Cyclopropanation of steroidal A-ring 2-enol derivatives

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Received November 28, 1977

JOHN FREELAND TEMPLETON, VOLKER GUSTAV PASLAT, and CHWI WAN WIE. Can. J. Chem. **56**, 2058 (1978).

Cyclopropanation of 2-enol derivatives of 17β-acetoxy-5α-androstan-3-one has been studied. The preparation of A-ring cyclopropanol derivatives from the Simmons–Smith reagent or dibromocarbene is described. Long range shielding effects of the cyclopropane ring in the ^{1}Hmr spectrum are discussed.

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On a étudié la cyclopropanation de dérivés énoliques en position 2 de l'acétoxy-17β androstan-5α one-3. On décrit la préparation de dérivés cyclopropanols attachés au cycle A faisant appel à la réaction de Simmons–Smith ou avec du dibromocarbène. On discute des effets de blindage à longue distance du cycle cyclopropane sur les spectres rmn du ^{1}H.
[Traduit par le journal]

Introduction

The synthesis of steroidal cyclopropanol derivatives has been carried out since the development of methylene yielding reagents (1, 2). The iodomethylzinc iodide reagent, prepared from a zinc–copper couple and diiodomethane (3), has been shown to react with enol ethers more rapidly than with the analogous double bond (4) but to be less reactive towards enol acetates (5, 6). Recently, the electron-rich silyl enol ethers have been shown to readily add methylene from this reagent (7). Addition of methylene to an oxygen substituted double bond is a direct way of forming oxygenated cyclopropane derivatives containing an oxygen atom derived from a parent molecule and a method of preparation of methyl substituted carbonyl compounds (8–10). Because cyclopropanols are sensitive to basic and acidic media and to heat, it is necessary that the enolic derivative be easily cleaved. An alternative approach to the direct methylenation of the enolic double bond is the initial addition of a dihalocarbene followed by dehalogenation (11, 12). A number of methods are available for the dehalogenation of unsubstituted dihalocyclopropane derivatives (13).

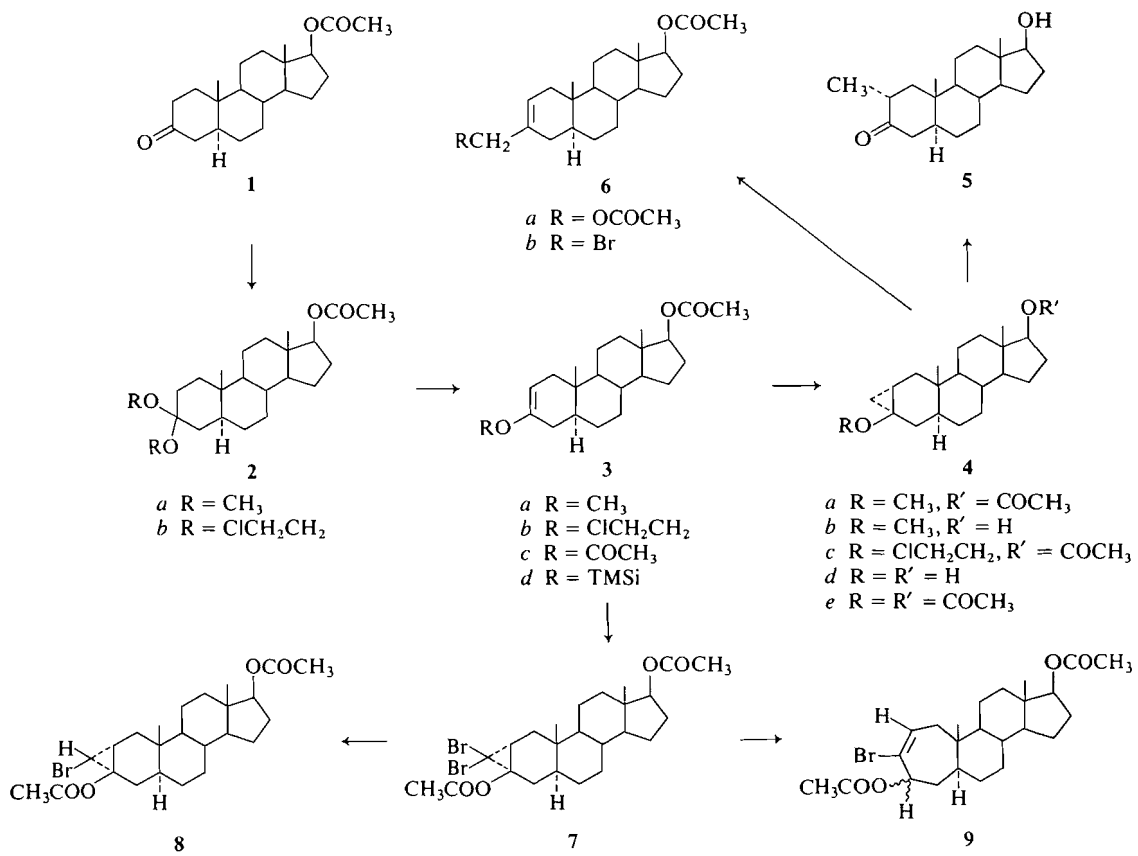
The addition of methylene, derived from either the Simmons–Smith reagent or via dibromocarbene, to enolic derivatives of 17β-acetoxy-5α-androstan-3-one (**1**) leading to tertiary 3β-oxygen substituted cyclopropanol derivatives has been investigated. A preliminary report has appeared (14).

