Anal. Calcd for $C_{20}H_{29}NO_3$: C, 72.47; H, 8.82; N, 4.23. Found: C, 72.61; H, 9.02; N, 4.21.

1,2,5,5-Tetramethyl-2,10-dihydroxy-1,2,3,4,4a,10b-hexahydro-8-*n*-amyl-*trans*-5*H*-[1]benzopyrano[4,3-*b*]pyridine (26). Methylmagnesium bromide (2 ml of a 3 *M* solution in Et_2O, 6 mmol) was added slowly to a solution of **25** (332 mg, 1 mmol) in THF (10 ml). The solution was heated at reflux for 24 hr. The solution was cooled to 0° before addition of saturated aqueous NH_4Cl (10 ml). The organic phase was separated and the aqueous phase was washed with Et_2O (2 × 10 ml). Evaporation of solvent from the combined organic layers left a semisolid residue which was triturated with Et_2O (2 ml). The colorless carbinolamine (49 mg, 14%) was filtered and washed with H_2O (2 × 1 ml) and Et_2O (1 ml): mp 101° dec; nmr ($CDCl_3$) δ 6.23 (d, J = 1 Hz, 1 aromatic), 6.18 (d, J = 1 Hz, 1 aromatic), 4.67 (br, H_A), 2.47 (br t, benzylic CH_2), 2.25 (s, NCH_3), 2.15–1.05 (br, H_B, $COCH_2CH_2$, 6 amyl methylene), 1.58 (s, C-2 CH_3), 1.38 (s, C-5 CH_3), 1.17 (s, C-5 CH_3), 0.88 (br t, terminal CH_3); electron impact mass spectrum *m/e* (rel intensity) 329 ($M^+ - H_2O$, 98), 328 (12), 315 (23), 314 (88), 301 (19), 283 (18), 259 (13), 243 (15), 232 (12), 231 (69), 174 (19), 150 (22), 84 (100).

Anal. Calcd for $C_{21}H_{33}NO_3$: C, 72.58; H, 9.57; N, 4.03. Found: C, 72.85; H, 9.81; N, 4.24.

Evaporation of solvent from the filtrate left the crude enamine **27** (199 mg, 60%) as a light amber oil.

1,2,5,5-Tetramethyl-1,4,4a,10b-tetrahydro-8-*n*-amyl-10-hydroxy-*trans*-5*H*-[1]benzopyrano[4,3-*b*]pyridine (27). Methylmagnesium bromide (10 ml of a 3 *M* solution in Et_2O, 30 mmol) was added slowly to a solution of **25** (1.66 g, 5 mmol) in THF (50 ml). The solution was heated at reflux for 24 hr. The clear solution was cooled to 0° before addition of saturated aqueous NH_4Cl (50 ml). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 × 50 ml). Evaporation of solvent from the combined, dried (Na_2SO_4) organic phases left a semisolid residue (1.65 g), which was dissolved in CH_2Cl_2 (50 ml). The solution was stirred over molecular sieves (3A, 10 g), for 4 hr. The sieves were filtered off and washed with CH_2Cl_2 (10 ml). Evaporation of solvent from the filtrate left the enamine as a light amber oil (1.34 g, 81%). The analytical sample was evaporatively distilled at 108° (0.1 mm): $n^{24}D$ 1.5379; ir (thin film) 1660 cm^{-1} (enamine C=C); nmr ($CDCl_3$) δ 6.28 (d, J = 1.5 Hz, 1 aromatic), 6.23 (d, J = 1.5 Hz, 1 aromatic), 5.05 (m, H_E, $t_{1/2}$ for D_2O exchange *ca.* 11 hr), 3.92 (d, J = 10 Hz, H_A), 2.49 (br t, benzylic CH_2), 2.25 (s, NCH_3), 1.99 (m, $H_{B,C,D}$), 1.84 (s, C-2 CH_3, $t_{1/2}$ for D_2O exchange *ca.* 40 min), 1.72–1.17 (m, 6 H, amyl methylene), 1.40 (s, C-5 CH_3), 1.13 (s, C-5 CH_3), 0.89 (br t, terminal CH_3); electron impact mass spectrum *m/e* (rel intensity) 329 (88), 328 (13), 315 (19), 314 (70), 301 (10), 300 (22), 283 (14), 259 (15), 243 (13), 232 (12), 231 (68), 174 (19), 150 (22), 84 (100).

Anal. Calcd for $C_{21}H_{31}NO_2$: C, 76.55; H, 9.48; N, 4.25. Found: C, 76.64; H, 9.34; N, 4.26.

