Anal. Calcd for $C_{22}H_{35}NO_4$: C, 69.99; H, 9.35; N, 3.71. Found: C, 70.00; H, 9.64; N, 3.89.

Similarly, the corresponding 11 ketone **19** (77.4 mg) was heated *in vacuo* for 90 sec at 250°. The product was purified by chromatography over 7.5 g of silica gel. After removal of a slight impurity with 10% ether–petroleum ether, the main product was obtained by elution with 20% ether–petroleum ether. The noncrystalline product, homogeneous by nmr, amounted to 44.1 mg (59%). It was identical with the 20-methoxime **24** of the Δ^{13} olefin **5** by the following criteria. The infrared spectra (Nujol mull of solid films) and nmr spectra were identical. The mass spectra of the two preparations showed identical fragmentation patterns and were nearly superimposable, except that the methoxime prepared from **5** showed a small impurity at *m/e* 488, attributable to formation of a small amount of the **11**, 20-bis methoxime of **5**. The high-resolution spectrum of the purified pyrolysis product exhibited a molecular ion peak at a *m/e* of 459.2647 (calcd 459.26207), and an M + 1 peak at 460.2708 (calcd 460.26543).

The reference sample of the methoxime **24** was prepared by condensation of the Δ^{13} olefin **5** with methoxyamine hydrochloride in pyridine using the method described above. The product was noncrystalline though very nearly homogenous as judged by thin layer chromatography and the nmr spectrum. A high-resolution mass spectrum showed a strong molecular ion peak at a *m/e* of 459.2645 (calcd 459.26207) and an $(M + 1)^+$ peak at 460.2704 (calcd 460.26543). A small impurity, estimated to be less than 5% by nmr, was revealed by the presence of a small peak at *m/e* 488. The impurity is assumed to be the 11,20-bis-methoxime of the olefin **5**.

Registry No.—**1**, 24298-90-6; **2**, 24298-91-7; **3**, 24298-92-8; **4**, 24298-93-9; **5**, 24343-86-0; **6**, 24298-94-0; **7**, 24298-95-1; **8**, 24298-96-2; **9**, 24428-66-8; **10**, 24381-50-8; **11**, 24298-97-3; **12**, 24381-51-9; **13**, 24298-98-4; **14**, 24298-99-5; **15**, 24343-87-1; **16**, 24299-00-1; **17**, 24299-01-2; **18**, 24299-02-3; **19**, 24299-03-4; **20**, 24381-52-0; **21**, 24299-04-5; **22**, 24299-05-6; **23**, 5067-60-7; **24**, 24299-07-8; **25**, 4970-39-2; **26**, 24343-88-2; hydrogen fluoride, 7664-39-3; triol of **21**, 24298-71-3; diol of **12**, 24298-72-4; diol of **6**, 24298-70-2.

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Solvolysis of 19-Substituted Androstane Derivatives[1,2]

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Dehydromesylation of 19-hydroxy-5α-androst-2-en-17-one mesylate (**1**) by the action of hot pyridine gives a mixture of steroidal olefinic products, the principal constituent of which is shown to be B(9a)-homo-2,5(10)-estradien-17-one (**2a**). 19-Hydroxy-5α-androstan-17-one mesylate (**7b**) behaves in an analogous fashion and gives rise to B(9a)-homo-5(10)-estren-17-one (**8a**) and B(9a)-homo-5α-estr-1(10)-en-17-one (**9**). Chemical degradation and mass spectral analysis confirmed the proposed structures.

Solvolysis of 19-substituted steroids is of interest both from a mechanistic viewpoint and as a pathway to structurally modified steroid hormones. Previous studies have indicated that the products formed upon solvolysis of 19-substituted steroids depend largely on the substituents in rings A and B. For example, homoallylic participation of a double bond has been noted with 3-oxo-19-mesyloxyandrost-4-ene and 3-ethylenedioxy- (or acetoxy-) androst-5-ene systems. In these instances, solvolysis afforded 6β,19-cyclo and 5β,19-cyclo steroids,[3,4] respectively. Moreover, the expansion of ring A to the A-homo-19-nor system was reported in the case of 3-oxo-19-tosyloxyandrostane[5] and 3-oxo-19-mesyloxyandrosta-1,4-diene systems.[6] With 2-oxo-19-mesyloxy steroids, however, no ring enlargement occurred, and the corresponding 1β,19-cyclo steroid derivative was isolated.[7] It is noteworthy that in all cases no expansion of ring B was reported.