Results and Discussion

17β-Acetoxy-5α-androstan-3-one (**1**) on treatment with methanol in the presence of acid gave the 3,3-dimethoxy ketal (**2***a*) which, on pyrolysis at reduced pressure, yielded the known methyl enol ether (**3***a*). Addition of methylene to the enolic double bond on treatment with the Simmons–Smith reagent was shown by the presence of high field resonance characteristic of cyclopropyl protons in the ^{1}Hmr spectrum, the absence of the enolic double bond in the ir spectrum, and an increase of 14 amu in the highest mass ion in the mass spectrum of the product. The iodomethylzinc iodide reagent has been shown to be sensitive to steric effects (15); therefore, the presence of the 19-methyl substituent would be expected to cause addition from the α face to give 17β-acetoxy-3β-methoxy-2α,3-cyclopropano-5α-androstane (**4***a*) as in the analogous addition of methylene to steroidal 2-olefins (16). Acidic hydrolysis of the cyclopropyl ether (**4***a*) at room temperature led to the 17β-alcohol (**4***b*) without opening of the cyclopropyl ether. Treatment with dilute acid in methanol at reflux gave 17β-hydroxy-2α-methyl-5α-androstan-3-one (**5**), identified by comparison with an authentic sample.

Treatment of the cyclopropyl ether (**4***a*) with boron trifluoride etherate in acetic anhydride gave the acetoxymethyl derivative (**6***a*). The ^{1}Hmr spectrum showed an olefinic proton and a two-proton singlet assigned to the methylene unit of the acetoxymethyl group. Reaction of the cyclopropyl ether (**4***a*) with boron tribromide gave a monobromo compound (**6***b*) in high yield with no indication of cyclopropanol formation.

Bis(2-chloroethoxy)-5α-androstan-17β-yl acetate (**2***b*) was prepared by azeotropic removal of water from a solution of 17β-acetoxy-5α-androstan-3-one (**1**) in benzene containing *p*-toluenesulfonic acid and 2-chloroethanol. Pyrolysis of the chloroethoxy ketal (**2***b*) gave the 2,3-unsaturated enol ether (**3***b*) of sufficient purity to be used directly in the next reaction with an excess of Simmons–Smith reagent to give the



cyclopropyl 2-chloroethyl enol ether (**4***c*). Treatment of this enol ether (**4***c*) with *n*-butyl lithium using the method of Schollköpf *et al.* (17) yield the tertiary cyclopropanol (**4***d*). This heat labile compound gave a melt showing two components on tlc corresponding to the starting material and 17β-hydroxy-2α-methyl-5α-androstan-3-one (**5**). On recrystallization from chloroform, retention of $\frac{1}{2}$ mol of solvent per mole of steroid was shown by ms and elemental analysis. Recrystallization from acetone gave, on the basis of elemental analysis, a hemihydrate. These solvates did not decompose when dried at room temperature under reduced pressure. In the ir the above product showed strong hydroxylic absorption and cyclopropyl C—H stretching and no carbonyl absorption. The ^{1}Hmr spectrum showed high-field resonance consistent with cyclopropyl protons (18). Treatment of the hemihydrate of the cyclopropanol (**4***d*) under either dilute acidic or basic conditions gave 17β-hydroxy-2α-methyl-5α-androstan-3-one (**5**), as shown by comparison of the spectra (ir, ^{1}Hmr, ms) and melting point when mixed with an authentic sample. Acetylation of the cyclopropanol (**4***d*) with acetic anhydride in pyridine gave the diacetate (**4***e*).

The enol acetate (**3***c*) of 17β-acetoxy-5α-androstan-3-one (**1**) was prepared by treatment of the ketone with acetic anhydride in the presence of phosphorous oxychloride. Addition of methylene from an excess of the Simmons–Smith reagent to the 2-enol acetate (**3***c*) gave the diacetate (**4***e*) in low yield. Simmons–Smith addition to the 16-enol acetate has been reported to take place more readily (11, 19), consistent with the greater reactivity of five-membered over six-membered ring olefins (15).

Dibromocarbene addition to the 2-enol acetate (**3***c*) was carried out using the phase-transfer technique (20) to give the expected dibromocyclopropano derivative (**7**). Treatment of the dibromocyclopropano derivative (**7**) with a zinc–copper couple removed the sterically less hindered *exo* bromine to give the *endo*-bromocyclopropane (**8**). The *endo* structure was assigned on the basis of the coupling constant (J = 9 Hz) in agreement with a *cis* cyclopropyl coupling in the monobromocyclopropano derivative (**8**) (21). Hydrogenation of the dibromocyclopropano derivative (**7**) over Raney nickel catalyst also effected removal of the *exo* bromine atom to yield **8**. Further treatment of the monobromocyclopropano derivative (**8**) with either the zinc–copper couple or Raney nickel was unsuccessful

