C. Horning, Ed., Wiley, New York, N.Y., 1955, p 432.
(36) B. Helferich and J. Zirner, *Ber.*, **95**, 2604 (1962).
(37) (a) G. M. Cree, D. M. Mackie, and A. S. Perlin, *Can. J. Chem.*, **47**, 511 (1969); (b) D. M. Mackie and A. S. Perlin, *Carbohydr. Res.*, **24**, 67 (1972).
(38) G. J. R. Chittenden, *Carbohydr. Res.*, **11**, 424 (1969).
(39) Reference 18a contains a probable report of the synthesis of **15**; however, no characterizing data were reported.
(40) C. E. Braun and C. D. Cook, "Organic Syntheses", Collect. Vol. V, H. E. Baumgarten, Ed., Wiley, New York, N.Y., 1973, p 887.
(41) E. Fischer and F. W. Lichtenthaler, *Angew. Chem., Int. Ed. Engl.*, **13**, 546 (1974).
(42) H. C. J. Ottenheijm and J. H. M. de Man, *Synthesis*, 163 (1975). It was not necessary to distill the pyruvoyl chloride prior to esterification if 2 equiv of pyridine (0.066 mmol) was used. This modification simplified the esterification process.

D-Homoandrostanes. 2.[1] Preparation and Properties of Some Dioxygenated D-Homo-5α-androstanes

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The synthesis of D-homo-5α-androstane-2,17a-, -3,6-, -3-7-, -3,16-, -3-17-, and -3,17a-diones and their properties are described. Prolonged reaction time in the dehydrobromination of the 17,17-dibromo-17a ketone (12) resulted in 3β-acetoxy-D-homo-5α-androsta-14,16-dien-17a-one (14).

The first publication in this series[2] dealt with the synthesis of the four D-homo ring A ketoandrostanes and their derivatives, which like the difunctional compounds described here were required for microbiological experiments. Of equal importance are their use as spectroscopic standards, principally in NMR, as analysis of chemical shifts of the methyl groups of oxygenated steroids according to the method of Zurcher[3] enables the location and orientation of microbial hydroxylation to be determined with some precision.

Ring D expansion of 3β-hydroxy-5α-androstan-17-one yielded the hydroxy ketone mixture **1** and **2** which on oxidation gave the easily separable diketone mixture **3** and **4**. As in the reported 17-keto steroid expansions via cyanohydrin[4] or spirooxirane[5] formation, the 17a ketone predominated; consequently a route to the 3,17-dione **4** was developed as shown in the reaction scheme. No purification of the mixtures obtained in each stage was attempted until the removal of the 17a-acetoxy group (**8** → **9**) as the reaction sequence is well documented[2,6] and spectroscopic examination was sufficient to monitor the transformations.

Synthesis of D-homo-5α-androstane-3,16-dione (**19**) required the effective transfer of the oxygen substituent at C-17a to C-16, by treatment of the epoxy ketone **16** with hydrazine,[7] followed by oxidative–reductive manipulation. In the first stage, bromination of 3β-acetoxy-D-homo-5α-androstan-17a-one (**10**) resulted in a mixture of starting material (8%), monobromo (**11**, 53%), and dibromo ketones. After chromatographic separation the dibrominated material **12** was recycled by dehydrobromination and reduction (**12** → **13** → **10**). However, prolonged refluxing during dehydrobromination, 18 h instead of 2 h, led to dienone[8] (**14**, 83%), characterized by an IR absorption at 1660 cm^{-1}. The ease of reaction suggests a convenient route to aromatized 18-nor-D-homo steroids, or, as Japanese workers have ably demonstrated,[8] to 5α,14β-steroids, although by a more laborious route involving two brominations. Dienone **14** formation could be explained by a sequence of elimination, addition, and elimination of HBr, initiated by nucleophilic attack of bromide ion on the initially formed bromo enone **13** as depicted in the reaction scheme.

The hydroxy ketone mixture **1** and **2** also provided the starting material for preparing the 2,17a diketone **25**, in which PLC using silver nitrate impregnated silica gel was found necessary to purify the unsaturated ketone **21**. Hydrobromination with freshly prepared N-bromosuccinimide, careful chromatographic separation of the hydrobromide **22**, epoxide **23** formation, and subsequent reduction gave D-homo-5α-androstane-2β,17β-diol (**24**), which yielded the desired material **25** on oxidation.