In the course of studies on the synthesis of C-19 radio-labeled steroids, we examined the solvolysis products of 19-hydroxy-5α-androst-2-en-17-one mesylate[8] (**1**) and the corresponding dihydro derivative (**7b**). Refluxing a solution of **1** in pyridine afforded a mixture of steroidal olefins which upon thin layer chromatography on silica gel G impregnated with silver nitrate indicated the presence of two products. Chromatography of the reaction mixture on alumina (activity II) yielded a crystalline product **2a** (25%), an oily product (20%),[9] and starting material (45%).

Compound **2a** was analyzed for $C_{19}H_{26}O$. The intense end absorption in the uv spectrum indicated the presence of nonconjugated double bonds as well as the presence of a highly substituted double bond. The nmr spectrum showed one angular methyl group corresponding to the C_{18} methyl at δ 0.97. This

(1) The work conducted in these laboratories was supported by the American Cancer Society Grant PRA-18 and National Institute of Health Grant CA-08349.

(2) (a) A preliminary account of this work has appeared: F. Kohen, L. K. Lala, W. Van Bever, and R. E. Counsell, *Chem. Commun.*, 347 (1969). (b) Presented in part at the VIth IUPAC Meeting on Steroids and Natural Products, Mexico City, April 1969, Abstract 5A, p 27.

(3) J. J. Bonet, H. Wehrli, and K. Schaffner, *Helv. Chim. Acta*, **45**, 2615 (1962).

(4) O. Halpern, P. Crabbe, A. D. Cross, I. Delfin, L. Cervantes, and A. Bowers, *Steroids*, **4**, 1 (1964).

(5) W. G. Dauben and D. A. Ben-Efraim, *J. Med. Chem.*, **11**, 287 (1968).

(6) P. Wieland and G. Anner, *Helv. Chim. Acta*, **51**, 1932 (1968).

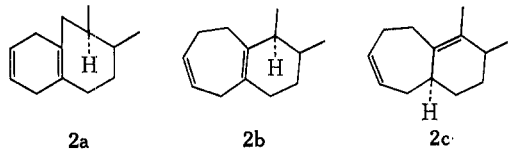
(7) M. E. Wolff and T. Morioka, *J. Org. Chem.*, **30**, 2553 (1965).

(8) R. E. Counsell, G. W. Adelstein, P. D. Klimstra, and B. Smith, *J. Med. Chem.*, **9**, 685 (1966).

(9) This product appeared homogeneous on tlc, but it showed three C-18 methyl peaks in the nmr, indicating that it was still a mixture. Because of the difficulty in purification, it was not further investigated.

indicated that the C_{19} methyl had become part of the steroid nucleus. The presence of two vinyl protons at δ 5.6 (multiplet) similar to that of starting material and the absence of cyclopropyl protons suggested that the suspected additional double bond was tetrasubstituted. This conclusion was substantiated by the formation of a monoepoxide **3**, which still showed two vinyl hydrogens at δ 5.6 and the absence of methine hydrogens attached to a carbon bearing an oxygen function. Treatment of **2a** with excess *m*-chloroperbenzoic acid, however, gave a product formulated as **4**, which can be viewed as arising from a *trans* diaxial opening in the initial diepoxide with *m*-chlorobenzoic acid. Reduction of **2a** with LiAl-(*t*-OBu)$_3$H and subsequent acetylation gave a crystalline acetate **5**.

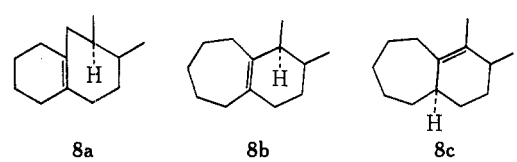
Of all the possible Wagner–Meerwein rearrangement products, only structures **2a–c** were consistent with the above data. A distinction between the A-homo structures (**2b** and **2c**) and **2a** was made by examination of the mass spectrum. The following pertinent peaks were observed: *m/e* 270 (M^+), 216 (M − 54, loss of butadiene), 106 (a C_8H_{10} fragment), 91 (loss of a methyl group from the 106 fragment to give a tropylium cation), and 65 (a cyclopentadienyl cation arising from *m/e* 91 by loss of HC≡CH). The fragments at *m/e* 106 and 91 can be easily derived from a B(9a)-homo steroid such as **2a** but not from the A-homo formulations **2b** or **2c** which would require extensive bond ruptures to form the observed fragment ions.



