give cortisone (235 mg, 88% yield): mp 223–225°; R_f 0.61 (solvent system B).

4-Chlorocortisone-TMBMD (**3d**, 500 mg) on heating with acetic acid (40 ml, 50%) at steam-bath temperature for 4 hr afforded 4-chlorocortisone (340 mg, 85% yield): mp 212–214° (lit.[5] mp 210–212°; uv max 254 mμ (ε 15,220); ir (KBr) 3500 and 3520 (17- and 21-OH), 1700 and 1710 (11- and 20-keto), 1685 (3-keto), and 1590 cm^{-1} (C=C); R_f 0.64 (solvent system B).

Hydrocortisone-TMBMD (**3a**, 400 mg) was heated with acetic acid (30 ml, 50%) at 90° for 3 hr. The reaction mixture was then taken to dryness *in vacuo*. The residue was crystallized from aqueous ethanol to give hydrocortisone (282 mg, 90% yield): mp 220–221°; R_f 0.37 (solvent system B).

Hydrolysis of 4-chlorohydrocortisone-TMBMD (**3b**, 370 mg) with aqueous acetic acid (50 ml, 50%) for 4 hr as in previous examples, followed by crystallization from benzene–acetone, gave 4-chlorohydrocortisone[5] (245 mg, 83% yield): mp 224–225°; R_f 0.42 (solvent system B). The identity of the material with that prepared by hydrochloric acid treatment of **2** was shown by mixture melting point and uv and ir spectral comparisons.

Registry No.—**1b**, 19551-06-5; **1d**, 19551-07-6; **1f**, 19551-08-7; **2**, 19594-74-2; **3a**, 19551-09-8; **3b**, 19581-61-4; **3c**, 19551-10-1; **3d**, 19551-11-2.

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Catalytic Hydrogenation of 17β-Hydroxyde-A-androst-9-en-5-one, (±)-17β-Hydroxy-18-methylde-A-androst-9-en-5-one, and (±)-17β-Hydroxy-18-methylde-A-D-homoandrost-9-en-5-one

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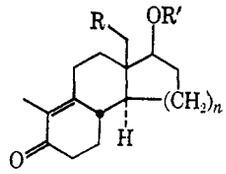
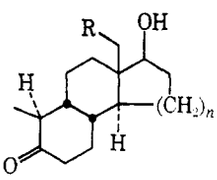
This Note describes the preparation of 17β-hydroxy-9β,10β-de-A-androstan-5-one (**2a**), (±)-17β-hydroxy-9β,10β-18-methylde-A-androstan-5-one (**2b**), and (±)-17β-hydroxy-9β,10β-18-methylde-A-D-homoandrostan-5-one (**2c**) by catalytic hydrogenation of the title compounds (**1a**, **1g**, and **1k**)[3] and their derivatives (Chart I). These compounds were required for our total synthesis of retro steroids (*i.e.*, 9β,10α steroids).[4]

Previous work reported from these laboratories[5] indicated that rhodium on alumina in ethanol–hydrochloric acid would favor formation of **2a** from **1a**, the major by-product being **3a**[6] which has the 9α,10α configuration. The best ratio of **2a**:**3a** obtainable by us under these conditions is shown in Table I (expt 1).

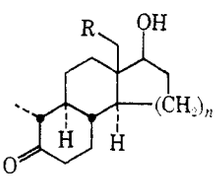
CHART I



1a, R = R′ = H; *n* = 1
b, R = H; R′ = $COCH_3$; *n* = 1[a]
c, R = H; R′ = COC_6H_{11}; *n* = 1
d, R = H; R′ = $COCH_2C(CH_3)_3$; *n* = 1
e, R = H; R′ = COH; *n* = 1
f, R = H; R′ = $C(CH_3)_3$; *n* = 1
g, R = CH_3; R′ = H; *n* = 1
h, R = CH_3; R′ = $COCH_3$; *n* = 1
i, R = CH_3; R′ = COC_6H_{11}; *n* = 1[a]
j, R = CH_3; R′ = $CO(CH_2)_2C_5H_9$; *n* = 1[a]
k, R = CH_3; R′ = H; *n* = 2
l, R = CH_3; R′ = $COCH_3$; *n* = 2



2a, R = H; *n* = 1
b, R = CH_3; *n* = 1
c, R = CH_3; *n* = 2



3a, R = H; *n* = 1
b, R = CH_3; *n* = 1
c, R = CH_3; *n* = 2

[a] Cycloalkyl derivatives.

Experiments with other solvents under neutral, acidic, or basic conditions failed to improve the ratio, and the same was true when palladium on barium sulfate or rhodium on carbon was used as the catalyst. Variation of the amount of hydrochloric acid used indicated that the best results were obtained when *ca.* 3 equiv were used. The optimum yield of **2a** proved to be 40%.