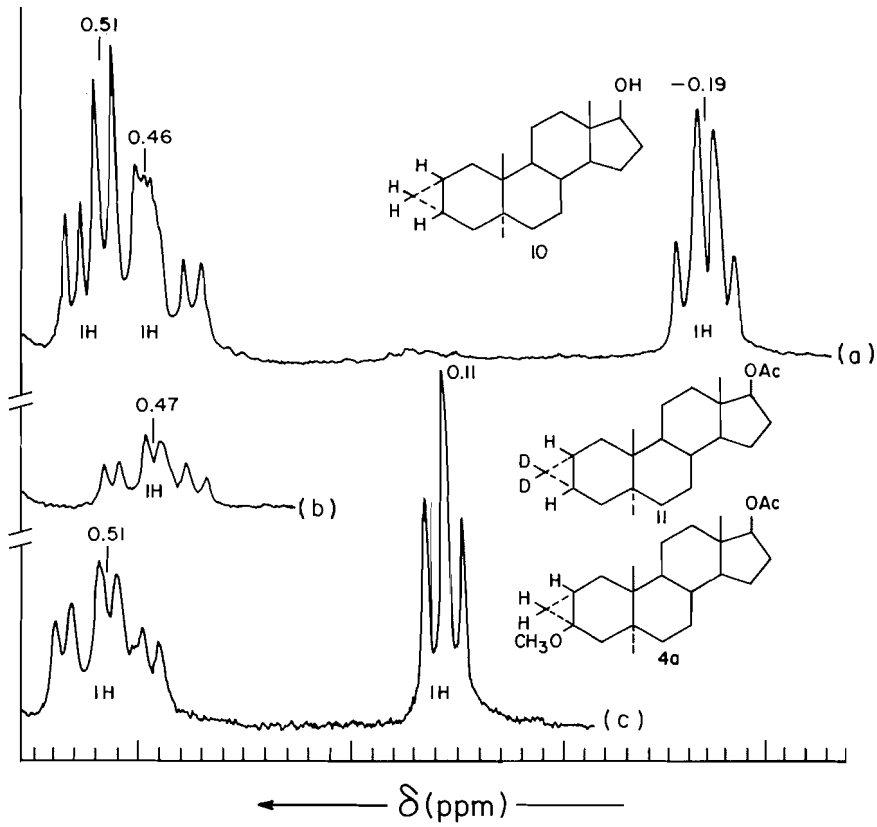


FIG. 1. High-field bands in the 220 mHz ^{1}Hmr spectra of 2α,3α-cyclopropanosteroid derivatives.

in removing the *endo* bromine atom. Lithium aluminium hydride reduction of the dibromocyclopropano derivative (**7**) resulted in the removal of one bromine atom and opening of the cyclopropane ring to yield the A-homoandrostene (**9**) after acetylation. Similar steroid ring enlargements have been observed (12).

The ^{1}Hmr spectrum of the crude reaction product obtained from treatment of the trimethylsilyl derivative (**3***d*) with the Simmons–Smith reagent showed high-field protons corresponding to cyclopropane formation but no crystalline products were obtained from the complex reaction mixture. Olefinic products have been isolated in similar reactions (22).

The ^{1}Hmr spectra of these cyclopropanoandrostanes show the presence of a six-line band at high field which cannot be assigned to a cyclopropyl proton. The spectrum of 17β-hydroxy-2α,3α-cyclopropano-5α-androstane (**10**) has three high-field protons (Fig. 1*a*). Comparison of this spectrum with the dideuterated derivative (**11**) shows the loss of two protons (Fig. 1*b*). These two protons are assigned to the *exo* and *endo* protons which are expected to appear as six- and four-line bands, respectively, as observed, because the *exo* proton undergoes two equivalent *cis* couplings ($J_{exo,2\beta} = J_{exo,3\beta} = 12$ Hz) and one smaller *gem* coupling ($J_{gem} = 5$ Hz) whereas the *endo* proton undergoes three equivalent couplings ($J_{endo,2\beta} = J_{endo,3\beta} = J_{gem} = 5$ Hz) (23). The remaining proton also appears as a six-line band. Examination of the 2β- and 3β-H shows that both are coupled to five protons from which a more complex coupling should result. Deuterium substitution of the 2β- and 4,4-protons does not alter the number of high-field protons observed, thereby eliminating them as the source of this six-line absorption. Substitution of the 3β-proton by an oxygen function causes the loss of one up-field proton leaving a six-line band and a triplet (Fig. 1*c*). The triplet is assigned to the *endo* proton which loses one *trans* coupling and has undergone a shift to lower field. The remaining six-line band is inconsistent with the *exo* proton because that proton should now show one less *cis* coupling and should undergo a shift to lower field. Similar overlapping high-field multiplets are observed in the ^{1}Hmr spectrum of the 4β- and 6α-hydroxyl derivatives of 17β-hydroxy-2α,3α-cyclopropano-5α-androstane (**10**) (24). Further evidence that the six-line proton is not due to a cyclopropyl proton follows from the spectra of the brominated derivatives both

of which show this signal centered at 0.66 ppm. The 2β-H, like the 1α- and 1β-H to which it is coupled, is expected to appear as a doublet of doublets. Similarly the unaltered coupling observed for the monobrominated derivative is inconsistent with assignment of the six lines to the 2β-proton. Of the remaining protons in the molecule the observed six-line band may arise, on the basis of the coupling constant, from the 9α-,12α-, or 14α-H.

Generally signals which occur at higher field than other alicyclic protons can be assigned to cyclopropyl protons. Bhacca *et al.* (25) has reported the presence of a high-field proton in the ^{1}Hmr spectrum of 3,3′-spirocyclopropano-5α-androstane not present in the spectrum of 5α-androstane which could not be assigned to a cyclopropyl proton. On the basis of the coupling constants, this signal was assigned to a proton at the 6α-,7β-,11α-position resulting from a very long range shielding effect of the cyclopropane ring by an unknown mechanism. The spectra of 2α,3α-cyclopropano-5α-androstane derivatives also show the presence of a high-field signal which cannot be assigned to a cyclopropyl proton and is, therefore, another example of this phenomenon.

These compounds were prepared in connection with studies on the metabolism of 17β-hydroxy-2α,3α-cyclopropano-5α-androstane (**10**) (24).

The above procedures yield 2α,3α-cyclopropano androstane derivatives having either a hydroxyl function at C-3 and C-17, or afforded disubstituted derivatives. A derivative at C-3, which would yield the 3-alcohol and selectively retain the 17-ester function, would give compounds of interest for biological testing, since they avoid the extremes of high and low lipid solubility of the disubstituted and diol compounds (26).

