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Reaction of Saturated (5α- and 5β-) 19-Hydroxy Steroids with Mixed Phosphorus and Halogen Containing Reagents[1a]

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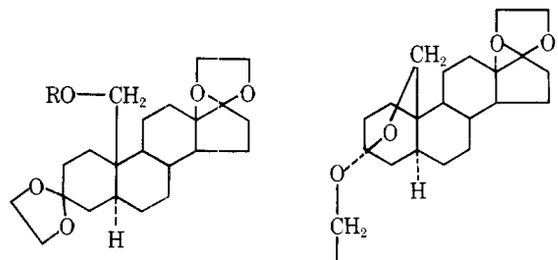
Attempts to convert saturated (5α- and 5β-) 19-hydroxylated steroids to 19-halogenated analogues with the use of mixed phosphorus and halogen containing reagents are described. The 19-halogenated analogues were not obtained, but certain transformations in the 5α series and rearrangements in the 5β series were noted and are discussed.

Previously, we have described the unsuccessful attempts to prepare saturated (5α- and 5β-) 10β-methyl sterols from 19-hydroxylated analogues via the hydrogenolysis of the corresponding sulfonate esters.[2a] In a search for an alternative approach, we considered the possibility of converting the 19 alcohol to a 19 halide (e.g., iodide) which, in turn, could be hydrogenolyzed to the 10β methyl. This approach suggested itself by the observations on the efficient conversion of numerous alcohols to halides with the use of mixed phosphorus and halogen containing reagents.[2b,3-9]

The attractiveness of the method was further enhanced by the observation that even alcohols prone to rearrangements gave unrearranged halides.[2b,8-10] For example, (1*S*)-neopentyl-*1-d* alcohol, on treatment with $(C_6H_5)_3P$–CCl_4, was transformed to presumably optically pure (1*R*)-neopentyl-*1-d* chloride.[11] In most instances, when the reaction is not assisted by a neighboring group, inversion of configuration takes place.[6,11] Retention of configuration in cases involving neighboring group participation was reported.[3,7] We have tested one of the procedures and obtained 17α-iodoestra-1,3,5(10)-trien-3-ol and 5α-cholestane 3α-iodide by treatment of estradiol and 5α-cholestan-3β-ol with $(C_6H_5O)_3P$–CH_3I, respectively.[12]

The preparation of the required 19-hydroxy-5α-androstane-3,17-bis(ethylene dioxide) (**1**) was previously described.[2a] Treatment of a dimethylformamide solution of **1a** with $(C_6H_5)_3P$ and bromine for 16 h at room temperature in the air resulted in the 19 formate **1b**. Formate ester formation under similar reaction conditions was previously observed.[13] Only starting material was recovered when the above mixture was refluxed (48 h) under nitrogen. Similarly, starting material was recovered when **1a** was refluxed (48 h) under nitrogen with $(C_6H_5)P_3$ in CCl_4.

The reaction of **1a** with triphenyl phosphite–methyl iodide [$(C_6H_5O)_3P$–CH_3I] (MTPI) gave an iodide, but did not proceed in the desired manner. When **1a** was stirred at room temperature with MTPI in formamide for 3 h under nitrogen, 3α-(2-iodo)ethoxy-3β,19-oxido-5α-androstan-17-ethylene dioxide (**2**) was obtained (60% yield). The mass spectrum of **2** showed peaks at *m/e* 502 (M^+), 348 (M − 154), and 99. The



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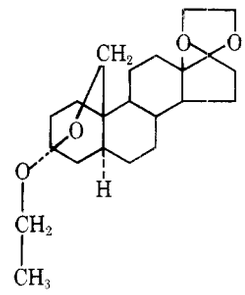

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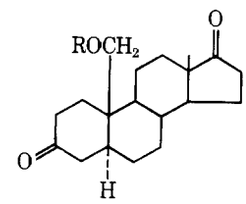

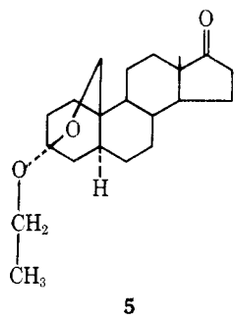

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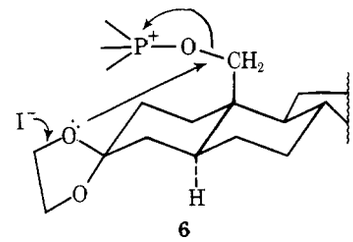