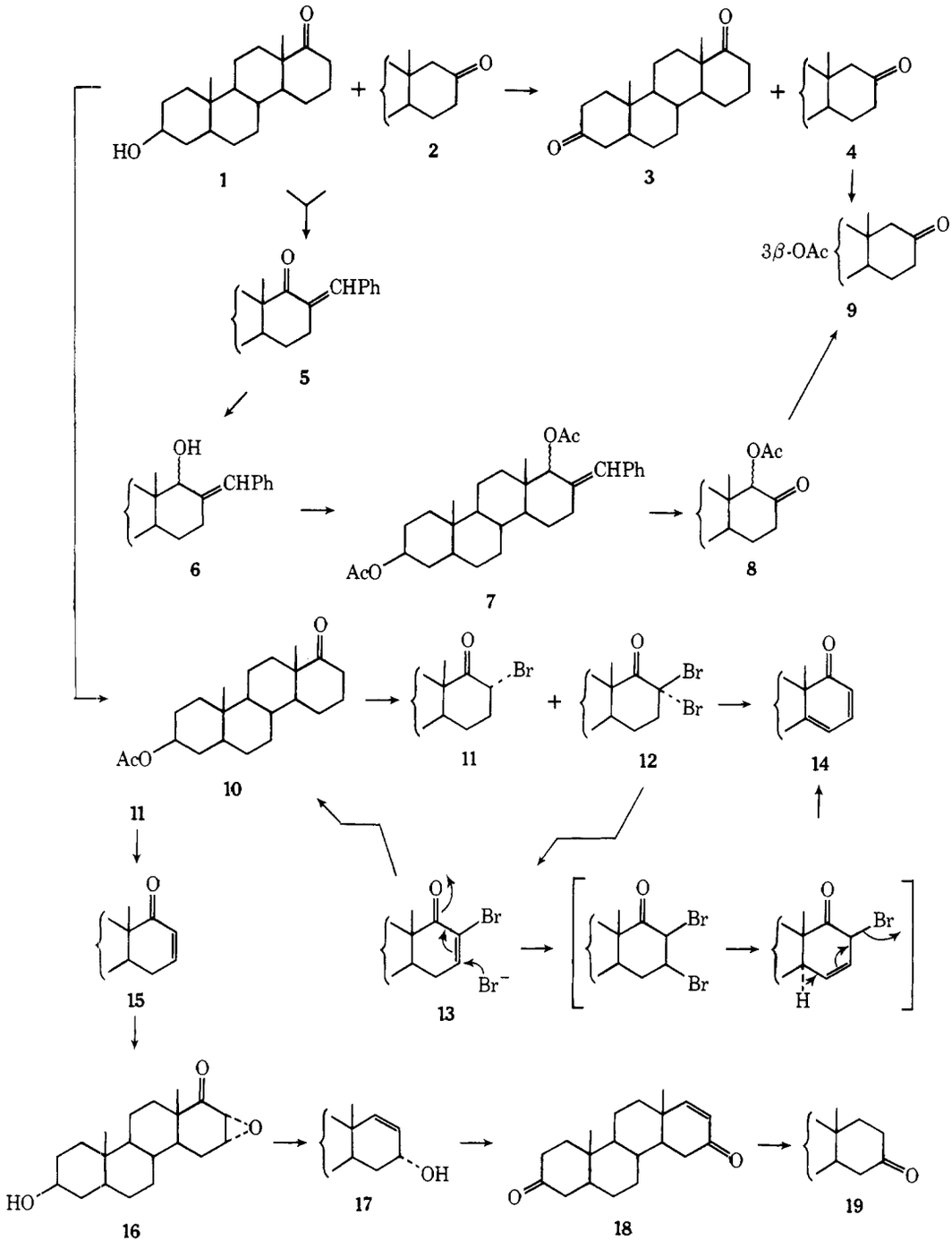
Recent work by authors[9] interested in generating 3,6-dioxygenated 5α-androstanes has indicated several available routes. We found that treatment of D-homoandrost-5-en-3β-ol with diborane generated externally, rather than in situ, followed by alkaline hydrogen peroxide gave a complex mixture which contained the diol **26** as major component. Column chromatography gave the 3β,6α-diol (**26**, 42%), D-homo-5α-androstan-3β-ol[2] (9%), and a mixture of the 3β,6β-diols epimeric at C-5 which could only be separated as their diacetates by PLC. An authentic sample of D-homo-5α-androstane-3β,6β-diol was prepared by borohydride reduction of the dione **30** derived from the 3β,6α-diol **26**. Ease of synthesis could be accomplished by prolonged Jones oxidation of the total crude hydroboration product, when a mixture of only D-homo-5α-androstan-3-one[2] and the dione **30** was obtained. During preliminary work on this reaction, treatment with Jones reagent during 15 min gave, in addition to the ketonic products, 6α-hydroxy-D-homo-5α-androstan-3-one (**31**).

D-Homoandrost-5-en-3β-ol also provided a convenient starting point for synthesis of the 3,7-dione **37**. Oxidation of the derived acetate **32** yielded the desired acetoxy enone **34**, together with the acetoxy ketol **33** as minor product exhibiting on mass spectrometric examination the appropriate molecular ion and characteristic fragmentation of 6-oxo steroids,[10] together with IR absorptions at 3580 and 3400 cm^{-1}. Standard reactions (**34** → **37**) completed the synthesis.

Experimental Section

General directions have been described previously.[2] Mass spectra were recorded with a Hitachi Perkin-Elmer RMU-6h at 70 eV.

D-Homo-5α-androstane-3,17a- and -3,17-diones (3 and 4). Oxidation of a mixture of 3β-hydroxy-D-homo-5α-androstan-17a- and -17-ones (**1** and **2**) (198 mg) by Jones reagent, followed by extraction and separation by PLC, gave 128 mg of dione **3** recrystallized from ethyl acetate [mp 182–184 °C (lit.[4] 183–185 °C); ν_{max} 1700 cm^{-1}; NMR τ 8.96 (CH_3-19), 8.86 (CH_3-18)] and 16 mg of dione **4** recrystallized from ethyl acetate [mp 168 °C (lit.[4] 168–170 °C); ν_{max} 1700 cm^{-1}; NMR τ 9.16 (CH_3-18), 8.96 (CH_3-19)].



3β-Hydroxy-17-benzylidene-*D*-homo-5α-androstan-17a-one (5). The hydroxy ketone mixture **1** and **2** (1.2 g) was allowed to stand with 2.5 ml of freshly distilled benzaldehyde in 20 ml of ethanol containing 250 mg of potassium hydroxide for 48 h in the dark. Dilution with water and extraction gave the benzylidene derivative **5** recrystallized from acetone–hexane (1.37 g): mp 165–167 °C; ν_{max} 1677 cm^{-1}; NMR τ 9.18 (CH_3-19), 8.92 (CH_3-18), 6.38 (m, $W_{1/2}$ = 20 Hz, H-3), 2.67 (m, olefinic and C_6H_4).