Experimental

For general experimental details of work-up procedures and the acetylation method see ref. 27. Unless otherwise stated, ir (Perkin-Elmer Model 267) and ^{1}Hmr (Varian A56/60A) spectra are recorded in carbon tetrachloride and specific rotations in chloroform. Proton magnetic resonance spectra of compounds **4***a*, **4***c–e*, **6***a–b*, 7, **8**, and **9** were recorded in deuteriochloroform on a Varian HR 220 instrument by the Canadian 220 MHz NMR Centre, Ontario Research Foundation, Toronto, Ontario. Proton magnetic resonance spectra of compounds containing a cyclopropane ring were recorded both with and without the internal TMS standard. Assignment of the six peaks at δ 0.46–0.52 ppm in the ^{1}Hmr spectra of compounds **4***a*, **4***c–e*, and δ 0.66 ppm in compounds 7 and **8** is discussed above. Brockmann Activity II alumina (35–40 × the weight of substance) was used for column chromatography. Neutral alumina was prepared by the ethyl acetate treatment described by Fieser and Fieser (28). Elemental analyses were performed by either Mr. George Crouch, School of Pharmacy, University of London, England, or Pascher and Pascher, Bonn, West Germany.

*3-Methoxy-5α-androst-2-en-17β-yl Acetate (**3**a)*

A flask containing 3,3-dimethoxy-5α-androstan-17β-yl acetate (**2***a*) (29) (7 g) under reduced pressure (water pump) was immersed in an oil-bath (200–210°C). Vigorous reaction ceased after 10 min and the residue was cooled; a drop of pyridine was added, followed by recrystallization from ether–methanol to give the methoxyenol ether (**3***a*) (5 g) mp 122–127°C. Recrystallization gave a sample mp 126.5–129.5°C (lit. (29) mp 127–129°C); ^{1}Hmr δ: 4.28–4.70 (2H, m, vinylic and 17α-protons), 3.44 (s, methoxy), 1.98 (s, 17-acetoxy), 0.78 (s, 18- and 19-methyl) ppm.

*3β-Methoxy-2α,3-cyclopropano-5α-androstan-17β-yl acetate (**4**a)*

The methoxyenol ether (**3***a*) (2.15 g) was treated with the Simmons–Smith reagent as described for the enol ether (**3***b*). Chromatography over alumina gave fractions from petroleum ether which on recrystallization from ether–methanol gave the cyclopropyl ether (**4***a*) (720 mg), mp 138–140°C; $[\alpha]_D^{24}$ +36° (*c* 0.23); ir ν_{max}: 3096 (cyclopropyl C—H), 1730 (ester C=O) cm^{-1}; ^{1}Hmr δ: 4.57 (t, J = 8 Hz, 17α-proton), 3.27 (s, methoxy), 2.04 (s, 17-acetoxy), 0.84 (s, 19-methyl), 0.77 (s, 18-methyl), 0.51 (1H, J = 4.5, 11.5, 12 Hz), 0.11 (1H, dd, $J_{gem} = J_{trans}$ = 5.5 Hz, *endo*-cyclopropyl proton) ppm; ms *m/e*: 360 (M$^+$). *Anal.* calcd. for $C_{23}H_{36}O_3$: C 76.61, H 10.07; found: C 76.39, H 10.28.

*3β-Methoxy-2α,3-cyclopropano-5α-androstan-17β-ol (**4**b)*

The cyclopropyl ether (**4***a*) (463 mg) was dissolved in methanol (22.5 ml) and diethyl ether (27.5 ml) containing concentrated hydrochloric acid (5.4 ml). After 22 h all starting material had disappeared (according to tlc) and a slower fraction had developed. The reaction was worked up to give a crude product which crystallized from petroleum ether 320 mg, mp 105–108°C. Several recrystallizations from petroleum ether gave 3β-methoxy-2α,3-cyclopropano-5α-androstan-17β-ol (**4***b*), mp 109–110°C; $[\alpha]_D^{23}$ +27° (*c* 0.16); ir ν_{max}: 3623 (free O—H), 3480 (bonded O—H), 3067 (cyclopropyl C—H) cm^{-1}; ^{1}Hmr δ: 3.47 (t, J = 8 Hz, 17α-proton), 3.16 (s, methoxy), 0.84 (s, 19-methyl), 0.67 (s, 18-methyl), −0.02 (1H, t, J = 4 Hz, cyclopropyl proton) ppm; ms *m/e*: 318 (M$^+$). *Anal.* calcd. for $C_{21}H_{34}O_2$: C 79.19, H 10.76; found: C 79.05, H 10.87.

*17β-Hydroxy-2α-methyl-5α-androstan-3-one (**5**) from Acid Treatment of the Cyclopropyl Ether (**4**a)*

The cyclopropyl ether (**4***a*) (121 mg) was dissolved in dioxane (4 ml) and methanol (12 ml) containing concentrated hydrochloric acid (1.44 ml). As the starting material decreased (by tlc) two slower fractions developed, the faster corresponding to the 17β-alcohol (**4***b*). After 4½ h only the slower fraction remained. The reaction product was worked up to yield after several recrystallizations from ether – petroleum ether, 17β-hydroxy-2α-methyl-5α-androstan-3-one (**5**) (62 mg), mp 151.5–153°C (lit. (30) 153–154°C); ir ν_{max} (KBr): 3509 (bonded O—H), 1706 (six-membered ring C=O) cm^{-1}; ^{1}Hmr δ: ($CDCl_3$) 3.62 (t, J = 8 Hz, 17α-H), 1.05 (s, 19-methyl), 0.99 (d, J = 6 Hz, 2α-methyl), 0.76 (s, 18-methyl) ppm.