TABLE I
HYDROGENATION OF DE-A-ANDROST-9-EN-5-ONES[a]

Expt	Compd 1	Relative ratio 2a:3a
1	**a**	75–83:25–17
2	**b**	88–90:12–10
3	**c**	82:18
4	**d**	85:15
5	**e**	75:25
6	**f**	65:35[b]
		2b:3b
7	**g**	56:44
8	**h**	84:16
9	**i**	94:6
10	**j**	87:13
		2c:3c
11	**k**	67:31
12	**l**	96:4

[a] All hydrogenations were performed using 5% Rh/Al_2O_3 in EtOH–HCl. The formate **1e** hydrolyzed during hydrogenation, the acetates were saponified with KOH—MeOH, and the other esters with NaOMe–MeOH prior to vpc determination of the isomer ratio in the products. The vpc analyses used system A for the products from **1a-f** and system B for the remainder (see Experimental Section). [b] The ether group was first removed with aqueous HCl in EtOH or with *p*-toluenesulfonic acid in benzene.

An improved ratio of **2a**:**3a** was obtained by hydrogenation of acetate **1b** (expt 2), and subsequent saponification. Three other esters (**1c**, **1d**, and **1e**) were also prepared as was the *t*-butyl ether **1f**. Bulky esters **1c** and **1d** (expt 3 and 4) gave results comparable with those obtained with acetate **1b** as regards the ratio of **2a**:**3a**; but the yields of **2a** after saponification and crystallization were only *ca.* 45% as opposed to 70% obtained from **1b**. This almost certainly reflects the strenuous hydrolysis conditions (sodium methoxide in boiling

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(3) It should be noted that all the compounds with R = Me referred to in Chart I are racemic, whereas those with R = H belong to the normal steroid series. Throughout the paper steroid nomenclature is used.
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methanol) necessary to effect complete removal of the ester moiety. Ester **1e**, which hydrolyzed during hydrogenation, and ether **1f** led to relatively unfavorable ratios of **2a**:**3a** (expt 5 and 6).

In the cases of **1g** and **1k**[7] none of the expected products was a known compound and it was therefore necessary to consider the likely outcome of the hydrogenations. Formation of **2b** and **2c** requires addition of hydrogen from the β faces of the molecules and the presence of 18-methyl substituents in **1g** and **1k** should hinder this process. However, as noted above, esterification of the 17β-hydroxyl group in **1a** promoted hydrogenation from the β face. This surprising result may be explained by examination of models which reveals that because of the bond angles of the sp^2 hybridized carbon atom of the carbonyl group of the ester function the alkyl moiety of the esters assumes a preferred conformation in which it hinders attack from the α side of the molecule. This is not true of a 17β ether group which hinders approach from the β face and should therefore impede the formation of the desired 9β,10β product. The result (expt 6) with **1f** supports this conclusion.

The hydrogenation products from **1g** and **1k** (expt 7 and 11) were subjected to vpc analysis and the scans obtained were compared to that for the product from **1a**. The only significant differences were in the areas of the major peaks, and on this basis peaks were assigned to **2b**, **2c**, **3b**, and **3c**. The relative ratios of **2b**:**3b** and **2c**:**3c** obtained from the alcohols and various esters are shown in Table I. It will be noted that the results confirm the predictions, the alcohols giving less favorable amounts of the desired 9β,10β compounds than obtained in the case of **1a**. For preparative purposes the acetates proved to be the preferred substrates for hydrogenation and **2b** and **2c** were obtained, by direct crystallization, in yields of 64 and 59%, respectively.

The nmr spectrum[7] of the 18-methyl compound **2b** compared favorably with that of the 9β,10β alcohol **2a**; in particular, the methylene envelopes of the two spectra were almost superimposable, and quite different from that found in the spectrum of the 9α,10α isomer **3a**. Also, the nmr data obtained for the pure D-homo-9β,10β analog **2c** were in agreement with the proposed structure.

Experimental Section

Melting points were determined with a Thomas–Hoover melting point apparatus and are corrected. Ultraviolet data refer to solutions in EtOH, and infrared data to *ca.* 3% solutions in $CHCl_3$. Nmr spectra were measured at 60 MHz in $CDCl_3$ with $SiMe_4$ as internal standard. Two systems were used for vpc measurements, system A [F & M Model 810 with dual flame detector; column 6 ft × 0.25 in. o.d. stainless steel, 2% neopentyl glycol succinate plus 2% fluorosilicone FS-1265 (QF-1) on 60–70 mesh Anakrom ABS; column temperature 200°, with He flow at 120 ml/min] and system B [F & M Model 810R-13N with H_2 flame detector; column 6 ft × 0.25 in. o.d. aluminum, 1% XE60 on 60–70 mesh Anakrom ABS; column temperature 170°, with N_2 flow at 100 ml/min].