2a **2b** **2c**

Further proof of the correctness of **2a** was derived by chemical means. Dehydrogenation of **5** with Pd–C (5%) in diethylene glycol solution gave the aromatic derivative, **6**: *m/e* 270 (M^+); uv max (EtOH) at 278 mμ (ϵ 400), 274 (shoulder, 370), and 269 (ϵ 460). The nmr spectrum of **6** showed four aromatic hydrogens at δ 6.85 (singlet) and four benzylic hydrogens at δ 2.76.[10] (See Chart I.)

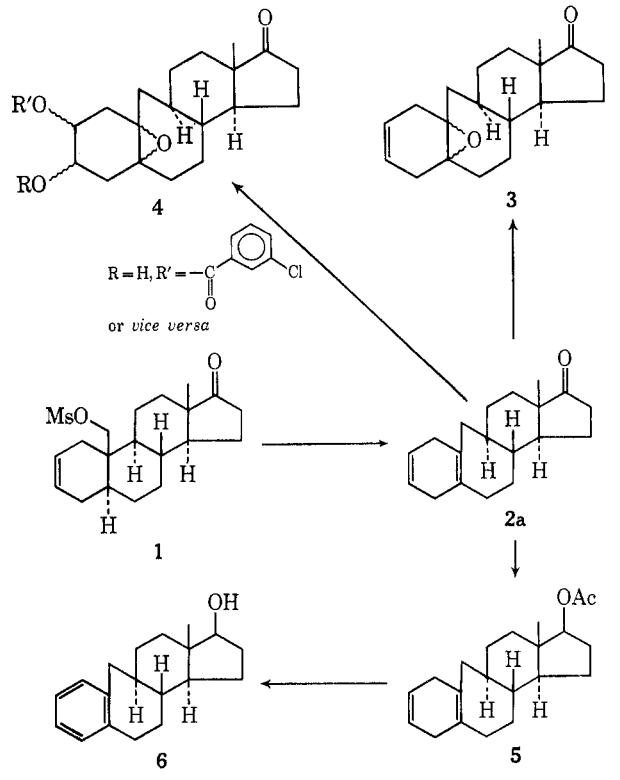
In the dihydro series we found that solvolysis of 19-hydroxy-5α-androstan-17-one mesylate (**7b**) in refluxing pyridine gave an olefinic mixture which was readily separated by chromatography into two components, **8a** and **9**. The more mobile component **8a** was analyzed for $C_{19}H_{28}O$ and displayed no vinyl or cyclopropyl protons in the nmr. Again, consideration of all the possible products that could arise from the solvolysis of **7b** revealed that only structures **8a–c** would fit the data.



8a **8b** **8c**

The correctness of the assignment of structure **8a** to the rearranged product was confirmed both by mass spectral analysis and chemical degradation. The mass spectrum of **8a** showed the following pertinent peaks: *m/e* 272 (M^+), 244 (M − 28, loss of ethylene), 108 (M − 164, a C_8H_{12} fragment), and 91 (tropylium cation). Loss of ethylene involves a retro Diels–Alder process and is typical of an olefinic linkage suitably placed in a cyclohexane ring.[11] Moreover, treatment of **8a** with *m*-chloroperbenzoic acid gave a monoepoxide **12**, identical in all respects with the product obtained by hydrogenation of **3** (Chart II).

CHART I



The more polar component **9** was isomeric with **8a**. It differed, however, in that the nmr spectrum showed the presence of one vinyl hydrogen at δ 5.40 (triplet, J = 6.5 cps) as well as the absence of a C-19 methyl group. Mass spectral analysis showed the molecular-ion peak at *m/e* 272, loss of ethylene at *m/e* 244, the C_8H_{12} fragment at *m/e* 108, and the tropylium cation at *m/e* 91. The B(9a)-homo structure **9** was thus assigned on the basis of this physical data.

