Registry No.—I, 2810-21-1; 1-(*p*-hydroxybenzyl)-6,7-dimethoxy-2-acetyl-1,2,3,4-tetrahydroisoquinoline, 16562-16-6; III, 4880-87-9; IV, 16562-06-4; V, 16562-07-5; VI; 524-20-9; VII, 517-97-5; X, 16562-08-6; XV, 16562-09-7; XIX, 13509-87-0; XX, 16562-11-1; (−) XXI, 16562-12-2; (−) XII, 16562-13-3; (±) XII, 16562-14-4; 1-(*p*-benzyloxybenzyl)-6,7-dimethoxy-2-acetyl-1,2,3,4-tetrahydroisoquinoline, 14347-98-9.

Acknowledgments.—We are grateful to the National Institutes of Health for grants (GM 05640 and NB 04529) in partial support of this work. We also thank the following of our colleagues for generous gifts of comparison samples: Dr. K. L. Stuart, (+)-pronuciferine and (−)-tuduranine hydrochloride; Professor C. K. Bradsher, (±)-corydalmine; Dr. R. H. F. Manske, (−)-scoulerine; Professor M. Tomita, isoquinolone XIX; and Dr. Y. Watanabe, imide XX.

Steroids. LXXIX. Synthesis and Reactions of Oxiranes Obtained from 3- and 17-Keto Steroids[1]

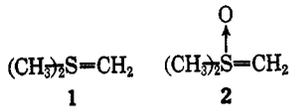
C. E. COOK, ROBERT C. CORLEY, AND MONROE E. WALL

Research Triangle Institute, Research Triangle Park, North Carolina 27709

Received January 19, 1968

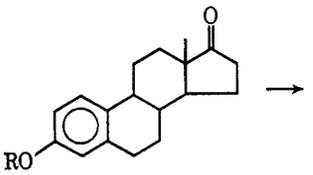
The synthesis of oxiranes from 3- and 17-keto steroids is described. Dimethylsulfonium methylide (1) reacted with estrone in a highly stereoselective manner by α-side addition of CH_2. α-Side addition also predominated in the reaction of 1 with 3-keto-5α steroids (although an earlier claim of stereospecificity has to be modified to stereoselectivity), whereas dimethyloxosulfonium methylide (2) gave products resulting from β-side attack on the 3-keto group. Stereochemistry of the products was demonstrated by chemical conversions. The oxiranes reacted with amines to yield amino alcohols. Spiro-17β-oxiranylestra-1,3,5(10)-trien-3-ol (4a) reacted with sodium cyanide at steam-bath temperature to yield 17α-cyanomethyl-3,17β-estradiol (5e), but under more strenuous conditions the product of this reaction was estrone.

The report by Corey and Chaykovsky[2] that dimethylsulfonium methylide (1) and dimethyloxosulfonium methylide (2) react with ketones and aldehydes to yield oxiranes opened a convenient route to a number of new steroid derivatives by reaction with readily available steroidal ketones. We report here on the preparation and properties of some new steroid oxiranes formed in this manner.[3]

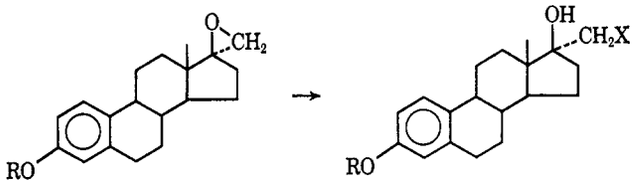


1 2

Estrone (**3a**) reacted smoothly with the sulfonium ylide 1 to yield a single oxirane (**4a**), identified as such by an infrared band at 3040 cm^{-1} and an AB quartet in the nmr spectrum.[4] The stereochemistry at C-17 was demonstrated by reduction with lithium aluminum hydride to the known 17α-methyl-3,17β-estradiol (**5a**).[5] The melting point of the crude diol was not depressed by admixture with authentic **5a** prepared from estrone and methyllithium.



3a, R = H
b, R = CH_3



4a, R = H
b, R = CH_3

5a, R = X = H
b, R = CH_3; X = H
c, R = H; X = $-NC_5H_{10}$
d, R = H; X = $-NHCH_2C_6H_5$
e, R = H; X = −CN

The nmr peak for the 18-CH_3 of oxirane **4a** was at 56 cps while that of the diol **5a** was at 54 cps. The observation that the 18-CH_3 is only slightly less shielded in the oxirane **4a** than in the alcohol **5a** is consistent with the results of Bertin and Nedelec in the androstane series. They reported the 18-CH_3 to shift upfield by δ 0.03 (*ca.* 2 cps) in going from 17β-oxirane to 17α-methyl-17β-ol. On the other hand, there was an upfield shift of δ 0.12 (7 cps) on going from a 17α-oxirane to a 17β-methyl-17α-ol.[3b]

While the conversion in high yield into essentially pure 17α-methyl-3,17β-estradiol was good evidence for stereospecific formation of the 17β-oxirane, the melting range of **4a** was wide enough to suggest a possibility of the presence of the C-17 epimer. When the reaction was repeated using the 3-methyl ether of estrone (**3b**) as substrate, oxirane **4b** (18-methyl resonance at 55.5 cps) and alcohol **5b** (18-methyl resonance at 54 cps) were obtained in high yield by the same sequence

(1) (a) For part LXXVIII, see D. Rosenthal, C. F. Lefler, and M. E. Wall, *Tetrahedron*, **23**, 3583 (1967). (b) This research was carried out under Contract SA-43-ph-4351 of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health. (c) Abstracted in part from work done by R. C. Corley in partial fulfillment of the requirements for the Ph.D. degree at North Carolina State University at Raleigh. (d) Portions of this work were presented at the 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965, Abstracts 92P. See also C. E. Cook, R. C. Corley, and M. E. Wall, *Tetrahedron Lett.*, 861 (1965).