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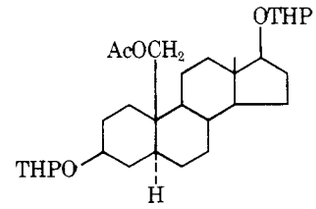
molecular ion of **2** (*m/e* 502) indicated that "the equivalent of a hydroxyl group" of **1a** was displaced with an iodine atom and that the product retained a ketal group (*m/e* 99). However, the fragment at *m/e* 348 (M − 154) was clearly inconsistent for a 19-iodo compound which was expected to have peaks at *m/e* 374 (M^+ − 128) and/or 360 (M − 142). Also, the NMR spectrum, which had a complex signal at ca. 4.12 ppm, was not in accord with the 19-iodo-3,17-diketal structure. These results indicated that, very likely, a transformation involving both carbon 19 and the 3-ketal moiety of **1a** occurred during the reaction. Treatment of **2** with $LiAlH_4$ resulted in the 3α-ethoxy product **3** [*m/e* 376 (M^+)]. The NMR spectrum of **3** had signals at 1.17 (t, 3 H) and 3.60 ppm (q, 2 H) and is in accord with the 3α-ethoxy structure. Hydrolysis of **3** gave **4a** which, on treatment with ethanol and *p*-toluenesulfonic acid, gave **5**. The obtained **5** was identical with an authentic sample.

It is likely that formation of **2** proceeds in a manner indicated in **6**. It is worthy of note that the ω-iodination proceeded only when rings A and B had the trans junction. This was evidenced by the fact that, when 19-hydroxy-5β-androstane-3,17-bis(ethylene dioxide) was treated with MTPI and DMF, even after 6 days, only starting material was recovered. Whether in the A/B cis series the reaction did not proceed because of steric factors or due to the lack of anchimeric assistance of the C-3 ketal moiety is not clear. As indicated in **6**, the anchimeric assistance of the C-3 ketal in the A/B trans series is very likely. However, the possibility of a 19-hydroxy → C-3β oxide formation occurring in the course of the reaction and resulting in 3α-(2-hydroxy)ethoxide 3β,19-oxide which, in turn, is converted to the iodide **2** cannot be ruled out.

In view of the negative results described above, the possibility that the 3-ketal may have a detrimental influence on the



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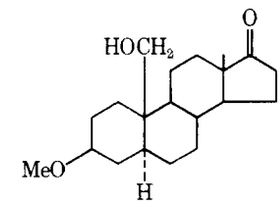

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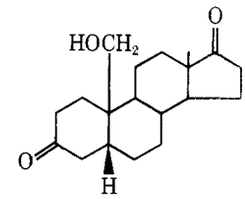
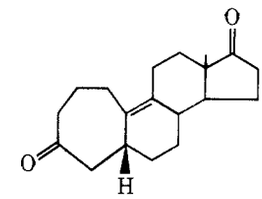


9a, H
b, *p*-Ts



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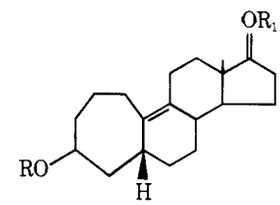
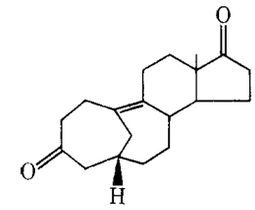


11a, R = R_1 = H
b, R = *p*-BrC_6H_4CO; R_1 = H
c, R = R_1 = Ac



12

C-19 halogenation was considered. Therefore, 5α-androstane-3β,17β,19-trihydroxy-3,17-bis(tetrahydropyranyl ether) was prepared and the iodination reaction was tested on this compound. Unfortunately, when **7** was treated with MTPI in DMF, a complex mixture of at least seven products was obtained. One of the products (ca. 8%) apparently contained iodine, but proved most unstable and decomposed on purification.

We have then tested the reaction on 19-hydroxy-5α-androstane-3β-methoxy-17-one (**8**). However, treatment of **8** with MTPI in DMF, under nitrogen for 7 h, gave a mixture of three products which were not investigated further because they did not contain iodine.

For studies in the 5β series, 19-hydroxy-5β-androstan-3,17-one (**9a**)[14] was used. When **9a** was treated (2 h) with MTPI in DMF at room temperature, a rearranged product later identified as **10** was obtained in ca. 40–50% yield. The unknown [mp 114–116 °C, MS *m/e* 286 (M^+)] was devoid of iodine and its IR spectrum had no bands for hydroxyls, but showed bands at 1740 and 1695 cm^{-1} for the C-17 and C-3 ketones. The NMR spectrum was lacking absorption for vinylic protons and had a signal at 1.00 ppm for the C-13 methyl and at 2.54 ppm (s, 2 H). The presence of a tetrasubstituted double bond in **10** was demonstrated by hydrogenation (EtOH–Pd/C) which was accompanied by the uptake of 1 equiv of hydrogen. The NMR of the saturated residue of the hydrogenation (*m/e* 288) indicated the presence of several isomers which were not investigated.