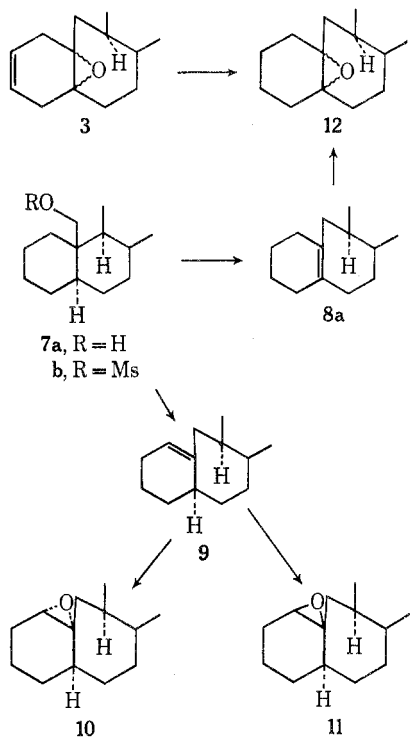
Epoxidation of **9** with *m*-chloroperbenzoic acid gave two epoxides which were separated by chromatography. Structure **10** was tentatively assigned to the more mobile α-epoxide and **11** to the more polar β-epoxide. The two epoxides exhibited different nmr spectra. In **10**, the 1β proton was less shielded and appeared at δ 3.35 (dd, J = 5 cps) in $CDCl_3$ solution and at δ 3.07 (dd, J = 5 cps) in C_6D_6 solution, whereas, in the β-epoxide, **11**, the 1α proton was more shielded and appeared at δ 3.15 (d, J = 6) in $CDCl_3$ solution and at δ 2.95 (d, J = 6 cps) in C_6D_6 solution.

Thus the solvolysis of 19-substituted steroids offers another approach to the B(9a)-homo steroid derivatives and complements the route developed by Kupchan and

(10) Compare with the nmr spectrum of tetralin, "Varian Spectra Catalog" Vol. 2, no. 577.

(11) H. Budzikiewicz, C. Djerassi, D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. II, Holden-Day Inc., San Francisco, Calif., 1964, p 98.

CHART II



coworkers which involves Wolff–Kishner reduction of 9β,19-cyclo-11-oxo steroids.[12]

Experimental Section[13]

Solvolysis of 19-Hydroxy-5α-androst-2-en-17-one Mesylate (1).—A solution of the methanesulfonate[8] (1) (1 g) in pyridine (25 ml) was heated under reflux for 1 week, then evaporated to dryness under reduced pressure. The residue was extracted with ether, and the ether extract was washed successively with water, dilute HCl, and water. The solvent was removed and the residue was examined by tlc on silica gel G impregnated with $AgNO_3$. This revealed three spots. The spot with the lowest R_f corresponded to starting material. The reaction mixture was then chromatographed.

Elution with petroleum ether–ether mixture (8:2) gave a crystalline solid (200 mg), identified as **B(9a)-homo-2,5(10)-estradien-17-one (2a)**: mp 99–100° (from CH_3OH); $[\alpha]D$ +116°; nmr ($CDCl_3$) δ 5.6 (m, 2, vinyl hydrogens at C-2 and C-3), 0.97 (s, 3, C-18 CH_3); mass spectrum (70 eV) *m/e* (relative intensity) 270 (100, M^+), 216 (32, loss of butadiene), 106 (38, C_8H_{10} fragment), 91 (46, tropylium cation), 65 (20, cyclopentadienyl cation).

Anal. Calcd for $C_{19}H_{26}O$: C, 84.39; H, 9.69. Found: C, 84.38; H, 9.61.

Further elution with the same solvent system gave an oil (150 mg) which failed to crystallize and was not examined further.[9] Further elution with petroleum ether–ether mixture (7:3) gave starting material (450 mg).

Action of *m*-Chloroperbenzoic Acid on B(9a)-Homo-2,5(10)-estradien-17-one. A.—A solution of *m*-chloroperbenzoic acid (100 mg) in chloroform (5 ml) was added to a solution of B(9a)-homoestra-2,5(10)-dien-17-one (2a) (150 mg) in the same solvent (5 ml). The mixture was allowed to stand at room temperature for 30 min and decomposed with aqueous KI solution. The organic layer was washed successively with saturated $Na_2S_2O_3$ solution, water, sodium bicarbonate solution, and water and was dried and evaporated. The oily residue was chromatographed, and elution with petroleum ether–ether (8:2) gave **5,10ξ-epoxy-B(9a)-homo-5ξ-estr-2-en-17-one (3)** (62 mg): mp 124–125° (from CH_3OH); $[\alpha]D$ +130°; nmr ($CDCl_3$) δ 5.6 (m, 2, vinyl hydrogens at C-2 and C-3), 0.97 (s, 3, C-18 CH_3).