Anal. Calcd for $C_{27}H_{36}O_2$: C, 82.6; H, 9.2. Found: C, 82.5; H, 9.2.

17-Benzylidene-*D*-homo-5α-androstane-3β,17a-diols (6). The benzylidene derivative **5** (1 g) was treated with 1 g of sodium borohydride in 30 ml of ethanol. Dilution with water and extraction gave the crude diol mixture **6** (800 mg): ν_{max} 3600, 3400 cm^{-1}.

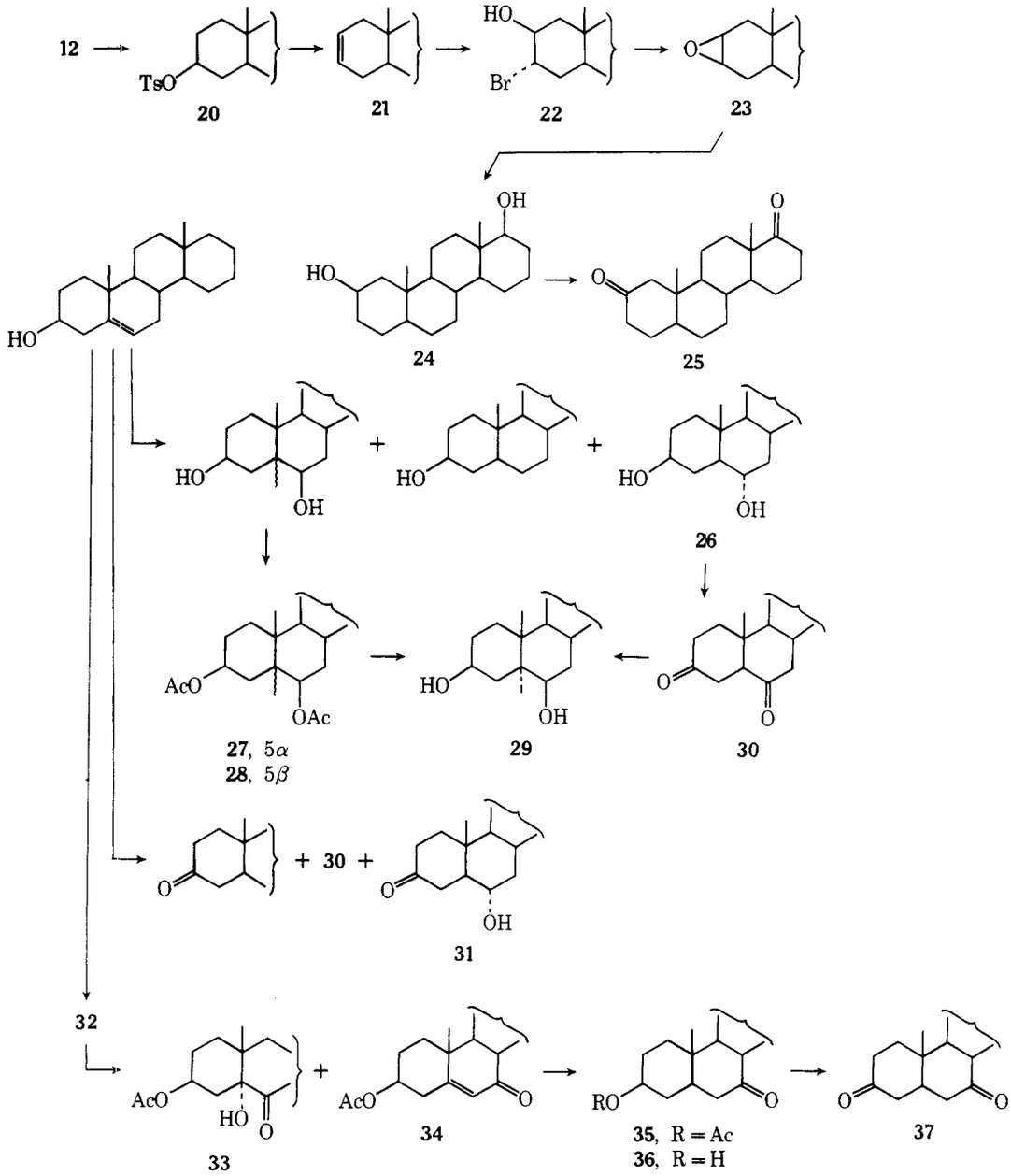
17-Benzylidene-*D*-homo-5α-androstane-3β,17a-diol Diacetates (7). The diol mixture **6** (800 mg) was acetylated with acetic anhydride–pyridine under the usual conditions producing the diacetates **7** (780 mg): ν_{max} 1725–1700, 1250 cm^{-1}.

3β,17a-Diacetoxy-*D*-homo-5α-androstan-17-ones (8). Ozone was passed through a solution of the benzylidene acetates **7** (640 mg) in 40 ml of methanol and 40 ml of ethyl acetate at −70 °C during 20 min, followed by nitrogen. Treatment with 10 g of zinc and 100 ml of glacial acetic acid at room temperature for 30 min, followed by filtration, dilution with water, and extraction, gave crude diacetoxy ketone **8** (510 mg): ν_{max} 1725–1700, 1250 cm^{-1}.

3β-Acetoxy-*D*-homo-5α-androstan-17-one (9). The diacetoxy ketone **8** (510 mg) and 10 g of activated zinc were boiled with 10 ml of glacial acetic acid for 1 h. After cooling, filtration, and addition of ice–water, extraction gave the keto acetate **9**, recrystallized from ethyl acetate (370 mg): mp 131–135 °C (lit.[4] 102–104 °C); ν_{max} 1725, 1708 cm^{-1}; NMR τ 9.19 (CH_3-18), 9.16 (CH_3-19), 5.28 (m, $W_{1/2}$ = 24 Hz, H-3).