Reduction of **10** with $NaBH_4$ gave the diol **11a** which could be reoxidized to **10**. Treatment of **10** with base or acid resulted in the recovery of starting material. The presented evidence indicated that **10** has a tetrasubstituted double bond which apparently is not located at the C-5 (**10**) position.

The results were consistent with the possibility that the unknown may haye structure **10** or **12**. Dauben and Ben Efraim[15] in the course of studies of the solvolysis of the 19 tosylester **9b** obtained a small amount of a product to which they assigned structure **10**. The reported[15] physical constants for **10** [mp 105–106.5 °C; IR ν_{max} 1740, 1705 cm^{-1}; NMR τ 9.04

Table I. Fractional Atomic Coordinates and Estimated Standard Deviations

Atom	X/A	Y/B	Z/C
C(1)	0.23192 (29)	0.4586 (12)	0.58746 (31)
C(2)	0.26004 (39)	0.2350 (14)	0.58514 (41)
C(3)	0.22004 (52)	0.0486 (13)	0.59623 (47)
C(4)	0.13804 (49)	0.0546 (12)	0.55453 (42)
C(4A)	0.10500 (37)	0.1869 (13)	0.59302 (37)
C(5)	0.12041 (27)	0.4308 (11)	0.60264 (33)
C(6)	0.08674 (27)	0.5370 (15)	0.64406 (35)
C(7)	0.13059 (25)	0.4821 (18)	0.73080 (30)
C(8)	0.20870 (27)	0.5653 (10)	0.76506 (30)
C(9)	0.24138 (24)	0.5370 (10)	0.71405 (29)
C(10)	0.20175 (23)	0.4803 (11)	0.64042 (27)
C(11)	0.32212 (28)	0.5940 (13)	0.75056 (32)
C(12)	0.36941 (25)	0.4904 (16)	0.82900 (30)
C(13)	0.33856 (26)	0.5356 (11)	0.88195 (28)
C(14)	0.25838 (27)	0.4559 (12)	0.84175 (32)
C(15)	0.23985 (32)	0.4614 (20)	0.90379 (34)
C(16)	0.31145 (41)	0.4045 (18)	0.97688 (41)
C(17)	0.36955 (32)	0.3978 (13)	0.95379 (37)
C(18)	0.34607 (43)	0.7729 (14)	0.90304 (40)
C(20)	0.07780 (28)	0.0187 (13)	0.41778 (33)
C(21)	0.05384 (25)	0.1345 (11)	0.34630 (29)
C(22)	0.00581 (29)	0.0335 (13)	0.27720 (34)
C(23)	−0.01830 (32)	0.1377 (12)	0.20833 (36)
C(24)	0.00526 (30)	0.3447 (15)	0.20971 (35)
C(25)	0.05279 (28)	0.4478 (11)	0.27795 (33)
C(26)	0.07651 (28)	0.3459 (11)	0.34471 (33)
Br(24)	−0.02884 (4)	0.5000 (0)	0.11700 (4)
O(4B)	0.10843 (32)	0.1472 (9)	0.47742 (25)
O(17B)	0.43953 (25)	0.4597 (11)	1.01526 (23)
O(20)	0.07263 (31)	−0.1735 (9)	0.42337 (31)

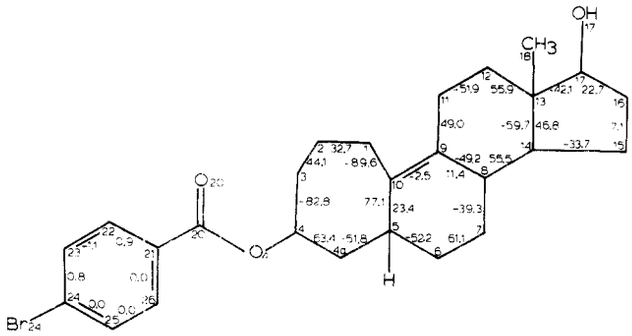


Figure 1. Endocyclic torsion angles. A torsion angle α–β–γ–δ is positive if, when viewed down the β–γ bond, the α–β bond will eclipse the γ–δ bond when rotated less than 180° in a clockwise direction.