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.51; H, 9.11.

B.—Under the same experimental conditions as above excess peracid yielded after chromatography a compound tentatively identified as **5,10ξ-epoxy-2ξ,3ξ-dihydroxy-B(9a)-homo-5ξ-estra-17-one 2- or 3-*m*-chlorobenzoate (4)**: mp 228–229° (from CH_3OH); $[\alpha]D$ +210°; nmr ($CDCl_3$) δ 7.95, 7.81, 7.45, 7.35, (four aromatic protons), 5.25 (m, 1, a methine hydrogen attached to a carbon bearing a benzoate group), 4.45 (m, 1, a methine hydrogen attached to a carbon bearing a hydroxy group), 0.97 (s, 3, C-18 CH_3); mass spectrum (70 eV) *m/e* 458 (M^+).

Anal. Calcd for $C_{26}H_{31}O_5Cl$: C, 67.96; H, 6.81. Found: C, 67.61; H, 6.64.

B(9a)-Homo-2,5(10)-estradien-17β-ol Acetate (5).—A solution of **2a** (200 mg) in THF (20 ml) was reduced with $LiAl(t\text{-}OBu)_3H$ (600 mg), and the mixture was allowed to stand at room temperature for 1 hr. The excess hydride was then decomposed with dilute HCl, and the organic layer was washed with water, dried, and evaporated. The residue was then acetylated to give B(9a)-homo-2,5(10)-estradien-17β-ol acetate (**5**) (120 mg): mp 86–87° (from CH_3OH); $[\alpha]D$ +51°; mass spectrum (70 eV) *m/e* (relative intensity) 314 (100, M^+), 260 (8, M − butadiene), 254 (29, loss of acetic acid), 200 (59), 106 (28, a C_8H_{10} fragment), 91 (33, tropylium cation).

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.18; H, 9.52.

B(9a)-Homo-1,3,5(10)-estratrien-17β-ol (6).—A solution of B(9a)-homo-19-nor-17β-hydroxy-androsta-2,5(10)-diene acetate (**5**) (50 mg) in diethylene glycol (5 ml) was dehydrogenated with Pd–C (5%) (50 mg) at 180° for 7 hr. The mixture was then allowed to cool, the catalyst was filtered, diluted with water, and extracted with chloroform. The organic layer was then dried and evaporated, and the residue was chromatographed. Elution with petroleum ether–ether (1:1) gave B(9a)-homo-1,3,5(10)-estratrien-17β-ol (**6**) (10 mg): mp 122–124° (from hexane); $[\alpha]D$ +59°; ir (KBr) λ_{max} 2.98 μ (hydroxy); uv max (EtOH) 278 mμ (ε 400), 274 (370), and 269 (460); nmr $CDCl_3$) δ 6.85 (s, 4, aromatic protons), 2.76 (m, 4, benzylic hydrogens), 0.97 (s, 3, C-18 CH_3); mass spectrum (70 eV) *m/e* 270 (M^+).

19-Hydroxy-5α-androstan-17-one (7a).—A solution of 19-hydroxy-5α-androst-2-en-17-one[8] (1 g) in ethanol (200 ml) was hydrogenated using Pd–C (10%) as a catalyst. The residual solid, obtained after removal of solvent and catalyst was crystallized from hexane to give 19-hydroxy-5α-androstan-17-one (**7a**): mp 145–146°; $[\alpha]D$ +88.6°.

Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.61; H, 10.41.

19-Hydroxy-5α-androstan-17-one Mesylate (7b).—A solution of **7a** (1 g) in methanesulfonyl chloride (1.5 ml) and pyridine (10 ml) was allowed to stand at room temperature for 15 min. The mixture was then poured into water and the precipitate was filtered. The product was then dissolved in chloroform and the organic layer was washed with dilute HCl and water dried, and evaporated. The residue was crystallized from hexane to give **7b**: mp 155–156°; $[\alpha]D$ +51°.

Anal. Calcd for $C_{20}H_{32}O_4S$: C, 65.19; H, 8.75. Found: C, 65.23; H, 8.65.

Solvolysis of 19-Hydroxy-5α-androstan-17-one Mesylate (7b).—A solution of **7b** (1 g) in pyridine (25 ml) was heated under reflux for a week. The reaction mixture was then poured into water and extracted with chloroform. The organic layer was then washed with dilute HCl and water, dried, and evaporated. Tlc analysis on silica gel G impregnated with $AgNO_3$ revealed two spots, each of equal intensity.