3β-Hydroxy-*D*-homo-5α-androstan-17-one (2). The keto acetate **9** (340 mg) was refluxed for 1 h in 10 ml of methanol containing 500 mg of potassium hydroxide. Dilution with water, extraction, and PLC yielded 280 mg of keto alcohol **2** from ethyl acetate: mp 181–183 °C (lit.[4] 170–172 °C); NMR τ 9.19 (CH_3-18), 9.21 (CH_3-19), 6.42 (m, $W_{1/2}$ = 24 Hz, H-3). Oxidation of this material with Jones reagent gave *D*-homo-5α-androstane-3,17-dione (**4**, 270 mg) having identical IR and NMR spectra with the authentic sample.

3β-Acetoxy-*D*-homo-5α-androstan-17a-one (10). 3β-Hydroxy-*D*-homo-5α-androstan-17a-one (**1**, 600 mg) was acetylated with acetic anhydride–pyridine under standard conditions giving the ac-



etate **10** as needles from methanol (630 mg): mp 127–129 °C (lit.[4] 124–125 °C); ν_{max} 1720, 1700 cm^{-1}; NMR τ 9.16 (CH_3-19), 8.89 (CH_3-18), 5.35 (m, $W_{1/2}$ = 20 Hz, H-3).

Bromination of 3β-Acetoxy-*D*-homo-5α-androstan-17a-one (10). Bromine (290 mg) was added dropwise with stirring to a solution of 630 mg of acetate **10** in 5 ml of glacial acetic acid. Addition of water, extraction, and separation of the product mixture by PLC resulted in 3β-acetoxy-17α-bromo-*D*-homo-5α-androstan-17a-one (**11**, 410 mg) from acetone [mp 238–240 °C (lit.[8] 239–241 and lit.[11] 246–248 °C); ν_{max} 1720 cm^{-1}; NMR τ 9.17 (CH_3-19), 8.85 (CH_3-18), 5.35 (m, $W_{1/2}$ = 20 Hz, H-3), 5.00 (q, J = 18, 6 Hz, H-17)] and 3β-acetoxy-17,17-dibromo-*D*-homo-5α-androstan-17a-one (**12**, 62 mg) recrystallized from hexane [mp 170–174 °C; ν_{max} 1740 cm^{-1}; NMR τ 9.15 (CH_3-19), 8.72 (CH_3-18), 6.95 (m, $W_{1/2}$ = 16 Hz, H-16α and -16β), 5.27 (m, $W_{1/2}$ = 20 Hz, H-3)] (Anal. Calcd for $C_{22}H_{32}O_3Br_2$: C, 52.4; H, 6.4. Found: C, 52.6; H, 6.4) together with 50 mg of starting material.

3β-Acetoxy-*D*-homo-5α-androst-16-en-17a-one (15). A suspension of 70 mg of lithium carbonate and 400 mg of bromo ketone **11** in 6 ml of dimethylformamide was refluxed under nitrogen for 2 h. Addition of water, extraction, and PLC gave 250 mg of solid **15** as needles from acetone–hexane, mp 162–163 °C (lit.[8] 161–161.5 °C).

Dehydrobromination of 3β-Acetoxy-17,17-dibromo-*D*-homo-5α-androstan-17a-one (12). Treatment of the dibromo ketone (**12**, 50 mg) as in the previous experiment gave 3β-acetoxy-17-bromo-*D*-homo-5α-androst-16-en-17a-one (**13**) recrystallized from ethyl acetate (40 mg): mp 225–226 °C; NMR τ 9.20 (CH_3-19), 9.02 (CH_3-18), 5.40 (m, $W_{1/2}$ = 18 Hz, H-3), 3.20 (m, $W_{1/2}$ = 6 Hz, H-16). Anal. Calcd for $C_{22}H_{31}O_3Br$: C, 62.4; H, 7.4. Found: C, 62.4; H, 7.5.

When the reaction was prolonged to 18 h reflux time 100 mg of dibromo ketone **12** gave 56 mg of 3β-acetoxy-*D*-homo-5α-androst-14,16-dien-17a-one (**14**) recrystallized from acetone–hexane, mp 174–176 °C (lit.[8] 174–174.5 °C).

Hydrogenation of 3β-Acetoxy-17-bromo-*D*-homo-5α-androst-16-en-17a-one (13). The bromo enone (**13**, 40 mg), in 5 ml of glacial acetic acid containing 25 mg of Adams catalyst, was shaken in a hydrogen atmosphere for 30 min. Removal of catalyst and solvent gave 30 mg of acetoxy ketone **10** having identical IR and NMR spectra with the authentic sample.

***D*-Homo-5α-androst-17-ene-3β,16α-diol (17).** 3β-Acetoxy-*D*-homo-5α-androst-16-en-17a-one (**15**, 75 mg) dissolved in 5 ml of dioxane was treated with 5 ml of 20% sodium hydroxide solution and 5 ml of 35% hydrogen peroxide. After 15 min the starting acetoxy enone was consumed but a further 2 h completed the hydrolysis of the acetoxy group. Extraction gave 200 mg of 3β-hydroxy-*D*-homo-5α-androstan-16α,17α-oxido-17a-one (**16**) recrystallized from ethyl acetate: mp 157–160 °C; ν_{max} 3600, 1720, 1035, 900 cm^{-1}; NMR τ 9.20 (CH_3-19), 9.03 (CH_3-18), 6.81 (d, J = 4 Hz, H-17), 6.40 (m, $W_{1/2}$ = 22 Hz, H-3 and 16).

Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.4; H, 9.5. Found: C, 75.2; H, 9.2.