*3-Acetoxymethyl-5α-androst-2-en-17β-yl acetate (**6**a)*

3β-Methoxy-2α,3-cyclopropano-5α-androstan-17β-yl acetate (**4***a*) (120 mg) was dissolved in acetic anhydride (4 ml) and cooled in an ice–salt bath. Boron trifluoride etherate (0.7 ml) was added and the solution allowed to stand at 0°C for 20 h. The reaction mixture was poured into ice-water and extracted with ether; removal of the ether yielded a brown crystalline residue (127 mg). Filtration through neutral alumina in petroleum ether gave fractions (80 mg) from which was obtained on recrystallization from ether–methanol, 3-acetoxymethyl-

5α-androst-2-en-17β-yl acetate (*6a*) (18 mg), mp 117–119°C C; ir ν_{max}: 1745, 1738 (ester C=O) cm^{-1}; ^{1}Hmr δ: 5.65 (m, olefinic proton), 4.59 (t, J = 8.5 Hz, 17α-H), 4.45 (s, acetoxymethyl protons), 2.07 (s) and 2.05 (s, acetoxy-methylene), 0.78 (s, 19-methyl), 0.73 (s, 18-methyl) ppm; ms *m/e*: 388 (M^+). *Anal.* calcd. for $C_{24}H_{36}O_4$: C 74.19, H 9.34; found: C 74.27, H 9.42.

3-Bromomethyl-5α-androst-2-en-17β-yl acetate (6b)

Boron tribromide (bromine free) (0.6 ml) was added to a solution of the cyclopropyl ether (*4a*) (256 mg) in dichloromethane (10 ml) cooled in a Dry Ice – acetone bath. After 2 h the reaction mixture was poured into ice-water and extracted with dichloromethane to give on recrystallization from dichloromethane–methanol, 3-bromomethyl-5α-androst-2-en-17β-yl acetate (*6b*) (243 mg), mp 158–161°C, recrystallization gave mp 163–164°C; ir ν_{max}: 1736 (ester C=O), 1662 w (C=C) cm^{-1}; ^{1}Hmr δ: 5.78 (br m, olefinic proton), 4.59 (t, J = 8.5 Hz, 17α-H), 3.94 (s, bromomethylene protons), 2.05 (s, 17-acetoxy), 0.79 (s, 19-methyl), 0.73 (s, 18-methyl) ppm; ms *m/e*: 408, 410 (M^+), 329 (M^+ − Br). *Anal.* calcd. for $C_{22}H_{33}O_2Br{\cdot}CH_3OH$: C 62.57, H 8.45; found: C 62.46, H 7.88.

3,3-Bis(2-chloroethoxy)-5α-androstan-17-yl Acetate (2b)

17β-Acetoxy-5α-androstan-3-one (**1**) (1.1 g) was added to a solution of benzene (90 ml) and 2-chloroethanol (10 ml) containing *p*-toluenesulfonic acid monohydrate (100 mg). The solution was fitted with a Dean–Stark apparatus for 3 h of reflux, cooled, and poured into excess cold aqueous sodium bicarbonate, washed with water, dried, and evaporated at reduced pressure with minimal heating. The crude product was recrystallized from ether–methanol containing a trace of pyridine to give the ketal (*2b*) (615 mg), recrystallization gave an analytical sample, mp 94–95°C; $[\alpha]_D^{24}$ +11° (*c* 1.01); ir ν_{max}: 1735 (ester C=O), 671 (C—Cl) cm^{-1}; ^{1}Hmr δ: 4.46 (t, J = 8 Hz, 17α-proton), 3.54 (m, chlorcethoxy protons), 1.93 (s, 17-acetoxymethyl), 0.78 (s, 19-methyl), 0.72 (s, 18-methyl) ppm; ms *m/e*: 474, 476, 478 (M^+). *Anal.* calcd. for $C_{25}H_{40}O_4Cl_2$: C 63.15, H 8.48, Cl 14.91; found: C 62.90, H 8.67, Cl 14.74.

3(2-Chloroethoxy)-5α-androst-2-en-17β-yl Acetate (3b)

A flask containing the ketal (*2b*) (600 mg) was immersed in an oil-bath (200–210°C) under reduced pressure (water pump). After 10 min reaction ceased and the crude product was recrystallized from methanol containing a trace of pyridine to give enol ether (*3b*) (200 mg), mp 123–126°C; $[\alpha]_D^{24}$ +44° (*c* 1.00); ir ν_{max}: 1735 (ester C=O), 1675 (C=C), 671 (C—Cl) cm^{-1}; ^{1}Hmr δ: 4.44 (m, olefinic and 17α-proton), 3.68 (m, chloroethoxy protons), 1.94 (s, 17-acetoxy methyl), 0.75 (s, 18- and 19-methyl) ppm; ms *m/e*: 394 (M^+). *Anal.* calcd. for $C_{23}H_{35}O_3Cl$: C 69.94, H 8.93, Cl 8.96; found: C 70.36, H 9.08, Cl 8.56.