1,2,5,5-Tetramethyl-1,2,3,4,4a,10b-hexahydro-8-*n*-amyl-1-hydroxy-*trans*-5*H*-[1]benzopyrano[4,3-*b*]pyridine (4 and 5). A solution of the enamine **27** (637 mg, 1.93 mmol) in acetic acid (90 ml) was hydrogenated over 5% Pd/C (150 mg) at 35 psi for 24 hr. The catalyst was filtered off and the solvent was sublimed at 16° (0.1 mm) from the frozen solution; aqueous 5% NaOH (30 ml) and Et_2O were added to the residue. The organic layer was separated and the aqueous layer was extracted with Et_2O (30 ml). Evaporation of solvent from the combined, dried (Na_2SO_4) organic layers left a diastereomeric mixture of amines **4** and **5** as an oil (537 mg, 84%). The ratio of major to minor diastereomer was 3:1 (by nmr). Recrystallization from MeOH (2 ml) gave a solid (380 mg, mp 72–81°). The ratio of major to minor diastereomer in the solid was 6:1 (by nmr). On glpc analysis (3% SE-30 on Chromosorb W, 155°, 37 ml/min), the solid produced two peaks with retention times of 42.5 (minor) and 45.0 min (major). When subjected to glpc–mass spectrum, these glpc peaks corresponded to the following mass spectra: minor diastereomer *m/e* (rel intensity) 331 (100), 316 (38), 314 (19), 285 (19), 275 (35), 260 (19), 259 (92), 245 (37), 231 (67); major diastereomer *m/e* (rel intensity) 331 (99), 316 (38), 314 (22), 285 (22), 275 (27), 260 (22), 259 (100), 245 (36), 231 (60); high resolution chemical ionization mass spectrum, 322.2581 (calcd for $C_{21}H_{34}NO_2$, 322.2589).

Registry No.—**4**, 51014-90-5; **5**, 51064-86-9; **6**, 22976-40-5; **8**, 3410-84-2; **9**, 51015-16-8; **10**, 51014-91-6; **11**, 51014-92-7; **14**, 51014-93-8; **16**, 51014-94-9; **18**, 51014-95-0; **19**, 51014-96-1; **20**, 51014-97-2; **22**, 51014-98-3; **24**, 51014-99-4; **25**, 51015-00-0; **26**, 51015-17-9; **27**, 51015-01-1; olivetol, 500-66-3.

References and Notes

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(11) The major impurity was the monomethyl ether, present in *ca.* 20% yield (by nmr).

D-Homoandrostanes. I. Preparation and Properties of *D*-Homo-5α-androstan-1-, -2-, -3-, and -4-ones[1a]

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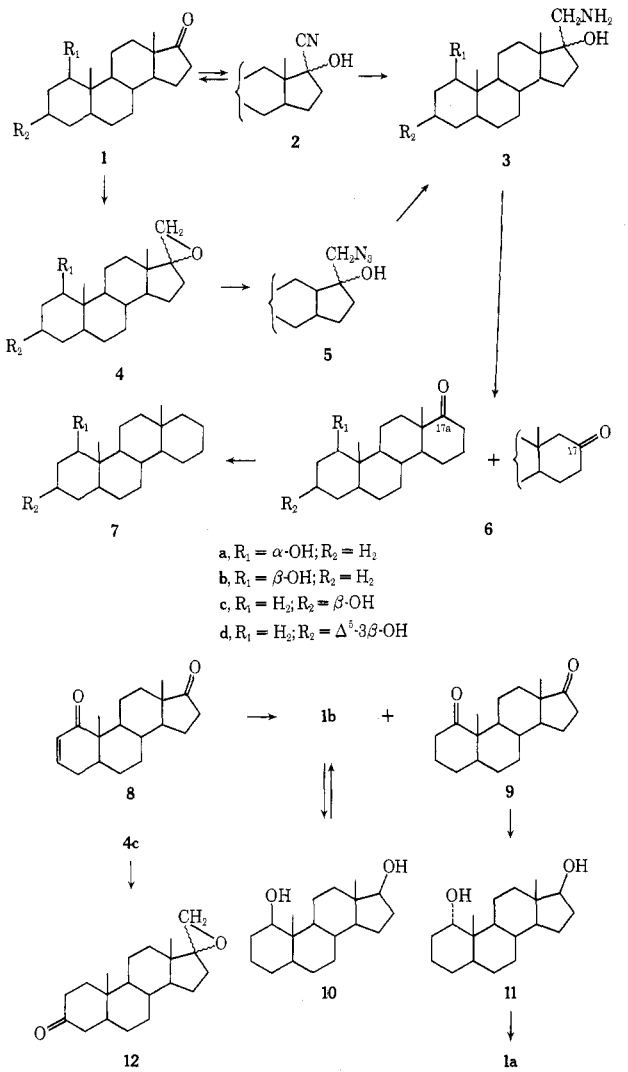
The synthesis of the four *D*-homo ketones from commercially available 17-oxo steroids is described. A key step in an alternate synthesis of the 1-ketone is a selective silver carbonate oxidation of a 17β-hydroxyl group in the presence of 1-hydroxyl groups in the 5α-androstane series. Sodium borohydride reduction of the ketones gives similar results to the analogs, while the almost exclusive 1α-alcohol formation can be explained in terms of "steric intermediate control."

Previous studies on monofunctional *D*-homoandrostanes have been concerned with those possessing functional groups in the expanded terminal ring.[2] In connection with other work we required the title compounds, thus excluding many *D*-homo rearrangements[3] as potential synthetic methods, as the products contain undesired groupings, such as alkyl groups, in the D ring. The earlier method[4] of expanding androstan-17-ones (**1**) has several disadvantages, discussed previously,[5] such as the reversible formation of cyanohydrins **2**, using potentially hazardous cya-

Scheme I



nides, and the difficulties encountered in their reduction to hydroxyamines **3**. Kirk and Wilson[5] also reported a more convenient synthesis *via* C(17)-spirooxiranes **4** and hydroxy azides **5**, which we have adopted in our preparation of the desired ketones.