(s, 3 H)] differed from those of the unknown obtained by us. This, at first, suggested that the rearranged product may have structure **12.**

The determination of the structure was carried out by x-ray crystallography on the 4-*p*-bromobenzoate **11b.**

The fractional atomic coordinates are given in Table I, and the atomic numbers, as well as the endocyclic torsion angles, are illustrated in Figure 1. The seven-membered A ring has a twist chair conformation as shown by the torsion angles, which agree quite closely with the theoretical values reported by Hendrickson[16] for a seven-membered twist chair ring. Beginning with the C(4a)–C(5) bond and proceeding in either direction around the ring, the theoretical values are −54.3, 72.3, −88.1, 39.1, 39.1, −88.1, and 72.3°. Another view of the A-ring conformation is provided by Figure 2. Figure 3 shows two ORTEP[17] drawings which illustrate the overall conformation of the molecules as well as the configurations at all asymmetric centers.

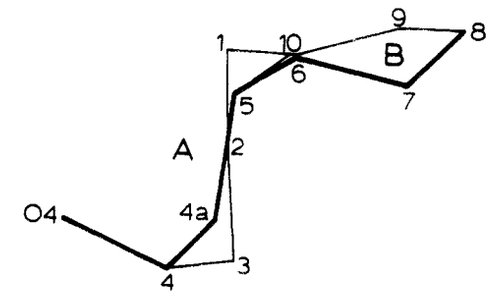


Figure 2. The seven-membered twist chain A ring looking from the midpoint of the C(4a)–C(5) bond to C(2).

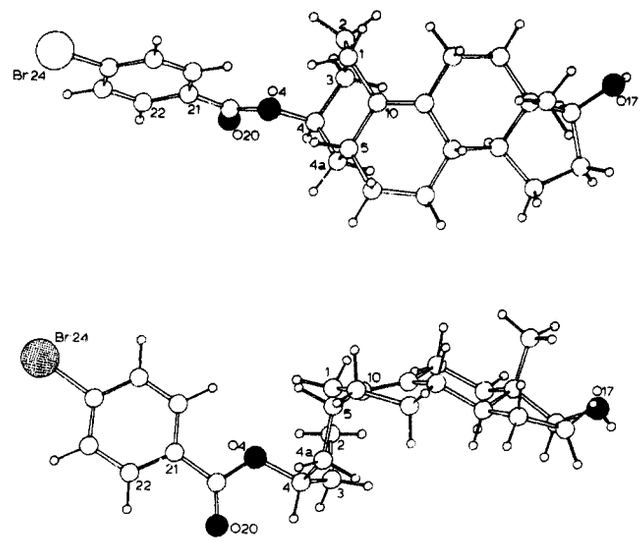


Figure 3. Perspective drawings of the *A*-homo-19-nor-5β-androst-9(10)-ene-4β,17β-diol 4-*p*-bromobenzoate molecule.

Experimental Section

Physical Measurements. Melting points were taken on a hot stage apparatus and are corrected. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 237 spectrophotometer as KBr wafers; absorption frequencies are quoted in reciprocal centimeters. Ultraviolet (UV) spectra were recorded on a Perkin-Elmer Model 202 spectrophotometer in methanol solutions.

Unless otherwise indicated, nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ on a Varian DA-60 spectrometer at 60 MHz. Chemical shifts are quoted in parts per million downfield from tetramethylsilane as internal standard (s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet). Mass spectra were recorded on a Du Pont 21-491 instrument, using the direct probe insertion system with a temperature of source of 210 °C and an ionization voltage of 70 eV. The masses of eliminated fragments are given in parentheses after the molecular ion.

Chromatography. Analytical thin layer chromatography (TLC) was carried out on precoated silica IB-F Baker Flex sheets in the indicated solvent systems. The products were detected under ultraviolet light and/or by spraying with an ethanolic solution of phosphomolybdic acid (10%) and heating to 105 °C for visualization.

Preparative layer chromatography was carried out on plates coated with silica gel (Merck HF 254-366). Column chromatography was carried out on silica gel (Merck, 70–230 mesh). The purity of steroidal samples was tested by gas–liquid chromatography (GLC) on a Hewlett-Packard 7620 A instrument using a 6-ft glass column (o.d. 6 mm, i.d. 2 mm) packed with SE-30 1% on Gas-Chrom (80–100 mesh) support. The temperature was set isothermally at 210–250 °C and the helium flow was 30 ml/min.