3β(2-Chloroethoxy)-2α,3-cyclopropano-5α-androstan-17β-yl Acetate (4c)

The enol ether (*3b*) (1.6 g) in dry ether (30 ml) was added to a 10 molar excess of the Simmons–Smith reagent prepared from zinc–copper couple (4 g) and methylene iodide (3.32 ml). After 24 h reflux the ir spectrum showed enolic double bond absorption; a second 10 molar excess was added after 48 h and the reaction heated to reflux for a total of 3 days. The reaction product was poured into aqueous sodium bicarbonate and extracted with ether. The residue from the ether extraction was taken up in petroleum ether and chromatographed over neutral alumina. Elution with petroleum ether afforded a major fraction (733 mg) which on crystallization from methanol yielded an analytical sample (433 mg) of the cyclopropyl ether (*4c*), mp 129–130°C; $[\alpha]_D^{24}$ +23° (*c* 1.03); ir ν_{max}: 3075 (cyclopropyl C—H), 1735 (ester C=O), 1235, 1031 (C—O), 669 (C—Cl) cm^{-1}; ^{1}Hmr δ: 4.58 (t, J = 8 Hz, 17α-proton), 3.52–3.82 (m, chloroethoxy protons), 2.04 (s, 17-acetoxy methyl), 0.84 (s, 19-methyl), 0.77 (s, 18-methyl), 0.51 (1H, J = 4, 11.5, 12.5 Hz), 0.15 (1, dd, $J_{gem} = J_{trans}$ = 6 Hz, *endo*-cyclopropyl proton) ppm; ms *m/e*: 408 (M^+). *Anal.* calcd. for $C_{24}H_{37}O_3Cl$: C 70.47, H 9.12, Cl 8.67; found: C 70.38, H 9.28, Cl 8.31.

2α,3-Cyclopropano-5α-androstane-3β,17β-diol (4d)

The 2-chloroethoxycyclopropane ether (*4c*) (1 g) in dry ether (20 ml) was cooled in an ice-bath under a nitrogen atmosphere. *n*-Butyl lithium in petroleum ether (2.3 *M*) (6 ml) was added to the stirred solution and after 15 min the reaction mixture was poured into one equivalent of cold dilute acetic acid (200 ml). The reaction was extracted with ether, the ether was washed with aqueous sodium bicarbonate, water, dried, and evaporated under reduced pressure at room temperature. The crude product was dissolved in acetone at room temperature and concentrated in a stream of nitrogen to yield the cyclopropanol (*4d*) (390 mg), mp 135–144°C. Recrystallization of the heat labile substance from acetone gave a mp 145–155°C. This material showed only one substance on tlc in the following four solvent systems 25% ethyl acetate – petroleum ether, 50% ether–benzene, 5% acetone–chloroform, and 5% methanol – carbon tetrachloride. Analysis by glc as the trimethylsilyl derivative (24) showed one fraction; $[\alpha]_D^{24}$ +18° (*c* 0.963, dioxane); ir ν_{max}: (KBr) 3400 (broad, O—H), 3090 (cyclopropyl C—H), 1058 (C—O) cm^{-1}, heating this disc at 180°C gave a diminished 3400 peak and a new absorption at 1725 (ketone C=O) cm^{-1}; ^{1}Hmr δ: (pyridine-d_5) 3.91 (t, J = 8.5 Hz, 17α-proton), 0.97 (s, 19-methyl), 0.93 (s, 18-methyl), 0.46 (1H, J = 12, 11.5, 4 Hz), 0.35 (1H, t, $J_{gem} = J_{trans}$ = 5 Hz, *endo*-cyclopropyl proton), ppm; ms *m/e*: 304 (M^+). *Anal.* calcd. for $C_{20}H_{32}O_2{\cdot}\frac{1}{2}H_2O$: C 76.62, H 10.61; found: C 76.71, H 10.48. Recrystallization from chloroform, mp 123–128°C. *Anal.* calcd. for $C_{20}H_{32}O_2{\cdot}\frac{1}{2}CHCl_3$: C 67.61, H 9.00, Cl 14.60; found: C 68.60, H 9.11, Cl 12.01.

2α,3-Cyclopropano-5α-androstane-3β,17β-diol Diacetate (4e)

The diol (*4d*) (25 mg) was acetylated (27) and the product (one component on tlc) recrystallized from acetone to give the diacetate (*4e*) (19 mg), mp 162–163°C; $[\alpha]_D^{22}$ +15° (*c* 1.58); ir ν_{max}: 3090 (cyclopropyl C—H), 1735 (ester C=O), 1235, 1176, 1087 (ester C—O) cm^{-1}; ^{1}Hmr δ: 4.55 (t, J = 8 Hz, 17α-proton), 2.03 (s) and 1.96 (s, 3- and 17-acetoxy methyl), 0.91 (s, 19-methyl), 0.77 (s, 18-methyl), 0.52 (1H, J = 12, 11.5, 4.5 Hz), 0.47 (1H, dd, $J_{gem} = J_{trans}$ = 5.5 Hz *endo*-cyclopropyl proton) ppm; ms *m/e*: 388 (M^+) 346 (M^+ − ketene). *Anal.* calcd. for $C_{24}H_{36}O_4$: C 74.19, H 9.34; found: C 74.35, H 9.24.

Acid Treatment of 2α,3-Cyclopropano-5α-androstane-3β,17β-diol (4d)

The diol (*4d*) (170 mg) was dissolved in a solution (17 ml) of concentrated hydrochloric acid in methanol (15% v/v) and heated to reflux for 1 h. The solution was then poured into excess aqueous saturated sodium bicarbonate and extracted with ether to yield a crude product (108 mg) which showed one fraction equivalent to 17β-hydroxy-2α-methyl-5α-androstan-3-one (**5**) on tlc. Recrystallization from acetone gave mp 152.5–153.5°C (lit. (30) mp 152–154°C); mp on admixture with an authentic sample of **5** was not depressed. Spectra (ir, ^{1}Hmr) were identical to those of authentic **5**.