Although the spirooxiranes **4**, formed from the 17-keto compounds **1**, were used directly for the subsequent step, an attempt was made to determine the epimeric composition of the oxiranes **4c** spectrographically, but overlapping of the methyl signals in the nmr necessitated an oxidation of the 3β-hydroxyl group under basic conditions[6] to the epoxy ketone **12**, in which it was estimated that the β-spirooxirane predominated in the ratio 3:1. The conversion of the 1-hydroxy 17-ketones **1a** and **b** could not be achieved even by prolonged contact with an excess of reagents. The reasons for this are not clear; in other work[7] we found that 5α-androstan-17-one could not be converted completely. The most reproducible method of reducing the hydroxyazides **5** utilized zinc–hydrochloric acid, but, in one case of extended reaction time with zinc–acetic acid and **5d**, copious amounts of *D*-homo ketones were obtained together with hydroxyamine **3d** (Scheme I).

Huang-Minlon reduction and subsequent oxidation of 3β-hydroxy-*D*-homo-5α-androstan-17A- and -17-one (**6c**) gave *D*-homo-5α-androstan-3-one (**13**).

Like the 3-ketone, *D*-homo-5α-androstan-1-one (**18**) was obtained by the same process from the ring expanded products, **6a** and **b**, derived from 1α- (**1a**) or 1β-hydroxy-5α-androstan-17-one (**1b**), the preparation of which we described in an earlier communication.[8] The ease of selective oxidation[9] of the 17-hydroxyl group in 5α-androstane-1α,17β-diol (**11**), prompted us to test it on the 1β,17β-diol (**10**) where it proceeded smoothly.[10]

At the same time we considered obtaining the 1-ketone from the 3-ketone by the established procedures[11] (**7c** → **18**). We were unable to convert the Δ^2-1α-ol **16** directly into the desired ketone by hydrogenation with 10% palladium on charcoal; the Δ^2-1,17-dione **8** likewise was unchanged under the same conditions. As in the androstane series (**8** → **1b** + **9**),[8] the oxidation product **17** of the Δ^2-1α-ol was hydrogenated, forming a 1:1 mixture of *D*-homo-5α-androstan-1-one (**18**) and the corresponding 1β-alcohol **7b** (Scheme II). Although variation in quantity of catalyst and reaction time did not lead to increased alcohol formation, it appears to be one of the few methods of obtaining reasonable amounts of 1β-orientated alcohols.

The available methods of converting 3- to 2-keto steroids have been summarized recently by authors[12] interested in the transposition of oxo groups with adjacent methylene groups. The intermediates were not purified until the final stages of the synthesis (**19** → **23**), which is an alternative to that previously reported,[13] where the 3-acetoxy 2-ketone **22** was obtained directly from 2α-acetoxy-*D*-homo-5α-androstan-3-one.

The first objective in the synthesis of *D*-homo-5α-androstan-4-one (**29b**) was *D*-homoandrost-4-ene (**27**), and, although lithium aluminum hydride–aluminum chloride has been used for the reduction of androst-4-en-3-one,[14] conversion to the thioketal **26** and desulfurization with sodamide in liquid ammonia was more effective. Hydroboration of **27** gave an alcohol mixture **28**, which was oxidized directly to a mixture of **29b** and the 5β-epimer **29a**, the former predominating as in the normal series.[15]

Scheme II

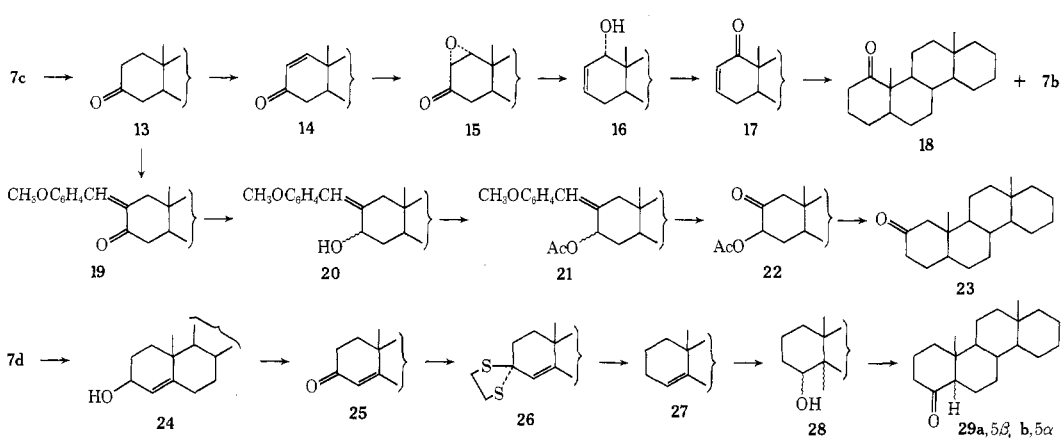


Table I
Borohydride Reduction Products (%) from D-Homo Ketones: Comparison with Normal Series

Ketone position	D-Homo alcohol		Androstane series		Ref
	Axial	Equatorial	Axial	Equatorial	
1	*ca.* 100	None detected	*ca.* 100	None detected	
2	66	34	68	32	*a*
3	20	80	14	86	*b*
4	83	17	90	10	*a*

[a] I. M. Clark, A. S. Clegg, W. A. Denny, E. R.H. Jones, G. D. Meakins, and A. Pendlebury, *J. Chem. Soc. Perkin Trans.*, 499 (1972). [b] Cholestane series: O. H. Wheeler and J. L. Mateos, *Can. J. Chem.*, **36**, 1049 (1958).