19-Hydroxy-5α-androstane-3,17-bis(ethylene dioxide) 19-Formate (1b). To a solution of $(C_6H_5)_3P$ (150 mg) in dry DMF (distilled from CaH_2 and stored over a molecular sieve) (2 ml) a solution of **1a** (180 mg) in DMF (3 ml) and bromine (27 μl) were added. The mixture was stored for 16 h in the air, then the pH was adjusted to 7 with a dilute solution of sodium hydrogen carbonate. After dilution

with water (10 ml), the product was recovered with ethyl acetate (3 × 10 ml), and processed in the usual manner. The obtained residue was fractionated on TLC [silica gel, benzene–ethyl acetate (4:1)] to yield the 19 formate (120 mg).

A sample was crystallized from methanol–water and showed mp 52–54 °C; IR ν_{max} 1715, 1175 cm^{-1}; NMR δ 0.83 (s, 3 H, 13-CH_3), 3.88 [m, 4 H, (17-OCH_2)$_2$], 4.40 (s, 2 H, 19-CH_2), 8.1 (s, 1 H, HCOO); MS *m/e* 420 (M$^+$) (−30, −44, −72, −89), 125, 99.

When the reaction was carried at reflux (48 h) under *nitrogen*, only starting material was recovered.

Treatment of 1a with $(C_6H_5)_3P$ in CCl_4.[6] A solution of **1a** (200 mg) and $(C_6H_5)_3P$ in CCl_4 (10 ml) was refluxed (48 h) under nitrogen. Following the usual workup, only starting material was obtained.

3α-(2-Iodo)ethoxy-3β,19-oxido-5α-androstan-17-ethylene Dioxide (2). To a stirred under nitrogen solution of **1a** (150 mg) in dry formamide (10 ml), MTPI[18] (260 mg) was added. The mixture was stirred for 3 h at ambient temperature, neutralized with aqueous sodium hydrogen carbonate, and diluted with water. The product was recovered with ethyl acetate, and the extract was washed with 5% $Na_2S_2O_3$ and water, dried, and concentrated to a residue. The residue was fractionated on TLC [silica gel, benzene–ethyl acetate (4:1)] to yield **2** (120 mg).

A sample was crystallized from ethyl acetate and showed mp 148–150 °C; IR ν_{max} 2920, 1450 cm^{-1}; NMR δ 0.80 (s, 3 H, 13-CH_3), 3.17 [t, 2 H, 3α-(–OCH_2–), *J* = 8 Hz], 3.90 [m, 4 H, 17-(OCH_2)$_2$], 4.12 [d, 2 H, 19-(CH_2O–), *J* = 2 Hz]; MS *m/e* 502 (M$^+$) (−154, −215), 155, 141, 99.

3α-Ethoxy-3β,19-oxido-5α-androstan-17-ethylene Dioxide (3). A solution of **2** (100 mg) in dry tetrahydrofuran (THF, 3 ml) was added to a stirred suspension of $LiAlH_4$ (100 mg) in THF (3 ml). The mixture was stirred (16 h) with the exclusion of moisture and, after a conventional workup, a crude residue (80 mg) was obtained. Following TLC purification [silica gel, benzene–ethyl acetate (4:1)] homogenous **3** (72 mg) was obtained.

A sample was crystallized from ethyl acetate–methanol and showed mp 165–167 °C; IR ν_{max} 2920, 2860 cm^{-1}; NMR δ 0.80 (s, 3 H, 13-CH_3), 1.17 [t, 3 H, 3α-(–OCH_2CH_3), *J* = 8 Hz], 3.60 [q, 2 H, 3α-(–OCH_2CH_3), *J* = 8 Hz], 3.98 [m, 4 H, 17-(–OCH_2)$_2$], 4.12 [d, 2 H, 19-(OCH_2–), *J* = 2 Hz]; MS *m/e* 376 (M$^+$) (−15, −29, −45, −87), 99.

3α-Ethoxy-3β,19-oxido-5α-androstan-17-one (5). The previously prepared 19-acetate **4b** (200 mg) was saponified [methanol (10 ml), water (5 ml), K_2CO_3 (100 mg), 4 h at room temperature] to yield **4a** (180 mg).

The obtained **4a** (170 mg) was immediately dissolved in absolute ethanol (5 ml), *p*-toluenesulfonic acid (40 mg) was added, and the mixture was stored (6 h) at room temperature. The ethanol was removed in a stream of nitrogen and the residue was fractionated on TLC [silica gel, benzene–ethyl acetate (4:1)] to afford **5** (120 mg): NMR δ 0.83 (s, 3 H, C-13 CH_3), 1.18 [t, 3 H, 3α-(–OCH_2CH_3), *J* = 6 Hz], 3.62 [q, 2 H, 3α-(–OCH_2CH_3), *J* = 6 Hz], 3.88 [d, 1 H, 19(CH_2), *J* = 8 Hz], 4.20 [d, 1 H, 19(CH_2), *J* = 8 Hz].