The hydrogenations listed in Table I were carried out at room temperature (20–25°) and atmospheric pressure using the methods and proportions described below. Esters **1c**, **1d**, **1i**, and **1j** were prepared from the corresponding acid chloride in pyridine by standard methods. The formate ester **1e** was prepared from HCO_2H and *p*-toluenesulfonic acid.[8] These esters were not completely characterized but they were purified by chromatography on alumina or by crystallization. They were homogeneous on tlc and spectral data were compatible with the assigned structures. The preparations of **1g**, **1h**, **1k** and **1l** are described elsewhere.[7]

Hydrogenation of 17β-Hydroxyde-A-androst-9-en-5-one (1a) (Expt 1).—A suspension of 15 g of 5% Rh/Al_2O_3 in EtOH (benzene free, 300 ml) and 3 *N* HCl (120 ml) was saturated with H_2. To this was added a solution of **1a** (30.0 g) in EtOH (900 ml), and the mixture was shaken in an atmosphere of H_2. After *ca.* 60 min the rate of uptake of H_2 slowed (uptake, 3401 ml, 118.8%; calcd 2865 ml). The catalyst was removed by filtration (Celite), the filtrate neutralized with $NaHCO_3$, and the solution concentrated *in vacuo* (40°) to *ca.* 350 ml. This concentrate was extracted with three 350-ml portions of Et_2O and the extracts were washed with three 225-ml portions of H_2O and two 225-ml portions of saturated NaCl solution. They were dried over Na_2SO_4. Vpc analysis of an aliquot of this solution showed the ratio **2a**:**3a** to be 83:17. The ether solution was concentrated on the steam bath to 80–100 ml and cooled to room temperature, then held at −20° overnight to yield **2a** (12.1 g), mp 135–144° with sintering (vpc assay 97–98%). The melting point of **2a** is not a criterion of purity as a trace of **3a** causes a marked depression. Crystallization from ether gave pure **2a**: mp 143–145.5°; $[\alpha]^{25}D$ −12.9° (*c* 1.065, $CHCl_3$). A further crystallization from CH_2Cl_2–Et_2O gave an analytical sample: mp 144–145.5°; $[\alpha]^{25}D$ −13.0 (*c* 1.0, $CHCl_3$); ir 3610 (OH) and 1705 (C=O) cm^{-1}; nmr δ 0.85 (13β-methyl) and 1.01 ppm (10β-methyl, d, J = 7 Hz).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23. Found: C, 75.96; H, 10.21.

Hydrogenation of 17β-Acetoxyde-A-androst-9-en-5-one (1b) (Expt 2).—Compound **1b**[6] (100 g) in EtOH (3.0 l.) was reduced in the presence of 5% Rh/Al_2O_3 (50 g) in EtOH (1.0 l.) and 3 *N* HCl (360 ml), as described above. After H_2 uptake ceased (110% of theory) the catalyst was removed, the solution was adjusted to *ca.* pH 11 with 40% KOH, and heated under reflux in a N_2 atmosphere for 1 hr. The solution was neutralized with 10% HCl and extracted with Et_2O to give crude product (87 g, **2a**:**3a** = 88:12 by vpc). This material was crystallized from CH_2Cl_2–Et_2O–petroleum ether (bp 30–60°) to yield **2a** (60.0 g), mp 137.5–145° (97.5% by vpc).

17β-*t*-Butoxyde-A-androst-9-en-5-one (1f).—A solution of **1a** (10.0 g) in CH_2Cl_2 (100 ml) was allowed to react with isobutylene (200 ml), 47% BF_3–Et_2O[9] (1.0 ml, 8.0 mmol), and 100% H_3PO_4 (0.42 ml. 8.0 mmol) overnight at room temperature. Isolation of the product in the usual manner gave a mixture of **1a** and **1f** (12.0 g), which was triturated with petroleum ether (bp 30–60°) and **1a** (*ca.* 1.0 g) was removed by filtration. Crystallization from EtOH–H_2O of the material in the filtrate gave **1f** (8.7 g): mp 78–80°; $[\alpha]^{25}D$ −12° (*c* 1.00, $CHCl_3$); uv max 249 mμ (ϵ 15,700); ir 1658 and 1605 cm^{-1}; nmr δ 0.87 (13β-methyl), 1.13 (17β-*t*-butyl) and 1.80 ppm (10-methyl).

Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.47; H, 10.61.

Registry No.—**1a**, 19614-34-7; **1b**, 19614-35-8; **1f**, 19614-36-9; **1g**, 18267-52-2; **1k**, 18267-50-0; **2a**, 10072-76-1.

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