A mixture of 200 mg of epoxide **16** and 3 ml of hydrazine hydrate was heated to 130–140 °C for 35 min. Extraction gave 170 mg of diol **17**, recrystallized from acetone–hexane as needles: mp 191–195 °C;

ν_{max} 3600, 1630 cm^{-1}; NMR τ 9.17 (CH_3-18 and -19 superimposed), 6.40 (m, $W_{1/2}$ = 18 Hz, H-3), 5.83 (m, $W_{1/2}$ = 10 Hz, H-16), 4.47–4.37 (H-17 and H-17a, poorly resolved).

Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.9; H, 10.6. Found: C, 78.9; H, 10.6.

D-Homo-5α-androstane-3,16-dione (19). Jones oxidation of 165 mg of unsaturated diol **17** gave *D*-homo-5α-adrost-17-ene-3,16-dione (**18**, 160 mg) as needles: mp 197–202 °C from acetone–hexane; ν_{max} 1705, 1665 cm^{-1}; NMR τ 8.93 (CH_3-19), 8.90 (CH_3-18), 4.15 (d, J = 9 Hz, H-17), 3.33 (d, J = 9 Hz, H-17a).

Anal. Calcd for $C_{20}H_{28}O_2$: C, 80.0; H, 9.4. Found: C, 79.7; H, 9.2.

The enedione (150 mg) was hydrogenated in 12 ml of glacial acetic acid containing 50 mg of Adams catalyst. Filtration and evaporation gave 145 mg of the dione **19**, recrystallized from methanol: mp 171–172 °C; ν_{max} 1705 cm^{-1}; NMR τ 8.95 (CH_3-19), 8.93 (CH_3-18).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.4; H, 10.0. Found: C, 79.6; H, 10.0.

D-Homo-5α-androst-2-en-17a-one (21). *p*-Toluenesulfonyl chloride (600 mg) and 600 mg of 3β-hydroxy-*D*-homo-5α-androstan-17a-one (**1**) were allowed to stand overnight in 12 ml of pyridine. Dilution and extraction gave, after purification by PLC, 420 mg of the tosylate **20**: mp 168–169 °C recrystallized from methanol–chloroform; ν_{max} 1700 cm^{-1}; NMR τ 9.23 (CH_3-19), 8.93 (CH_3-18), 7.56 (CH_3-aromatic), 2.46 (4 H, broad, C_6H_4–).

Anal. Calcd for $C_{27}H_{38}O_4S$: C, 70.7; H, 8.4. Found: C, 70.9; H, 8.1.

A solution of 400 mg of tosylate in 15 ml of collidine was refluxed during 2 h. Dilution with water and extraction gave 240 mg of a gum which was purified with silica gel plates containing 20% silver nitrate, yielding 213 mg of enone **21**, recrystallized from methanol: mp 160–163 °C; ν_{max} 1700, 1655 cm^{-1}; NMR τ 9.23 (CH_3-19), 8.91 (CH_3-18), 5.48 and 4.40 (CH=CH, poorly resolved).

Anal. Calcd for $C_{20}H_{30}O$: C, 83.9; H, 10.6. Found: C, 83.5; H, 10.2.

2β,3β-Oxido-D-homo-5α-androstan-17a-one (23). To the enone (205 mg) in 20 ml of dioxane, 1 ml of water, and 0.5 ml of 10% perchloric acid was added 200 mg of freshly prepared *N*-bromosuccinimide. After stirring for 2 h, extraction and PLC gave 110 mg of bromohydrin **22** recrystallized from ethyl acetate–petroleum ether (bp 60–80 °C): mp 190–192 °C; ν_{max} 3595, 1700 cm^{-1}; NMR τ 9.01 (CH_3-19), 8.91 (CH_3-18), 5.71 (m, $W_{1/2}$ = 24 H, H-2 and -3).

Anal. Calcd for $C_{20}H_{31}O_2Br$: C, 62.7; H, 8.2. Found: C, 63.2; H, 8.4.

This bromohydrin (100 mg) and 250 mg of potassium hydroxide were stirred in 12 ml of methanol for 1 h. Extraction with ethyl acetate gave 88 mg of epoxide **23** recrystallized from aqueous acetone: mp 174–176 °C; ν_{max} 1698, 820 cm^{-1}; NMR τ 9.16 (CH_3-19), 8.92 (CH_3-18), 6.86 (m, poorly resolved, H-2 and -3).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.4; H, 10.0. Found: C, 79.5; H, 9.8.

D-Homo-5α-androstane-2,17a-dione (25). The epoxide (82 mg) and 100 mg of lithium aluminum hydride were refluxed under nitrogen in 10 ml of dry tetrahydrofuran for 8 h. Careful addition of water and extraction gave *D*-homo-5α-androstane-2β,17aβ-diol (**24**, 80 mg), as needles from ethyl acetate: mp 247–248 °C; NMR τ 9.20 (CH_3-18), 9.00 (CH_3-19), 6.76 (m, $W_{1/2}$ = 18 Hz, H-17a), 5.83 (m, $W_{1/2}$ = 8 Hz, H-2).

Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.4; H, 11.1. Found: C, 78.4; H, 10.8.

The diol (75 mg) was oxidized with Jones reagent to the dione **25** (70 mg) recrystallized from aqueous acetone: mp 169–171 °C; ν_{max} 1705 cm^{-1}; NMR τ 9.25 (3 H, d, J = 2 Hz, CH_3-19), 8.93 (CH_3-18).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.4; H, 10.0. Found: C, 79.3; H, 9.9.