Treatment of a solution of **3** in aqueous acetone with *p*-toluenesulfonic acid (16 h at room temperature) gave **4a**, which was converted to **5** as above described.

3β,17β,19-Trihydroxy-5α-androstane-3,17-bis(tetrahydropyranyl Ether) 19-Acetate (7). The previously prepared 3β,19-dihydroxy-5α-androstan-17-one 19-acetate was used.[2a] The diol 19-acetate (1 g) was dissolved in dry methanol (20 ml) and then $NaBH_4$ (300 mg) was added in small portions. The reaction was allowed to proceed for 1 h when the mixture was made slightly acidic by the addition of 0.2 M hydrochloric acid. The mixture was diluted with water, and the obtained solid was collected by filtration and dried (0.85 g). The recrystallized sample (chloroform–hexane) of the 19-acetoxy-5α-androstane-3β,17β-diol showed mp 186–188 °C; IR ν_{max} 3400, 2940, and 1740 cm^{-1}; NMR δ 0.74 (s, 3 H, 13-CH_3), 2.10 (s, 3 H, 19-acetate-CH_3), 3.50 [m, 1 H, 17α-(H)], 4.31 [s, 2 H (19-CH_2)]; MS *m/e* 350 (M$^+$) (−18, −30, −48, −81, −112).

The above 19-acetoxy-3β,17β-diol (800 mg) was dissolved in dry THF (30 ml), then dihydropyran (1 ml) and *p*-toluenesulfonic acid (60 mg) were added and the mixture was stored for 6 h at ambient temperature. The reaction was terminated with solid sodium hydrogen carbonate, then a saturated solution of sodium hydrogen carbonate (70 ml) was added and the product was recovered with ethyl acetate. After the conventional workup, 3β,17β,19-trihydroxy-5α-androstane-3,17-bis(tetrahydropyranyl ether) 19-acetate (0.9 g) was obtained: IR 2920, 1740 cm^{-1}; NMR δ 0.78 [C-13 (CH_3)], 1.63 (m, THP-methylene H), 2.05 [s, 19-acetate (–CH_3)], 3.80 (m, 5 H, –CH_2O– of THP and 17α-H), 4.32 (s, 2 H, 19-CH_2O–), 4.70 (m, 2 H, CHO– of THP). The crude material (0.8 g) was dissolved in ether (30 ml) and added dropwise to a stirred suspension of $LiAlH_4$ (800 mg) in ether (20 ml). The mixture was refluxed (2 h) and processed in the conventional manner to yield a residue (680 mg). Following TLC fractionation [silica gel, benzene–ethyl acetate (7:3)] homogenous **7** (500 mg) was obtained.

A sample was crystallized from ethyl acetate and showed mp 165–167 °C; IR ν_{max} 3470, 2920 cm^{-1}; NMR δ 0.83 [s, 3 H, C-13 (CH_3)], 1.67 (m, THP methylene H), 3.62 (m, CH_2O– of THP and 17α-H), 3.90 (s, 2 H, 19-CH_2O), 4.72 (m, 2 H, CHO– of THP); MS *m/e* 476 (M$^+$), 392 (M − 102, −124, −134, −144, −156, −169), 85.

Treatment of 7 with MTPI in DMF. A mixture of **7** (300 mg), MTPI (350 mg), and DMF (5 ml) was stirred (7 h) under nitrogen at room temperature. The mixture was diluted with brine, and the products were collected by filtration and purified by TLC (benzene). A complex mixture of at least seven products was detected. The least mobile product showed IR ν_{max} 2910, 2870 cm^{-1}; NMR (all signals were broad) δ 0.87 (s, 3 H, 13-CH_3), 1.62 (m, THP methylene H), 3.62 (m, CH_2O of THP and 17α-H), 4.16 (m, 2 H,19-CH_2O), 5.00 (m, 2 H, CHO of THP); MS *m/e* 586 (M$^+$) 430 (M − 156) (M − 186, −204, −260, −314, −331). The product decomposed rapidly during purification.

