EtOH, m.p. 180°, no depression on admixture with the diol (II) obtained by reduction and hydrolysis of (I) with $NaBH_4$. IR spectrum of this product also agreed with that of (II).

**3β-Acetoxy-17β-hexahydrobenzoyloxyandrostane (VIII)**—i) Catalytic reduction with 5% Rh on $Al_2O_3$ and Adams $PtO_2$: A solution of 11 g. of (V) in 300 cc. of pure AcOH was shaken with 0.7 g. of 5% Rh on $Al_2O_3$ and 0.4 g. of Adams $PtO_2$ until the theoretical amount of $H_2$ corresponding to 4 moles had been absorbed (8 hr.). After the catalyst was filtered off and AcOH was evaporated *in vacuo*, the product was recrystallized from EtOH to needles, which were identified as (VIII) by a mixed m.p. determination. Yield, 8.3 g. (73%) of m.p. 126~129°. IR $\lambda_{\max}^{\text{Nujol}}$ μ: 5.78, 8.00.

ii) Catalytic reduction with Raney Ni: A mixture of 10.2 g. of (V), 150 cc. of dioxane, and 4 g. of

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*2 All m.p.s are uncorrected.

[7] K.R. Bharucha: Experientia, **14**, 5(1958).

Raney Ni catalyst was shaken in an autoclave for 6 hr. at 140~160° with initial $H_2$ pressure of 100 kg./$cm^2$. After the catalyst was filtered off and dioxane was evaporated *in vacuo*, the product was recrystallized from EtOH to needles, which were identified as (VIII) by a mixed m.p. determination. Yield, 7.5 g. (72.2%) of m.p. 124~127°.

**17β-Hexahydrobenzoyloxyandrostan-3-one (X)**—A mixture of 2 g. of 3β-hydroxy-17β-hexahydrobenzoyloxyandrostane (IX), 7 g. of activated $Al_2O_3$, 15 cc. of cyclohexanone, and 60 cc. of toluene was refluxed for 8 hr. in an oil bath. After $Al_2O_3$ was filtered off, the solution was concentrated *in vacuo* and the residue was recrystallized from MeOH. Yield, 1.97 g. (99%) of m.p. 146~150°, undepressed on mixed m.p. determination with (X), obtained by the method of Wilds and Djerassi. IR $\lambda_{\max}^{\text{Nujol}}$ 5.81 μ.

**17β-Hydroxyandrostan-3-one (XI)**—A mixture of 0.4 g. of (X) and 10 cc. of 5% MeOH-KOH was refluxed for 2 hr., poured into ice-weter, and the precipitated crystals were collected to 0.28 g. (96.7%) of m.p. 181.5°, $[\alpha]_D$ +31°, which was identified as (XI) by a mixed m.p. determination with stanolone (N. N. D.). IR $\lambda_{\max}^{\text{Nujol}}$ μ: 2.93, 5.86. Oxime: m.p. 208.5°.

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## Summary

In the synthesis of 17β-hydroxyandrostan-3-one from 3β-acetoxy-5-androsten-17-one, carbonyl group at 17-position is reduced to 17β-hydroxyl almost quantitatively by means of sodium borohydride without accompanying saponification of 3-ester. By catalytic hydrogenation over Raney nickel under high pressure and heating, double bond at 5—6 position of the steroidal B-ring is saturated and the *trans*-form is produced. In this case, aromatic ring at 17-ester is first reduced, followed by the double bond at 5-position. 3-Hydroxyl is oxidized to 3-keto group in a good yield on heating with activated alumina and cyclohexanone in nonpolar solvent. Finally, 17-ester is saponified quantitatively to 17β-hydroxyandrostan-3-one.

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