The reaction mixture was chromatographed on alumina (60 g), collecting 125-ml fractions. Fractions 3–6 (hexane) yielded 350 mg of **8a**, **B(9a)-homo-5(10)-estren-17-one**: mp 132–134° (from CH_3OH); $[\alpha]D$ +64.5°; nmr ($CDCl_3$) δ 0.95 (s, 3, C-18 CH_3); mass spectrum (70 eV) *m/e* (relative intensity) 272 (100, M^+), 244 (22, loss of ethylene), 108 (9, a C_8H_{12} fragment), 91 (40, tropylium cation).

Anal. Calcd for $C_{19}H_{28}O$: C, 83.77; H, 10.36. Found: C, 83.68; H, 10.36.

Fractions 7–10 (hexane–ether 9:1) yielded 460 mg of **9**, **B(9a)-homo-5α-estr-1(10)-en-17-one**: mp 88–90° (from CH_3OH); $[\alpha]D$ −17°; nmr δ 5.4 (t, 1, J = 6.5 cps), 0.87 (s, 3, C-18 CH_3); mass spectrum (70 eV) *m/e* (relative intensity) 272 (100, M^+), 244

(12) S. M. Kupchan, E. Abushanab, K. T. Shamasundra, and A. W. Bly, *J. Amer. Chem. Soc.*, **89**, 6327 (1967).

(13) The nmr spectra were obtained with a Varian A-60A spectrometer. The optical rotations were obtained in $CHCl_3$. The melting points were obtained on a Fisher-Johns apparatus and are not corrected. Woelm neutral alumina (activity II) was used for chromatography.

(43, loss of ethylene), 108 (80, a C_8H_{12} fragment), 91 (49, tropylium cation).

Anal. Calcd for $C_{19}H_{28}O$: C, 83.77; H, 10.36. Found: C, 83.81; H, 10.49.

5,10ξ-Epoxy-B(9a)-homo-5ξ-estran-17-one (12). A. By Epoxidation of B(9a)-Homo-5(10)-estren-17-one (8a).—*m*-Chloroperbenzoic acid (50 mg) was added to a solution of **8a** (100 mg) in chloroform (10 ml), and the mixture was allowed to stand at room temperature for 30 min. After the usual work-up, the residue was crystallized from CH_3OH to give **12**: mp 124–125°; $[\alpha]D$ +75.5°; nmr ($CDCl_3$) δ 0.97 (s, 3, C-18 CH_3).

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.18; H, 9.68.

B. By Hydrogenation of 5,10ξ-Epoxy-B(9a)-homo-5ξ-estr-2-en-17-one (3).—A solution of **3** (50 mg) in EtOH (50 ml) was hydrogenated using Pd–C (5%) as a catalyst. After removal of solvent and catalyst, the residue was crystallized from CH_3OH to give **12**, mp 124–125°, identical in all respects (R_f, melting point, nmr, and ir) with the product described above.

Action of *m*-Chloroperbenzoic Acid on B(9a)-Homo-5α-estr-1(10)-en-17-one (9).—*m*-Chloroperbenzoic acid (400 mg) was added to a solution of **9** (400 mg) in chloroform (10 ml), and the mixture was allowed to stand at room temperature for 10 min. After the usual work-up the residue was chromatographed. Elution with petroleum ether–ether (9:1) (150 ml) yielded a crystalline solid (100 mg), identified as the α-epoxide **1α,10-epoxy-B(9a)-homo-5α-estran-17-one (10)**: mp 114–115° (from CH_3OH); $[\alpha]D$ +15.5°; nmr ($CDCl_3$) δ 3.30 (dd, 1, J = 4 cps, 1β proton), 0.85 (s, 3, C-18 CH_3); nmr (C_6D_6) δ 3.07 (dd, 1, J = 5 cps).

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.17; H, 9.80.

Further elution with the same solvent system (600 ml) yielded a crystalline solid (200 mg) identified as the β-epoxide **1β,10-epoxy-B(9a)-homo-5α-estran-17-one (11)**: mp 140–142° (from CH_3OH); $[\alpha]D$ +32.5°; nmr ($CDCl_3$) δ 3.15 (d, 1, J = 6, 1α proton), 0.85 (s, 3, C-18 CH_3); nmr (C_6D_6) δ 2.95 (d, 1, J = 6 cps).