19-Hydroxy-3β-methoxy-5α-androstan-17-one (8). The required starting material 19-acetoxy-3β-hydroxyandrost-5-en-17-one was prepared as described by Djerassi and Kielczewski.[19]

To a solution of 19-acetoxy-3β-hydroxyandrost-5-en-17-one (760 mg) in purified dioxane (10 ml) containing 70% perchloric acid (5 drops), methyl orthoformate (2.5 ml) was added dropwise. The solution was stored at room temperature and, as soon as it started to turn dark, the reaction was terminated by the addition of solid $NaHCO_3$. The mixture was diluted with water, and the product recovered (ethyl acetate) and processed in the usual manner. The residue was chromatographed on a column packed with Alox III. The fractions eluted with benzene–ethyl acetate (7:3) gave the 19-acetoxy-3β-methoxyandrost-5-en-17-one (420 mg): NMR δ 0.90 (13-CH_3), 2.03 (19-acetate CH_3) 3.38 (s, 3 H, OCH_3), 3.82 (d, 1 H, 19-CH_2–, *J* = 12 Hz), 4.52 (d, 1 H, 19-CH_2–, *J* = 12 Hz), 5.70 (m, 1 H, C-6 vinylic H).

The above 5-en-3-methyl ether (300 mg) was dissolved in dry methanol (30 ml), then 5% Pd on charcoal catalyst (200 mg) was added and the mixture was shaken (16 h) in an atmosphere of H_2 at room temperature. The catalyst was removed by filtration and the filtrate was concentrated to yield the 19-acetoxy-3β-methoxy-5α-androstan-17-one (269 mg): NMR δ 0.85 (13-CH_3), 2.04 (19-acetate CH_3), 3.34 [s, 3 H, 3β-(OCH_3)], 4.14 (d, 1 H, 19-CH_2–, *J* = 12 Hz), 4.42 (d, 1 H, 19-CH_2–, *J* = 12 Hz).

A mixture of the saturated (5α)-19-acetoxy-3-methyl ether (269 mg), methanol (10 ml), and 2 N NaOH (2 ml) was refluxed (30 min) under nitrogen. After neutralization with 1 N HCl, water was added and the product was recovered (ether) and processed in the usual manner. The obtained residue was fractionated on TLC [silica gel, benzene-ethyl acetate (7:3)] to yield **8** (200 mg): IR ν_{max} 3450, 2900, 1740 cm^{-1}; NMR δ 0.90 (13-CH_3), 1.90 (OH, exchangeable with D_2O), 3.38 [s, 3 H, 3β-(OCH_3)], 3.87 (2 H, 19-CH_2–).

Treatment of 8 with MTPI in DMF. A mixture of **8** (90 mg) and MTPI (180 mg) in DMF (4 ml) was stored (7 h) at room temperature. The reaction mixture was worked up to yield a residue (51 mg) whose NMR indicated that it was a mixture of at least three products (δ 0.83, 0.85, 0.93, three singlets at a ratio of 1.6:1:1.1). The mixture was not investigated further because it did not contain iodine.

19-Nor-*A*-homo-5β-androst-9(10)-ene-4,17-dione (10). The 19-hydroxy-5β-androstane-3,17-dione (**9a**) was prepared by the method of Knox et al.[14] A mixture of **9a** (100 mg) and MTPI (225 mg) in dry DMF (10 ml) was stirred (2 h) under nitrogen at room temperature. After dilution with brine, the products were recovered with ethyl acetate. The extract was washed with 10% aqueous $Na_2S_2O_3$, brine, and water, dried and concentrated to a residue (120 mg). The residue was fractionated on TLC [silica gel, benzene–ethyl acetate (4:1)] to yield **10** (42 mg).

A sample was crystallized from ether–pentane and showed mp 114–116 °C; IR ν_{max} 2910, 1735, 1695 cm^{-1}; NMR δ 1.0 (s, 3 H, 13-CH_3), 2.54 (s, 2 H); MS *m/e* 286 (M$^+$) (−15, −43); UV end absorption at 220 nm.

A mixture of **10** (13 mg), ethanol (1 ml), and 2 N NaOH (5 drops) was refluxed (1 h) under nitrogen. After the conventional workup, starting material was recovered. Similarly, only starting material was recovered from a solution of **10** (15 mg) in methanol (2 ml) containing concentrated HCl (5 drops) which was refluxed for 4 h, then diluted with water and processed as usual.

A mixture of **10** and 5% Pd on charcoal (20 mg) in ethanol (10 ml) was shaken (16 h) in an atmosphere of hydrogen at room temperature. The NMR of the recovered saturated residue indicated the presence

of several compounds (isomers): NMR δ 0.83 (s), 0.91 (s), 0.96 (s) (ratio 0.2:2:1); MS *m/e* 288 (M^+) (−44, −58, −103).

The mixture was not investigated further.

A-Homo-19-nor-5β-androst-9(10)-ene-4β,17β-diol (11a). A solution of **10** (40 mg) and $NaBH_4$ (50 mg) in methanol (2 ml) was stored (15 min) at room temperature. The recovered product was purified by TLC [silica gel, benzene–ethyl acetate (7:3)] to yield the diol **11a** (32 mg): IR no carbonyl absorption; NMR (pyridine) δ 1.03 (s, 3 H, 13-CH_3), 3.90 (broad m, 1-H), 4.15 (broad m, 1-H).