Hydroboration of D-Homoandrost-5-en-3β-ol. Diborane generated from 1 g of lithium aluminum hydride and 4.8 ml of boron trifluoride etherate was passed into an ice-cooled solution of the Δ^5-3β-ol in 180 ml of dry ether during 6 h. Treatment with 100 ml of alkaline hydrogen peroxide during 1 h and extraction with ethyl acetate gave 2.3 g of a yellow solid which was chromatographed on 200 g of silica containing 8% water. Elution with 20% ethyl acetate–benzene gave 150 mg of *D*-homo-5α-androstan-3β-ol, 50% ethyl acetate–benzene gave 400 mg of a 1:1 mixture of *D*-homo-5α-androstane-3β,6β-diol and *D*-homo-5β-androstane-3β,6β-diol, and finally 70% ethyl acetate–benzene yielded *D*-homo-5α-androstane-3β,6α-diol (**26**, 1 g) recrystallized from acetone: mp 194–195 °C; ν_{max} 3600, 3450, 1030 cm^{-1}; NMR τ 9.19 (CH_3-19 and -18 superimposed), 6.50 (m, $W_{1/2}$ = 24 Hz, H-3 and -6).

Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.4; H, 11.1. Found: C, 78.5; H, 11.1.

Repetition of the reaction with 500 mg of Δ^5-3β-ol followed by treatment of the crude product with a large excess of Jones reagent for 15 min gave 600 mg of an oil which was separated by PLC into 6α-hydroxy-*D*-homo-5α-androstan-3-one (**31**, 172 mg) recrystallized from acetone [mp 145–148 °C; ν_{max} 3580, 3400, 1700 cm^{-1}; NMR τ 9.17 (CH_3-18), 9.00 (CH_3-19), 6.50 (m, $W_{1/2}$ = 16 Hz, H-6) (Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.9; H, 10.6. Found: C, 79.0; H, 10.5.)], *D*-homo-5α-androstane-3,6-dione (**30**, 128 mg) recrystallized from methanol [mp 200–203 °C; ν_{max} 1700 cm^{-1}; NMR τ 9.15 (CH_3-19), 9.06 (CH_3-18) (Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.4; H, 10.0. Found: C, 79.2; H, 10.0.)], and *D*-homo-5α-androstan-3-one (47 mg).

When the oxidation reaction time was extended to 1 h only the 3,6-dione **30** and *D*-homo-5α-androstan-3-one were obtained, and in separate experiments, treatment of 1.1 g of diol **26** and 150 mg of hydroxy ketone **31** with Jones reagent gave 1 g and 126 mg, respectively, of dione **30** having identical spectra.

Acetylation of D-Homo-5α- and -5β-androstane-3β,6β-diols. The diols (300 mg) were acetylated with acetic anhydride–pyridine under the usual conditions. Evaporation gave 270 mg of a mixture separated by PLC into 3β,6β-diacetoxy-*D*-homo-5α-androstane (**27**, 120 mg), a glass [mp 177–180 °C; ν_{max} 1730 cm^{-1}; NMR τ 9.15 (CH_3-18), 8.95 (CH_3-19), 5.29 (m, $W_{1/2}$ = 5 Hz, H-6), 4.97 (m, $W_{1/2}$ = 8 Hz, H-3) (Anal. Calcd for $C_{24}H_{38}O$: C, 73.8; H, 9.8. Found: C, 74.2; H, 10.0)], and 3β,6β-diacetoxy-*D*-homo-5β-androstane (**28**, 120 mg), an oil [ν_{max} 1730 cm^{-1}; NMR τ 9.15 (CH_3-18), 8.99 (CH_3-19), 5.29 (m, $W_{1/2}$ = 5 Hz, H-6), 4.97 (m, $W_{1/2}$ = 8 Hz, H-3) (Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.8; H, 9.8. Found: C, 74.0; H, 9.9.)].

D-Homo-5α-androstane-3β,6β-diol (29). Sodium borohydride (200 mg) was added to 100 mg of dione **30** in 10 ml of ethanol during 1 h. Dilution and extraction gave 98 mg of an oil which after PLC and recrystallization from acetone–hexane resulted in 90 mg of needles: mp 176–178 °C; ν_{max} 3600 cm^{-1}; NMR τ 9.16 (CH_3-18), 8.98 (CH_3-19), 6.34 (m, $W_{1/2}$ = 18 Hz, H-3), 6.28 (m, $W_{1/2}$ = 8 Hz, H-6).

Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.4; H, 11.1. Found: C, 78.0; H, 11.1.

Hydrolysis of diacetate **27** under standard conditions gave the same diol **29** by melting point and mixture melting point and having identical spectra.

3β-Acetoxy-D-homoandrost-5-en-7-one (34). Acetylation of 3β-hydroxy-*D*-homoandrost-5-ene (1.4 g) with acetic anhydride–pyridine and extraction gave 1.5 g of 3β-acetoxy-*D*-homoandrost-5-ene (**32**) from acetone: mp 150–153 °C; ν_{max} 1730 cm^{-1}; NMR τ 9.18 (CH_3-18), 8.98 (CH_3-19), 5.40 (m, $W_{1/2}$ = 15 Hz, H-3), 4.66 (m, $W_{1/2}$ = 7 Hz, H-6).

Anal. Calcd for $C_{22}H_{34}O_2$: C, 80.0; H, 10.4. Found: C, 79.8; H, 10.5.