Reduction of the Title Ketones. The results of borohydride reduction are presented in Table I; those for the 2-, 3-, and 4-ketones are very similar to the values for the normal series. It is interesting to compare the metal hydride reduction of 1-ketones with the similarly situated *D*-homo 17A-ketones which yield the more stable 17Aβ-alcohol as the major product.[2b] Inspection of models indicates that the only appreciable difference between the surroundings of the two carbonyl groups is the close proximity of C(11) to C(1). Since reagent approach occurs from the α side of the molecule in the 17A-ketone, then it should approach from that side in the 1-ketone, as access is even more limited on the β side by the C(11) hydrogens. That the reagent evidently attacks from the β face must be due to steric compression between the 11α hydrogen and any bulky borohydride–carbonyl complex as it is forced into the 1β position. Hence a less desirable approach from the β direction is aided by the relative ease with which the intermediate complex can assume the 1α configuration. Thus the 1-ketone is a special case, in which the controlling factor is not "steric approach control"[16] but rather what we term "steric intermediate control."

Experimental Section[17]

Melting points determined with a Reichert apparatus are uncorrected. Infrared spectra were obtained as chloroform solutions with a Perkin-Elmer 257. Nmr spectra were run on a Varian S-60T, as deuteriochloroform solutions containing tetramethylsilane. Singlets are undesignated but the notation d = doublet, t = triplet, q = quartet, sx = sextet, m = multiplet is used to describe the multiplicity of more complex signals, and $W_{1/2}$ = width at half peak height. Thin layer chromatography, tlc, and preparative layer chromatography, plc, employed Camag silica gel type D, in thicknesses of 0.25 and 1 mm, respectively. In plc the samples were applied by an automatic applicator,[18] in amounts of 50 to 80 mg per 20 × 20 cm plate, and developed with mixtures of acetone–petroleum ether or ethyl acetate–benzene. The products isolated are described in order of increasing polarity. The elemental analyses were obtained with a Hewlett-Packard 185B, or determined by Dr. F. B. Strauss, Oxford. "Extraction" indicates chloroform extraction, followed by washing with sodium carbonate solution where appropriate, drying, etc., unless otherwise indicated.

5α-Androstane-1α,17β-diol (11) and 5α-Androstane-1β,17β-diol (10). 5α-Androstane-1,17-dione (**9**,[19] 174 mg) was stirred with 150 mg of sodium borohydride in 10 ml of methanol for 1 hr. Addition of water and extraction gave the diol **11** (163 mg): nmr τ 9.25 (CH_3-18), 9.18 (CH_3-19), 6.30 (m, $W_{1/2}$ = 12 Hz, H-1, H-17 overlapped).

The 1β-hydroxy 17-ketone[8] **1b** (50 mg) was treated similarly with 42 mg of sodium borohydride in 3 ml of methanol giving the 1β,17β-diol (47 mg): mp 186–188° from acetone–hexane; ν_{max} 3610 cm^{-1}; nmr τ 9.25 (CH_3-18), 9.14 (CH_3-19), 6.63 (q, J = 10, 5 Hz, H-1), and 6.37 (t, J = 8, 8 Hz, H-17) overlapped.

Anal. Calcd for $C_{19}H_{32}O_2$: C, 78.0; H, 11.0. Found: C, 78.2; H, 11.1.

1α-Hydroxy-5α-androstan-17-one (1a) and 1β-Hydroxy-5α-androstan-17-one (1b). The crude diol **11** (160 mg) was refluxed with 8.5 g of silver carbonate on Celite[9] in 25 ml of dry toluene for 1 hr, the reaction being monitored by tlc. Filtration of insoluble material, which was washed with acetone, and evaporation gave an oil which was separated by plc into the diketone **9** (10 mg), and hydroxy ketone **1a** (112 mg), mp[8] 152–153°.

Similarly the diol **10** (30 mg) was refluxed with 1.5 g of silver carbonate on Celite in 10 ml of toluene for 30 min giving the hydroxy ketone **1b** (22 mg), mp 168°, undepressed on admixture with the hydrogenation product of the endione **8**.[8]

Ring A Hydroxy-D-homoandrostan-17A- and -17-ones 6. Sodium hydride (50% in oil, 12 g) was washed with dry benzene, and added in portions to a stirred suspension of 25 g of trimethyloxosulfonium iodide in 120 ml of dimethylformamide under nitrogen. After hydrogen evolution, 10 g of 3β-hydroxy-5α-androstan-17-one (**1c**) was added and stirring continued until tlc analysis by green spot formation in iodine vapor, and the lack of carbonyl absorption in the ir, indicated completion of the reaction. Addition of water and extraction with ethyl acetate gave a quantitative yield of solid spirooxiranes **4c**: ν_{max} 3600, 3420, 1023 cm^{-1}; nmr τ 9.16 (CH_3-19 and CH_3-18 of 17α-oxirane), 9.11 (CH_3-18 of 17β-oxirane), 7.43 and 7.13 (2d, J = 5 Hz, H-20), 6.45 (m, $W_{1/2}$ = 24 Hz, H-3).