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.15; H, 9.68.

Registry No.—**2a**, 22602-70-6; **3**, 24467-52-5; **4**, 24467-53-6; **5**, 24467-54-7; **6**, 22602-71-7; **7a**, 24467-56-9; **7b**, 24467-57-0; **8a**, 24467-58-1; **9**, 24467-59-2; **10**, 24467-60-5; **11**, 24467-61-6; **12**, 24467-62-7.

Acknowledgments.—The authors are grateful to Dr. P. Klimstra and G. D. Searle and Co. for the mass spectra.

Geminal Substitution *via* Steroidal 2- and 4-Cyano-3-ones

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The conversion of 3-cholestanone (**1**) into 2,2-dimethylcholestan-3-one (**15**) *via* 2β-cyano-2α-methylcholestan-3-one, to 2,2-dimethyl-5β-cholestan-3-one (**4**) *via* 2α-cyano-2β-methyl-5β-cholestan-3-one (**9**), and to 4,4-dimethylcholestan-3-one (**17**) *via* 4β-cyano-4α-methylcholestan-3-one (**13**) are reported as a model study of the site and stereoselectivity of alkylations. The assignments of the stereochemistry are made on the basis of nmr spectral correlations and chemical conversions. The preparation of 2,2-dimethyl-7-cholesten-3-one illustrates the conversion for an acid-sensitive compound. The syntheses of 4,4-dimethylcholestan-3β-ol-3,30-d_2 (**25**) and 4,4-dimethylcholestan-3-one-30-*d* (**26**) provide compounds for model-independent assignments of chemical shift for the axial and equatorial geminal methyls.

A key step in a number of terpene syntheses is the construction of a geminal center adjacent to the keto group on a cyclohexanone ring. A widely used method for carrying out this substitution, the carbon alkylation of enolate anions of β-keto esters, appears to give epimeric mixtures in most cases.[1,2] As part of a synthetic study designed to furnish labeled compounds for biosynthetic studies, we have carried out a model study of the site and stereoselectivity of carbon substitution in the methylation of potassium enolates of 2-cyanocholestan-3-one, 2-cyano-4-cholesten-3-one, 4-cyanocholestan-3-one, and 4-cyano-1-cholesten-3-one. Our results, which provide a route for control of the site of substitution of unsymmetrical ketones and give geminally substituted compounds which have stereochemistry not previously readily obtained, are reported herein.

2-Cyano ketones have been used occasionally in natural product synthesis.[3,4] The work of Kuehne[3,4] is especially pertinent since it suggests that alkylation of the cyanocholestanones may be stereospecific.

Results and Discussion

The synthesis of 2β-cyano-2α-methylcholestan-3-one (**4**) in 39% yield from cholestan-3-one (**1**) is outlined in Scheme I. Stereochemistry at C-2 is determined by the course of the methylation of the potassium enolate of **3**. The assignment of stereochemistry at the geminal center of **4** rests on spectral and chemical criteria (*vide infra*). The 2β-cyano-2α-methyl ketone **4** is accompanied by approximately 18% oxygen alkylated enol ether isomer. A careful search for the C-2 epimer of **4** led only to the estimate that, if present, this compound is formed in less than 5% yield. The conversion of **1** to **4** illustrates geminal substitution at the preferentially formylated α-methylene of an unsymmetrical cyclohexanone.

The effect of a Δ^4 double bond on the stereospecificity of the methylation is of interest for its potential in controlling stereoselectivity.[4] *A priori* it would be assumed that the flattening of the ring caused by the

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(3) (a) W. S. Johnson, J. W. Peterson, and C. D. Butsche, *J. Amer. Chem. Soc.*, **69**, 2942 (1947); (b) D. K. Banerjee, S. Chatterjee, C. N. Pillai, and M. V. Bhatt, *il id.*, **78**, 3769 (1956); (c) M. Kuehne, *ibid.*, **83**, 1492 (1961).

(4) After completion of our work we learned of similar studies by M. Kuehne [*J. Org. Chem.*, **35**, 171 (1970)] and M. Kuehne and J. A. Nelson [*ibid.*, **35**, 161 (1970)] on monocyclic, bicyclic, and tricyclic systems. The stereochemical results in that work and the present report are in agreement. We are grateful to Professor Kuehne for kindly providing prepublication copies of the manuscripts.