To a solution of 1.3 g of acetate **32** in 100 ml of carbon tetrachloride heated to 80 °C was added 14.4 g of *tert*-butyl chromate, 4.5 ml of acetic acid, and 1.8 ml of acetic anhydride during 30 min. Refluxing was continued for 12 h. After cooling to 5 °C, 1.5 g of oxalic acid in 50 ml of water was added dropwise to the stirred solution, followed by 2.1 g of solid oxalic acid. After stirring for 2 h the layers were separated, and the aqueous layer further extracted with carbon tetrachloride. Evaporation of the combined organic phase gave 1.42 g of oil which was chromatographed on 120 g of silica gel. Elution with ethyl acetate–benzene (1:9) yielded 970 mg of 3β-acetoxy-*D*-homoandrost-5-en-7-one (**34**) from methylene chloride–acetone [mp 171–173 °C; ν_{max} 1730, 1670, 1640 cm^{-1}; NMR τ 9.17 (CH_3-18), 8.77 (CH_3-19), 5.31 (m, $W_{1/2}$ = 15 Hz, H-3), 4.30 (H-6) (Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.7; H, 9.4. Found: C, 76.4; H, 9.6.)], and ethyl acetate–benzene (2:3) gave 180 mg of 3β-acetoxy-5α-hydroxy-*D*-homoandrostan-6-one (**33**) from acetone [mp 290–292 °C; ν_{max} 3580, 3440, 1695 cm^{-1}; NMR τ 9.20 (CH_3-19 and CH_3-18), 5.00 (m, $W_{1/2}$ = 20 Hz, H-3); M^+ m/e 362 (Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.9; H, 9.5. Found: C, 72.5; H, 9.7.)].

D-Homo-5α-androstane-3,7-dione (37). A solution of 3β-acetoxy-*D*-homoandrost-5-en-7-one (**34**, 960 mg) in 30 ml of ethyl acetate and 15 ml of ethanol containing 250 mg of Adams catalyst was shaken in an atmosphere of hydrogen. Filtration and evaporation gave 860 mg of 3β-acetoxy-*D*-homo-5α-androstan-7-one (**35**) from methanol–water: mp 171–173 °C; ν_{max} 1730, 1700 cm^{-1}; NMR τ 9.18 (CH_3-18), 8.89 (CH_3-19), 5.31 (m, $W_{1/2}$ = 15 Hz, H-3).

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.3; H, 9.9. Found: C, 76.3; H, 9.8.

The acetate **35** (850 mg) was stirred with 860 mg of potassium hydroxide in 80 ml of methanol for 2 h. Dilution with water and extraction gave 690 mg of 3β-hydroxy-*D*-homo-5α-androstan-7-one (**36**) recrystallized from acetone–hexane: mp 174–177 °C; ν_{max} 3600, 1700 cm^{-1}; NMR τ 9.18 (CH_3-18), 8.91 (CH_3-19), 6.37 (m, $W_{1/2}$ = 18 Hz, H-3).

Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.9; H, 10.6. Found: C, 78.8; H, 10.5.

Treatment of 650 mg of hydroxy ketone **36** with Jones reagent gave

640 mg of dione **37** recrystallized from acetone–water: mp 180–183 °C; ν_{max} 1700 cm^{-1}; NMR τ 9.15 (CH_3-18), 8.73 (CH_3-19).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.4; H, 10.0. Found: C, 79.3; H, 10.1.

Reduction of Diones 3, 4, and 37. Standard conditions, as described in the third epxeriment, were employed in the reduction of the title ketones. The 3,17a-dione *3* (150 mg) gave *D*-homo-5α-androstane-3β,17aβ-diol (**38**, 135 mg) [mp 199–202 °C (lit.[4] 219–220 °C; NMR τ 9.18 (CH_3-19 and CH_3-18), 6.80 (m, $W_{1/2}$ = 14 Hz, H-17a), 6.50 (m, $W_{1/2}$ = 24 Hz, H-3)], and 350 mg of the 3,17-dione **4** gave after separation on PLC *D*-homo-5α-androstane-3β,17β-diol (**39**, 155 mg) from acetone–hexane [mp 220–222 °C; ν_{max} 3600 cm^{-1}; NMR τ 9.20 (CH_3-19), 8.93 (CH_3-18), 6.30 (m, $W_{1/2}$ = 18 Hz, H-3), 6.00 (m, $W_{1/2}$ = 8 Hz, H-17) (Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.4; H, 11.1. Found: C, 78.0; H, 11.0.)] together with 65 mg of *D*-homo-5α-androstane-3β,17α-diol (**40**) from acetone–hexane: mp 176–178 °C; ν_{max} 3600 cm^{-1}; NMR τ 9.20 (CH_3-19 and CH_3-18), 6.50–6.00 (H-3 and H-17) (Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.4; H, 11.1. Found: C, 78.2; H, 11.3.). Finally 130 mg of 3,7-dione **37** gave *D*-homo-5α-androstane-3β,7α-diol (**41**, 90 mg) recrystallized from methanol: mp 205–208 °C; ν_{max} 3600 cm^{-1}; NMR τ 9.20 (CH_3-19), 9.19 (CH_3-18), 6.37 (m, $W_{1/2}$ = 18 Hz, H-3), 6.00 (m, $W_{1/2}$ = 8 Hz, H-7) (Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.4; H, 11.1. Found: C, 77.9; H, 11.1.).