Spirooxirane **4d** was similarly prepared in ca. 98% yield, from 10 g of **1d**, while conversions of 132 mg of **1a** and 167 mg of **1b** resulted in yields of *ca.* 70%, due to incomplete reaction, subsequent separation of product from starting material by plc, and recyclization. **4a**: nmr τ 9.16 (CH_3-19 and CH_3-18 of 17α-epoxide), 9.10 (CH_3-18, β-epoxide), 7.40 and 7.10 (2d, J = 5 Hz, H-20), 6.30 (m, $W_{1/2}$ = 7 Hz, H-1). **4b**: nmr τ 9.17 (CH_3-18, α-epoxide), 9.14 (CH_3-19), 9.10 (CH_3-18, β-epoxide), 7.43 and 7.10 (2d, J = 5 Hz, H-20), 6.61 (m, $W_{1/2}$ = 18 Hz, H-1). **4d**: ν_{max} 3600, 1615, 1050 cm^{-1}; nmr τ 9.09 (CH_3-19), 8.95 (CH_3-18), 7.30 and 6.90 (2d, J = 5 Hz, H-20), 6.50 (m, $W_{1/2}$ = 20 Hz, H-3), 4.63 (m, $W_{1/2}$ = Hz, H-6).

The spirooxiranes **4c** (10 g) were heated at reflux temperature with 10 g of sodium azide and 10 g of boric acid for 4.5 hr. Dilution with water and extraction with ethyl acetate gave a 98% yield of hydroxy azide **5c**. The hydroxy azides **5a, b,** and **d** were similarly prepared. All showed the characteristic azide absorption ν_{max} 2100 cm^{-1}.

The crude hydroxy azide **5c** obtained in the above reaction was dissolved in 150 ml of acetone and 50 ml of concentrated hydrochloric acid, and zinc powder was added in small portions until nitrogen evolution had ceased. The remaining zinc was filtered out and washed with acetone. The combined filtrate and washings were diluted with 500 ml of water and extracted with ether to remove neutral components. The stirred layer was cooled to below 5° and 24 g of sodium nitrite added in portions. The solution was kept at this temperature overnight, before extraction gave 7.3 g of 3β-hydroxy-*D*-homo-5α-androstan-17A- and -17-ones (**6c**): ν_{max} 3600, 1700 cm^{-1}; nmr τ 9.19 (CH_3-19), 8.90 (CH_3-18), 6.42 (m, $W_{1/2}$ = 22 Hz, H-3). Similarly obtained, with corresponding quantities, were 3β-hydroxy-*D*-homoandrost-5-en-17A- and -17-ones (**6d**) [ν_{max} 3600, 1695, 1615 cm^{-1}; nmr τ 8.99 (CH_3-19), 8.87 (CH_3-18), 6.42 (m, $W_{1/2}$ = 19 Hz, H-3), 4.67 (m, $W_{1/2}$ = 8 Hz, H-6) in comparable yield to **6c**], 1β-hydroxy-*D*-homo-5α-androstan-17A- and -17-ones (**6b**, 26 mg) [ν_{max} 1710 cm^{-1}; nmr τ 8.93 (CH_3-18), 9.15 (CH_3-19), 6.53 (m, $W_{1/2}$ = 16 Hz, H-1)], and 1α-hydroxy-*D*-homo-5α-androstan-17A- and -17-ones (**6a**, 29 mg) [ν_{max} 1712 cm^{-1}; nmr τ 9.15 (CH_3-18), 9.01 (CH_3-19), 6.30 (m, $W_{1/2}$ = 5 Hz, H-1)].

17,20-Epoxy-21-nor-17-norpregnan-3-ones (12). A standard Sarrett reaction converted **4c** (1 g) into the epoxy ketones **12** (870 mg): ν_{max} 1710, 1050 cm^{-1}; nmr τ 9.14 (CH_3-18 of α-epoxide), 9.07 (CH_3-18 of β-epoxide), 8.94 (CH_3-19), 7.37 and 7.13 (2d, J = 5 Hz, H-20).

Huang-Minlon Reduction of Hydroxy Ketones 6. The usual reaction conditions were used to convert hydroxy ketone **6a** (24 mg) to *D*-homo-5α-androstan-1α-ol (**7a**, 16 mg), hydroxy ketone **6b** (24 mg) to *D*-homo-5α-androstan-1β-ol (**7b**, 17 mg), and hydroxy ketone **6c** (4 g) to *D*-homo-5α-androstan-3β-ol (2.3 g). (See Table II for properties.) Similarly the enol **7d**, recrystallized from methanol (1.8 g), mp 137–138° (lit.[5] 137–139°), was obtained from hydroxy ketone **6d** (2.2 g).

***D*-Homo-5α-androstan-3-one (13).** Oxidation of the 3β-alcohol **7c** (2.2 g) by Jones reagent gave 2.15 g **13**, recrystallized from methanol: mp 167–168° (lit.[20] 168.5–170°); ν_{max} 1700 cm^{-1}; nmr τ 9.14 (CH_3-18), 8.98 (CH_3-19).