The diacetate **11c** was prepared in the conventional manner, using **11a** (25 mg), pyridine (2 ml), and acetic anhydride (1 ml). The obtained **11c** was purified on TLC [silica gel, benzene–ethyl acetate (7:3)]: NMR δ 0.92 (s, 3 H, 13-CH_3), 2.06 (s, 6 H, 2-acetate methyls), 4.60 (broad m, 1 H), 4.80 (broad m, 1 H).

A-Homo-19-nor-5β-androst-9(10)-ene-4β,17β-diol 4-*p*-Bromobenzoate (11b). A mixture of **11a** (75 mg), *p*-bromobenzoyl chloride (250 mg), methylene chloride (distilled from a molecular sieve) (4 ml), and triethylamine (1.2 ml) was stirred (16 h) at room temperature. Water (10 ml) was then added and the recovered product was purified by TLC [silica gel, hexane–ethyl acetate (3:1)] to yield a homogenous material which was later identified by x-ray crystallography as **11b**. The sample was slowly crystallized from ethanol and showed mp 166–168 °C; NMR δ 0.87 (s, 3 H, 13-CH_3), 3.65 (broad m, 1 H), 5.20 (broad m, 1 H), 7.55 (d, 2 H, J = 8 Hz, aromatic H), 7.90 (d, 2 H, J = 8 Hz, aromatic).

A single crystal having dimensions 0.1 × 0.2 × 0.4 mm was used for the x-ray measurements of the lattice parameters and intensities. The systematic absences in the diffraction pattern indicated the space group to be $C2$. The unit cell constants were determined from least-squares analysis of the θ values for 30 reflections to be a = 21.196 (2), b = 6.223 (1), c = 20.340 (1) Å, and β = 120.34° resulting in a unit cell volume of 2316 Å^3. The density was calculated to be 1.36 g cm^{-3} based on the presence of four molecules (Z = 4) in the cell. Integrated intensities for 1989 independent reflections having θ <75° were measured on an Enraf-Nonius CAD-4 diffractometer using Cu Kα radiation. After the Lorentz and polarization corrections [$(1 + \cos^2 2\theta)/2 \sin 2\theta$] had been applied to the intensity data, normalized structure factor amplitudes were computed, and the structure was solved by straightforward application of heavy atom techniques and found to be **11b** ($C_{26}H_{33}O_3Br$, mol wt 473.5).

The positional and anisotropic thermal parameters of all nonhydrogen atoms were refined by full-matrix least squares using the 1353 reflections for which the observed intensity was greater than twice the corresponding standard deviation. These reflections were regarded as having intensities significantly greater than the background. The weights used were the quantities $(1/\sigma_F^2)$ where σ_F is defined by equation H.14 of Stout and Jensen[20] using 0.06 rather than 0.01 as the instability correction. The hydrogens bonded to carbons were placed at their geometrically expected positions and included in the final three refinement cycles although their parameters were not refined. The hydroxyl hydrogen was located on a Fourier difference map. The final reliability index, R (defined as $\Sigma\|F_o| - |F_c\|/\Sigma|F_o|$), was 4.9% for the 1353 reflections used in the refinement and 6.0% for all data.

Registry No.—**1a,** 2220-69-1; **1b,** 60803-07-8; **2,** 60803-08-9; **3,** 60803-09-0; **4a,** 2229-24-5; **4b,** 14550-51-7; **5,** 17916-20-0; **7,** 60803-10-3; **8,** 60803-11-4; **9a,** 2059-53-2; **10,** 60803-12-5; **11a,** 60803-13-6; **11b,** 60803-14-7; **11c,** 60803-15-8; $(C_6H_5)_3P$, 603-35-0; MTPI, 4387-41-1; 3β,19-dihydroxy-5α-androstan-17-one, 14456-03-2; 19-acetoxy-5α-androstane-3β,17β-diol, 60803-16-9; dihydropyran, 25512-65-6; 19-acetoxy-3β-hydroxyandrost-5-en-17-one, 13328-60-4; methyl orthoformate, 149-73-5; 19-acetoxy-3β-methoxyandrost-5-en-17-one, 2857-43-4; bromobenzoyl chloride, 586-75-4.

Supplementary Material Available. Tables of the anisotropic thermal parameters of the nonhydrogen atoms, coordinates of the hydrogens, and interatomic distances and valency angles (3 pages). Ordering information is given on any current masthead page.

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