Registry No.—**1**, 26729-16-8; **2**, 51057-15-9; **3**, 61231-79-6; **4**, 20377-71-3; **5**, 61258-86-4; 71aα-**6**, 61231-80-9; 17aβ-**6**, 61277-41-6; 17aα-**7**, 61249-41-0; 17aβ-**7**, 61231-81-0; 17aα-**8**, 61231-82-1; 17aβ-**8**, 61231-83-2; **9**, 30040-16-5; **10**, 26729-18-0; **11**, 61277-42-7; **12**, 61231-84-3; **13**, 29172-67-6; **15**, 29172-56-3; **16**, 61231-85-4; **17**, 61231-86-5; **18**, 61231-87-6; **19**, 61231-88-7; **20**, 61231-89-8; **21**, 60243-73-4; **22**, 61231-90-1; **23**, 61231-91-2; **24**, 61231-92-3; **25**, 61231-93-4; **26**, 61231-94-5; **27**, 61231-95-6; **28**, 61231-96-7; **29**, 61231-97-8; **30**, 61231-98-9; **31**, 61231-99-0; **32**, 31552-74-6; **33**, 61232-00-6; **34**, 61232-01-7; **35**, 61232-02-8; **36**, 61232-03-9; **37**, 61232-04-0; **38**, 60269-01-4; **39**, 61232-05-1; **40**, 61232-06-2; **41**, 61232-07-3; benzaldehyde, 100-52-7; acetic anhydride, 108-24-7; *p*-toluenesulfonyl chloride, 98-59-9; 3β-hydroxy-*D*-homoandrost-5-ene, 31552-60-0; *D*-homo-5α-androstane-3β,6β-diol, 61231-97-8; *D*-homo-5β-androstane-3β,6β-diol, 61232-08-4; oxalic acid, 144-62-7.

References and Notes

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(2) L. E. Contreras, J. M. Evans, D. de Marcano, L. Marquez, M. Molina, and L. Tempestini, *J. Org. Chem.*, **39**, 1550 (1974).
(3) R. F. Zurcher, *Helv. Chim. Acta*, **46**, 2045 (1963).
(4) M. W. Goldberg and E. Wydler, *Helv. Chim. Acta*, **20**, 1142 (1943); N. L. Wendler, D. Taub, and H. L. Slates, *J. Am. Chem. Soc.*, **77**, 3559 (1955).
(5) D. N. Kirk and M. A. Wilson, *J. Chem. Soc. C*, 414 (1971).
(6) J. E. Bridgeman, C. E. Butchers, E. R. H. Jones, A. Kasal, G. D. Meakins, and P. D. Woodgate, *J. Chem. Soc. C*, 244 (1970).
(7) H. Powell, D. H. Williams, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **86**, 2623 (1964).
(8) T. Nambara, S. Iwamura, and K. Shimada, *Chem. Pharm. Bull.*, **23**, 1834 (1975).
(9) E. R. H. Jones, G. D. Meakins, J. Pragnell, W. E. Muller, and A. L. Wilkins, *J. Chem. Soc., Perkin Trans. 1*, 2376 (1974).
(10) F. J. Hammerschmidt and G. Spiteller, *Tetrahedron*, **29**, 3995 (1973).
(11) D. A. Parins and C. W. Shoppe, *J. Chem. Soc.*, 494 (1946).

A New Synthesis of the Pyrrolizidine Alkaloids (±)-Isoretronecanol and (±)-Trachelanthamidine[1]

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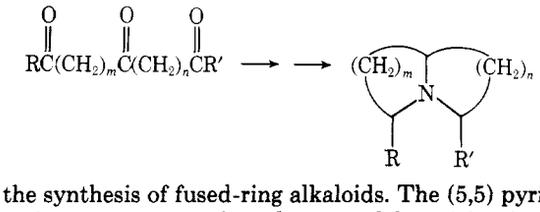
The pyrrolizidine alkaloids (±)-isoretronecanol (**1a**) and (±)-trachelanthamidine (**1b**) were synthesized using as a key step the oxidation of a carbon–carbon double bond and subsequent in situ reductive amination with sodium cyanoborohydride. 2-Carbethoxycyclohept-4-en-1-one (**2b**) was synthesized via three independent routes and was utilized as the key intermediate. Ozonolysis followed by reduction of the ozonide and reaction with NH_4NO_3–$NaBH_3CN$ afforded carbethoxypyrrolizidines **5a** and **5b** in 7% yield along with pyrrole **6** in 14% yield. Reductive amination of **2b** to give amino esters **6a** and **6b** followed by OsO_4–$NaIO_4$ oxidation and $NaBH_3CN$ reductive cyclization gave **4a** and **4b** in 35% yield. Reduction of **4a** and **4b** with $LiAlH_4$ gave the alkaloids (±)-isoretronecanol (**1a**) and (±)-trachelanthamidine (**1b**), respectively.

The reaction of aldehydes and ketones with an amine and sodium cyanoborohydride ($NaBH_3CN$) has been described as a general method for the synthesis of substituted amines,[2,3] and it has been applied to the formation of nitrogen-containing rings in alkaloid syntheses.[4,5] We were interested to know whether this method could be generalized to the insertion of nitrogen via reductive amination into an acyclic tricarbonyl compound, viz.



for the synthesis of fused-ring alkaloids. The (5,5) pyrrolizidine ring system was selected as a model, anticipating that intramolecular reactions in a polyfunctional acyclic precursor would be maximized for the five-membered rings. We report here a successful example of this synthetic approach applied to (±)-isoretronecanol (**1a**)[6] and (±)-trachelanthamidine (**1b**).[7]

Results and Discussion

The synthesis was based on β-keto ester **2b** as the key intermediate, inasmuch as appropriate oxidation of the olefin would provide the necessary keto dialdehyde with which to test the reductive cyclization reaction. The diastereomeric pyrrolizidines thus formed would contain the requisite substituent for facile reduction to **1a** and **1b**. Cyclohept-4-en-1-one (**2a**) was prepared by two separate routes based on published procedures.[8–12] However, the relative complexity and poor overall yields from these routes prompted investigation of a more direct route to β-keto ester **2b** utilizing the alkylation of a β-keto ester dianion.[13] Reaction of the dianion of methyl acetoacetate[13] with excess 1,4-dichloro-*cis*-2-butene[14] in THF at 0 °C afforded a 25% yield of monoalkylated product **3**. Cyclization of keto ester **3** by gradual addition over