***D*-Homoandrost-1-en-3-one (14).** Bromine (284 mg) dissolved in 2 ml of glacial acetic acid was added dropwise to a stirred solution of 445 mg of 3-ketone **13** in 6 ml of acetic acid and 3 drops of

Table II[a]

Registry no.		Anal. found, % C	Anal. found, % H	Mp, °C	C-19	C-18	Nmr, τ, H-C-OH	$W_{1/2}$, Hz
				Alcohol				
51056-93-0	1α	83.0	11.6	128–129	9.22	9.18	6.30	6
51056-94-1	1β	82.7	11.6	109–112	9.18	9.17	6.60	13
51064-96-1	2α	82.6	12.0	145–148	9.21	9.19	6.33	22
51056-95-2	2β	82.9	11.8	153–154	8.98	9.17	5.84	8
51056-96-3	3α			171–174[b]	9.17	9.22	5.97	7
51056-97-4	3β			141–144[c]	9.19	9.19	6.40	24
51056-98-5	4α	82.6	11.9	167–169	9.20	9.19	6.60	18
51056-99-6	4β	82.4	11.5	123	8.95	9.20	6.20	6
				Acetate				
51108-11-3	1α	79.7	10.7	65–67	9.16	9.19	5.16	5
51057-00-2	1β	79.7	10.7	51–52	9.07	9.21	5.40	10
51057-01-3	2α	79.6	11.0	89–91	9.18	9.18	5.16	18
51057-02-4	2β	79.7	11.0	80–81	9.07	9.19	4.93	9
51057-03-5	3α	79.8	11.0	98–104	9.21	9.17	5.00	7
51064-97-2	3β	79.8	10.9	113–117	9.18	9.18	5.31	24
51057-04-6	4α	79.7	10.7	150–153	9.16	9.18	5.24	22
51057-05-7	4β	79.5	10.9	133–135	8.98	9.19	5.10	4

[a] Calcd for $C_{20}H_{34}O$: C, 82.7; H, 11.8, and $C_{22}H_{36}O_2$: C, 79.5; H, 10.9. Acetate protons appear at *ca.* τ 8.0. [b] Lit.[20] mp 168–169°. [c] Lit.[20] mp 143.5°.

48% hydrobromic acid; dilution with water and extraction left 481 mg of a gum which was refluxed in 10 ml of dimethylformamide with 300 mg of lithium carbonate–lithium bromide. Addition of water and extraction gave a gum. Purification by plc yielded **14** (210 mg), recrystallized from methanol: mp 135–138°; ν_{max} 1670 cm^{-1}; nmr τ 9.13 (CH_3-18), 8.97 (CH_3-19), 4.18 (d, J = 10 Hz, H-1), 2.99 (d, J = 10 Hz, H-2).

Anal. Calcd for $C_{20}H_{30}O$: C, 83.9; H, 10.6. Found: C, 83.8; H, 10.6.

1α,2α-Oxido-*D*-homo-5α-androstan-3-one (15). The Δ^1-3-ketone (200 mg), in 5 ml of dioxane was treated with 5 ml of 5% sodium hydroxide solution, and 3 ml of 35% hydrogen peroxide. After 3 hr the solution was diluted with water and extracted continuously giving after plc, 191 mg of white solid, recrystallized from methanol: mp 132–135°; ν_{max} 1710, 875 cm^{-1}; nmr τ 9.14 (CH_3-18 and -19 superimposed), 6.80 (d, J = 4 Hz, H-2), 6.47 (d, J = 4 Hz, H-1).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.4; H, 10.0. Found: C, 79.2; H, 9.9.

D-Homo-5α-androst-2-en-1α-ol (16). A mixture of 156 mg of epoxide **15** in 3 ml of hydrazine hydrate was heated at 135° for 35 min. Dilution with water and extraction gave 152 mg of solid recrystallized from methanol: mp 96–97°; ν_{max} 3605, 1610 cm^{-1}; nmr τ 9.29 (CH_3-19), 9.17 (CH_3-18), 6.30 (m, $W_{1/2}$ = 7 Hz, H-1), 4.20 (2d superimposed, J = 3 Hz, H-2, and H-3).

Anal. Calcd for $C_{20}H_{32}O$: C, 83.3; H, 11.2. Found: C, 83.6; H, 10.9.

D-Homo-5α-androst-2-en-1-one (17). Oxidation of allylic alcohol **16** (130 mg) with Jones reagent gave the enone **17**, recrystallized from methanol (123 mg): mp 106–108°; ν_{max} 1673 cm^{-1}; nmr τ 9.15 (CH_3-18), 8.93 (CH_3-19), 4.25 (sx, J = 11, 2, 2 Hz, H-2), 3.35 (m, one coupling of 11 Hz discernible, H-3).

Anal. Calcd for $C_{20}H_{32}O$: C, 83.9; H, 10.6. Found: C, 83.6; H, 10.9.

Catalytic Hydrogenation of Enone 17. The enone (103 mg) was hydrogenated in 8 ml of glacial acetic acid containing 40 mg of Adams catalyst. Filtration and solvent evaporation gave a gum which was separated by plc into the 1β-alcohol **7b** (39 mg), identical with that obtained previously, and *D*-homo-5α-androstan-1-one (**18**, 37 mg): mp 100–102°; ν_{max} 1697 cm^{-1}; nmr τ 9.17 (CH_3-18), 8.84 (CH_3-19).

Anal. Calcd for $C_{20}H_{30}O$: C, 83.3; H, 11.2. Found: C, 83.3; H, 11.0.