Base Treatment of 2α,3-Cyclopropano-5α-androstane-3β,17β-diol (4d)

The diol (*4d*) (60 mg) was heated under reflux for 2 h with a solution (100 ml) of methanolic potassium hydroxide (2%

w/v). The reaction, which showed one fraction moving faster than the starting material on tlc, was concentrated and dilute hydrochloric acid was added. Extraction with ether gave a residue which was recrystallized from acetone, mp 146–148°C; ir and ^{1}Hmr spectra were identical to authentic 17β-hydroxy-2α-methyl-5α-androstan-3-one (**5**).

5α-Androst-2-ene-3,17β-diol Diacetate (3c)

Acetic anhydride (10 ml), followed by phosphorous oxychloride (2 ml), were added to a solution of 17β-hydroxy-5α-androstan-3-one (5 g) in dichloromethane (50 ml). The solution was allowed to stand at room temperature overnight and then poured into cold water. The organic layer was separated, washed with water and excess sodium bicarbonate solution, dried over anhydrous sodium sulfate, and evaporated at reduced pressure to yield the diol diacetate (**3c**). Recrystallization from dichloromethane–methanol gave crystals (3.3 g), mp 168–171°C (lit. (31) mp 168–170°C); ir ν_{max}: 1750 (enol acetate C=O), 1735 (17β-acetate C=O), 1695 (C=C) cm^{-1}; ^{1}Hmr δ: 5.25 (m, vinyl proton), 4.62 (t, J = 7 Hz, 17α-proton), 2.08 (s, 3-acetoxy methyl), 2.02 (s, 17β-acetoxy methyl), 0.85 (s, 19-methyl), 0.85 (s, 18-methyl) ppm.

Simmons–Smith Treatment of 5α-Androst-2-ene-3,17β-diol Diacetate (3c)

The enol acetate (**3c**) (1.05 g) was treated with a 10 molar excess of the Simmons–Smith reagent, prepared by the method of Rawson and Harrison (32). After 25 h a second 10 molar excess was added and reflux continued for a further 20 h. Chromatography of the crude product over alumina in petroleum ether gave on elution with 5–25% benzene – petroleum ether fractions (207 mg) from which was obtained on recrystallization from ether the cyclopropyl diacetate (**4e**), mp 163–164°C, identical with the previously prepared cyclopropyl diacetate (**4e**) by comparison of the ir, ^{1}Hmr, and mixture mp.

2α,3α-Dibromocyclopropano-5α-androstane-3β,17β-diol Diacetate (7)

A stirred solution of cetyltrimethylammonium bromide (2 g) in 50% aqueous sodium hydroxide (100 ml) was heated to reflux and a solution of 5α-androst-2-ene-3,17β-diol diacetate (**3c**) (4.6 g) in tribromomethane (25 ml) was added dropwise. After 1 h the exothermic reaction was cooled, diluted with brine, neutralized with 6 *N* sulfuric acid and extracted with chloroform. Evaporation of the chloroform left a dark gummy residue which on filtration through alumina in benzene gave a crystalline product (4 g). Successive recrystallizations from acetone gave the dibromocyclopropanoandrostane (**7**) (1.3 g), mp 199–200°C; $[\alpha]_D^{23}$ +20° (*c* 0.995); ir ν_{max}: 1765 (cyclopropyl ester), 1735 (17β-acetoxy C=O) cm^{-1}; ^{1}Hmr δ: 4.62 (t, J = 8 Hz, 17α-proton), 2.10 (s, 3β-acetoxy), 2.02 (s, 17β-acetoxy), 0.83 (s, 19-methyl), 0.78 (s, 18-methyl), 0.66 (1H, J = 12, 11.5, 4 Hz) ppm; ms *m/e*: 544, 546, 548 (M^+), 502, 504, 506 (M^+ − ketene), 465, 467 (M^+ − Br), 423, 425 [M^+ − (ketene + Br)]. *Anal.* calcd. for $C_{24}H_{34}Br_2O_4$: C 52.76, H 6.27, Br 29.25; found: C 53.04, H 6.36, Br 29.33.

*2α,3-(*endo*)-Bromocyclopropano-5α-androstane-3β,17β-diol Diacetate (8)*

(*a*) A stirred mixture of Zn dust (3.3 g) and cuprous chloride (4.9 g) in dry ether (10 ml) were heated to reflux for 30 min to give a zinc–copper couple (32). The dibromocyclopropanoandrostane (**7**) (546 mg) was added and reflux continued for a further 4.5 h. The reaction mixture as poured into aqueous sodium bicarbonate and extracted with ether to give a crude residue (344 mg). Recrystallization from ether–methanol gave the monobromo derivative (**8**), mp 163–164°C; ir ν_{max}: 1752 (cyclopropyl ester), 1735 (17β-acetoxy C=O) cm^{-1}; ^{1}Hmr δ: 4.58 (t, J = 8 Hz, 17α-proton), 3.37 (d, J = 10 Hz, *exo*-cyclopropyl proton), 1.98, 2.03 (2 × s, 3β- and 17β-acetoxy methyl) 0.88 (s, C-19 methyl), 0.77 (s, C-18 methyl), 0.66 (1H, J = 12, 12, 4 Hz) ppm; ms *m/e*: 387 (M^+ − Br), 345 [M^+ − (Br + ketene)], 285 [M^+ − (Br + ketene + HOAc)]. *Anal.* calcd. for $C_{24}H_{35}O_4Br$: C 61.66, H 7.55; found: C 61.87, H 7.59.