2-*p*-Methoxybenzylidene-*D*-homo-5α-androstan-3-yl Acetates (21). The anisylidene alcohols **20** (1.6 g) were acetylated with dehyde, and 5 g of potassium hydroxide in 3 ml of water with 10 ml of ethanol was stirred for 6 hr at room temperature in the dark. Filtration and recrystallization from ethanol gave **19** (1.8 g): mp 206–207°; ν_{max} 1670 cm^{-1}; nmr τ 9.24 (CH_3-19), 9.20 (CH_3-18), 7.20 (CH_3O-), 6.88 (d, J = 15 Hz, H-1), 2.86 (4 H, symmetrical m, C_6H_4-), 2.40 (m, H-olefinic).

Anal. Calcd for $C_{28}H_{38}O_2$: C, 82.7; H, 9.4. Found: C, 82.8; H, 9.4.

2-*p*-Methoxybenzylidene-*D*-homo-5α-androstan-3-ols (20). The anisylidene ketone **19** (1.8 g) was reduced with sodium borohydride as in the first experiment to the anisylidene alcohols (**20** (1.6 g): ν_{max} 3570 cm^{-1}; nmr τ 9.33 (CH_3-19), 9.22 (CH_3-18), 7.03 (d, J = 13 Hz, H-1), 6.21 (s, CH_3O-), 5.83 (m, $W_{1/2}$ = 18 Hz, H-3), 3.43 (m, $W_{1/2}$ = 8 Hz, H-olefinic), 3.06 (4 H, symmetrical m, C_6H_4-).

2-*p*-Methoxybenzylidene-*D*-homo-5α-androstan-3-yl Acetates (21). The anisylidene alcohols **20** (1.6 g) were acetylated with acetic anhydride–pyridine under the usual conditions producing the acetates **21** (1.6 g), ν_{max} 1730 cm^{-1}.

3β-Acetoxy-*D*-homo-5α-androstan-2-one (22). Ozone was passed through a solution of 0.5 g of anisylidene acetate **21** in 34 ml of methanol and 27 ml of ethyl acetate at −70° until a blue color persisted, followed by nitrogen. Glacial acetic acid was added, and after warming to 30°, 10 g of zinc dust was added carefully. The zinc was filtered off and washed with ethyl acetate. Plc of the concentrated filtrate and washings gave the 3β-acetoxy-2-one **22** (186 mg), mp[13] 188–191°.

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.2; H, 9.9. Found: C, 76.5; H, 9.8.

D-Homo-5α-androstan-2-one (23). The acetoxy ketone **22** (80 mg) was refluxed for 3 hr with 6 g of activated zinc in 17 ml of glacial acetic acid. The solution was filtered and the zinc washed with acetic acid. After dilution with water, the combined filtrate and washings were extracted. Separation by plc yielded material of low polarity, probably hydrocarbons, starting material (11 mg), and the ketone **23** (52 mg), mp[13] 160–163°.

Anal. Calcd for $C_{20}H_{32}O$: C, 83.3; H, 11.2. Found: C, 83.4; H, 11.3.

D-Homoandrost-4-en-3-one (25). Solvent (40 ml) was distilled from a solution of 1.64 g of 3β-hydroxy-*D*-homoandrost-5-ene in 100 ml of dry toluene, using a Dean–Stark apparatus. Cyclohexanone (18 ml) was added and another 15 ml of solvent distilled off, followed by the dropwise addition of 900 mg of aluminum isopropoxide in 20 ml of dry toluene, while simultaneously distilling off 20 ml of solvent. The mixture was cooled and treated with 20 ml of saturated solution of sodium potassium tartrate. The resulting yellow residue was steam distilled and extracted, leaving 1.42 g Δ^4-3-one **25**, recrystallized from methanol: mp 145°; ν_{max} 1670, 1610 cm^{-1}; nmr τ 9.12 (CH_3-18), 8.79 (CH_3-19), 4.34 (H-4).

Anal. Calcd for $C_{20}H_{30}O$: C, 83.9; H, 10.6. Found: C, 83.8; H, 10.5.

Ethylene Thioketal of *D*-Homoandrost-4-en-3-one 26. Boron trifluoride etherate (1 ml) and 2 ml of ethylene thioglycol were added to 1.5 g of enone **25** in 40 ml of glacial acetic acid. After 30 min the precipitate was collected, washed with 80% acetic acid, and dried under vacuum, giving **26** (1.75 g): mp 151° from methanol; ν_{max} 1640, 635 cm^{-1}; nmr τ 9.15 (CH_3-18), 8.97 (CH_3-19), 6.66 [t, J = 2, 2 Hz, (SCH_2-)], 4.53 (H-4).

Anal. Calcd for $C_{22}H_{34}S_2$: C, 72.5; H, 10.0. Found: C, 72.4; H, 9.8.

D-Homoandrost-4-ene (27). The thioketal **26** (730 mg) in 25 ml of dry tetrahydrofuran was added to a stirred solution of sodamide in liquid ammonia during 1 hr at −70°. The usual work-up gave 596 mg of alkene **27** recrystallized from methanol: mp 80–82°; ν_{max} 1640 cm^{-1}; nmr τ 9.17 (CH_3-18), 8.97 (CH_3-19), 4.72

(m, $W_{1/2}$ = 8 Hz, H-4).

Anal. Calcd for $C_{20}H_{32}$: C, 88.2; H, 11.8. Found: C, 88.3; H, 11.7.

Hydroboration of *D*-Homoandrost-4-ene and Subsequent Oxidation. Diborane was bubbled into a solution of 500 mg of alkene in 15 ml of tetrahydrofuran during 1.5 hr. After the excess reagent was destroyed with ice, oxidation (as of **7c**) produced 480 mg of oil separated by plc into *D*-homo-5β-androstan-4-one (**29a**, 78 mg): mp 154–159° from methanol; ν_{max} 1700 cm^{-1}; nmr τ 9.18 (CH_3-18), 8.88 (CH_3-19); a portion sublimed for analysis had mp 166–167° (*Anal.* Calcd for $C_{20}H_{32}O$: C, 83.3; H, 11.2. Found: 83.0; H, 11.2) and *D*-homo-5α-androstan-4-one (**29b**, 105 mg), recrystallized from methanol: mp 122–124°; nmr τ 9.27 (CH_3-19), 9.18 (CH_3-18); ν_{max} 1710 cm^{-1} (*Anal.* Calcd for $C_{20}H_{32}O$: C, 83.3; H, 11.2. Found: C, 83.5; H, 11.2).

Borohydride Reduction of the Title Ketones and Acetylation of the Alcohols. Similar reduction conditions to those of the first experiment were employed. Except for the 1-ketone which yielded the 1α-alcohol **7a**, all gave mixtures, separated by plc into the components shown in Table I. The acetates were formed under standard conditions, and their properties together with those of the alcohols are presented in Table II. All were recrystallized from methanol.

Registry No.—**1a**, 29220-43-7; **1b**, 42548-29-8; **1c**, 481-29-8; **1d**, 53-43-0; **4a** isomer A, 51057-06-8; **4a** isomer B, 51057-07-9; **4b** isomer A, 51057-08-0; **4b** isomer B, 51057-09-1; **4c** isomer A, 51057-10-4; **4c** isomer B, 4503-01-9; **4d** isomer A, 847-74-5; **4d** isomer B, 847-75-6; **6a** 17-one, 51057-11-5; **6a** 17A-one, 51057-12-6; **6b** 17-one, 51057-13-7; **6b** 17A-one, 51057-14-8; **6c** 17-one, 51057-15-9; **6c** 17A-one, 26729-16-8; **6d** 17-one, 3278-90-8; **6d** 17A-one, 3278-99-7; **9**, 10455-05-7; **10**, 51153-08-3; **11**, 7417-23-4; **12** isomer A, 51057-16-0; **12** isomer B, 51057-17-1; **13**, 39851-65-5; **14**, 51057-18-2; **15**, 51057-19-3; **16**, 51057-20-6; **17**, 51057-21-7; **18**, 51057-22-8; **19**, 51057-23-9; **3α-20**, 51057-24-0; **3β-20**, 51057-25-1; **3α-21**, 51057-26-2; **3β-21**, 51057-27-3; **22**, 39851-67-7; **23**, 39851-68-8; **24**, 51057-28-4; **25**, 51057-29-5; **26**, 51057-30-8; **27**, 51057-31-9; **29a**, 51057-32-0; **29b**, 51057-33-1.

References and Notes

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3-Acyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-Dioxides. I. Alkylation, Amination, and Ethoxycarbonylation

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Preparation of ethyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide (**2c**) is described. Treatment of **2c** with ammonia gave carboxamide **8**, whose reactions with ethyl chloroformate could be directed to afford either 3-(ethoxycarbonyl)carbamoyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide (**22**), ethyl 3-(ethoxycarbonyl)-carbamoyl-4-hydroxy-2*H*-1,2-benzothiazine-2-carboxylate 1,1-dioxide (**25**), or 2*H*,5*H*-1,3-oxazino[5,6-c][1,2]benzothiazine-2,4(3*H*)-dione 6,6-dioxide (**24a**). Alkylation reactions of **2c** with methyl iodide and 1,2-dibromoethane are compared with those of 3-acetyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide (**2b**). Mass spectral evidence is presented for the assignment of structure **13** to the products of **2b** with ammonia and primary amines.

In 1956, Abe, Yamamoto, and Matsui[1] reported the base-induced rearrangement of *N*-phenacylsaccharin **1a** to 3-benzoyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide (**2a**) (Scheme I). Since then, rearrangements of a wide variety of *N*-β-keto-substituted saccharins have been studied.[2a,b]

Our interest in the chemistry of ring system **2** was stimulated by its apparent polydentate character, which offered potential versatility for preparation of a variety of novel derivatives for pharmacological testing.

We wish to report here and in an accompanying paper[3] our findings with some alkylation and amination reactions carried out on the known 3-acetyl derivative **2b** and the previously unreported ethyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide (**2c**).[4]

Results and Discussion

Synthesis of ester **2c** was carried out analogously to that reported for ketones **2a**[1] and **2b**;[2a] however, higher base concentration and longer reaction times were required to achieve satisfactory yields.[5]

Conventional alkylation reactions of **2a** and **2b** have been shown to occur preferentially at sulfonamide nitrogen.[2a] Ester **2c** behaves similarly, providing alkylated products **3c** and **3d**[6] upon treatment with methyl iodide and ethyl bromoacetate, respectively (Scheme I).

Ketone **2b** and ester **2c** both undergo cycloalkylation when treated with 1,2-dibromoethane. However, the course of these reactions differs, as illustrated in Scheme II. Formation of oxazine **4** from **2b** and azetidine **6** from **2c**