(*b*) To a solution of the dibromocyclopropanoandrostane (**7**) (292 mg) in dry dioxane (30 ml) and triethylamine (0.2 ml) was added 2 teaspoonsful of Raney nickel which had been stored under ethanol. This mixture was vigorously stirred under a hydrogen atmosphere for 32 h after which time the catalyst was filtered off and washed with diethyl ether. The ether filtrate was washed with dilute hydrochloric acid, distilled water, and brine. After drying over magnesium sulfate, the ether phase was evaporated at reduced pressure to give a crystalline material (106 mg), mp 160–161°C; recrystallization from hot methanol gave 2α,3-(*endo*)-bromocyclopropano-5α-androstane-3β,17β-diol diacetate (**8**), mp 162–162.5°C; ir ν_{max}: (KBr) 3070 (cyclopropyl, C—H), 1740 (3β-ester, C=O), 1734 (17β-ester, C=O) cm^{-1}; ms *m/e*: 387 (M^+ − Br), 345 [M^+ − (Br + ketene)], 285 [M^+ − (Br + ketene + HOAc)].

3-Bromo-5α-A-homoandrost-2-ene-3aξ,17β-diol Diacetate (9)

A stirred solution of the dibromocyclopropanoandrostane (**7**) (548 mg) and lithium aluminium hydride (500 mg) was heated to reflux in dry ether (15 ml). After 40 h the reaction mixture was poured onto crushed ice and extracted with ether. The crude product was treated overnight at room temperature with acetic anhydride and pyridine. Chromatography of the acetylation product over neutral alumina gave fractions on elution with 5% ether – petroleum ether (77 mg) which on recrystallization from ether – petroleum ether gave the A-homoandrostene (**9**), mp 158–159.5°C; ir ν_{max}: 1740 (3ξ-ester, C=O), 1733 (17β-ester, C=O) cm^{-1}; ^{1}Hmr δ: 6.13 (heptet, J = 10, 6, 2.5 Hz, vinyl proton), 5.50 (d, J = 11 Hz, 3aξ-proton) 4.89 (dd, J = 7, 8.5 Hz, 17α-proton), 2.41 (dd, J = 15, 10 Hz, 1α- or 1β-proton), 2.03, 2.13 (2 × s, 3β- and 17β-acetoxy methyl), 0.75, 0.77 (2 × s, C-18 and C-19 methyl) ppm; ms *m/e*: 466, 468 (M^+), 406, 408 (M^+ − HOAc), 387 (M^+ − Br), 327 [M^+ − (HOAc + Br)].

3-Trimethylsiloxy-5α-androst-2-en-17β-yl Acetate (3d)

The silyl enol ether (**3d**) was prepared by the procedure of House *et al.* (Method A, ref. 33), mp 90–103°C; ir ν_{max}: 1736 (ester C=O), 1669 (enolic C=C cm^{-1}; ^{1}Hmr δ: 4.1–4.6 (m, vinyl and 17α-protons), 1.81 (s, acetoxy), 0.64 (s, C-18 and C-19 methyl), 0 (s, trimethylsiloxy) ppm. *Anal.* calcd. for $C_{24}H_{40}O_3Si$: C 71.24, H 9.96; found: C 71.23, H 10.01.

Simmons–Smith Treatment of 3-Trimethylsiloxy-5α-androst-2-en-17β-yl Acetate (3d)

The silyl enol ether (**3d**) was treated with an excess of the Simmons–Smith reagent as described above for **3c**. The crude product showed the presence of a complex multiplet centered at δ 0.56 ppm (cyclopropyl protons) in the ^{1}Hmr spectrum. Chromatography over alumina gave no clearly defined products or crystalline fractions.

17β-Hydroxy-2α,3α-cyclopropano-5α-androstane (10)

This product was prepared by the Simmons–Smith procedure in ref. 24, mp 129–130°C (lit. (16) mp 130–132°C).

17β-Acetoxy-2α,3α-deuteriocyclopropano-5α-androstane-d_2 *(11)*

Prepared by the procedure in ref. 24, using CD_2I_2, mp 99–101.5°C; ms 98% d_2 (lit. (16) mp 105–106°C).

17β-Hydroxy-2α,3α-cyclopropano-5α-androstane-2β,4,4-d_3

17β-Acetoxy-5α-androstan-3-one-2,2,4,4-d_4 was prepared by

the procedure in ref. 34. Treatment of the crude product with 1 equiv. of bromine in CH_2Cl_2 gave the 2α-bromo derivative which was reduced to the 3ξ-alcohols with sodium borohydride. The epimeric mixture was treated with a zinc–copper couple in acetic acid as in ref. 24 to give 17β-acetoxy-5-androstene-2,4,4-d_3, mp 95–99°C (lit. (35) mp 96°C); ms: d_3 35%, d_2 40%, d_1 21%; ^{1}Hmr the ratio of 17α-H to vinyl proton shows 75% 2β-D. Treatment of the olefin with CH_2I_2 as in ref. 24 gave a product which on hydrolysis yielded 17β-hydroxy-2α,3α-cyclopropano-5α-androstane-2β,4,4-d_3, mp 128–129°C (lit. (16) mp 130–132°C); ms: d_3 24%, d_2 46%, d_1 25%; ^{1}Hmr δ −0.18 (1H, m), 0.50 (2H, m) ppm.

Acknowledgements

We wish to thank Mr. R. C. Linklater, Mr. Dennis Michiel, and Ms. Mohani Singh for their technical assistance and Mr. Mark West for comments on the typescript. Financial assistance from the Faculty of Graduate Studies, Research Board, University of Manitoba, and the Medical Research Council of Canada, is gratefully acknowledged.

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