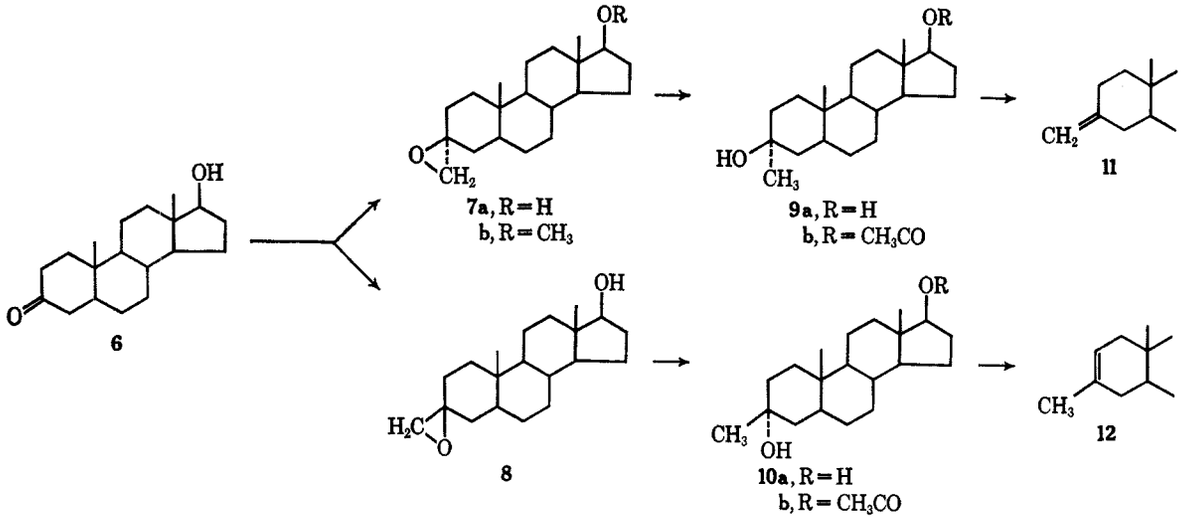
(2) (a) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **84**, 3782 (1962); (b) E. J. Corey and M. Chaykovsky, *ibid.*, **87**, 1353 (1965).

(3) For results of other workers in this area, see, *inter alia*, (a) G. Drefahl, K. Ponsold, and H. Schick, *Ber.*, **97**, 3529 (1964); (b) D. Bertin and L. Nedelec, *Bull. Soc. Chim. Fr.*, 2140 (1964); (c) H. G. Lehmann, O. Engelfried, and R. Wiechert, *J. Med. Chem.*, **8**, 383 (1965).

(4) Unless otherwise noted, all nmr spectra were obtained at 60 Mc in deuteriochloroform with tetramethylsilane as internal standard.

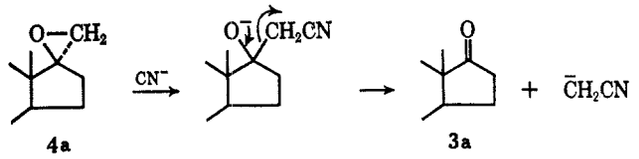
(5) (a) E. Haack, G. Stoek, and H. Voigt, *Naturwissenschaften*, **41**, 429 (1954); (b) L. F. Fieser, *Experientia*, **6**, 312 (1950).

SCHEME I



of steps. Nmr spectra showed trace peaks at 50.5 and 43 cps in the oxirane and alcohol, respectively, which could be due to 18-methyl resonances of not more than 5% of the 17 epimers.[6] Thin layer chromatography also showed only traces of the epimers. Thus with 17-ketones the reaction of sulfonium ylide **1** is highly stereoselective, in contrast to that of oxosulfonium ylide **2**, which yields mixtures of C-17 epimers.[3a,b]

The spirooxirane **4a** reacted smoothly with piperidine and benzylamine in the presence of phenol[7] to yield the substituted amino alcohols **5c** and **5d**. However, prolonged heating of **4a** with sodium cyanide in N,N-dimethylformamide at 110° gave neither the expected β-hydroxynitrile (**5e**) nor its dehydration product. Instead a high yield of estrone was obtained. Acetonitrile was identified in the solution by its retention time on gas chromatography, and the reaction appears to be simply a reverse aldol-type reaction of the anion of the hydroxynitrile **5e**. Reaction in ethylene



4a **3a**

glycol for 24 hr at 120–130° also gave a 40% yield of estrone, but milder conditions (ethylene glycol on a steam bath for 2 hr) gave the desired nitrile **5e**.

When the 3 ketone, dihydrotestosterone (**6**), was treated with ylide **1**, the major product was the β-spirooxirane **7a**, readily obtained in high purity by chromatography on alumina, which separated a small amount of by-product, believed to be the methyl ether of **7a** (**7b**) on the basis of analysis, nmr peaks at 46 (18-CH_3), 53 (19-CH_3), 154 (epoxide CH_2), and 202 cps (OCH_3), and absence of OH bands in the infrared spectrum (Scheme I). Our earlier report of stereospecificity in this reaction[1d] should now be modified to stereoselectivity, since the α isomer (**8**) is also obtained (see below). The α isomer **8** is obtained exclusively when ketone **6** is treated with oxosulfonium ylide **2**.

The stereochemistry of epoxides **7a** and **8** was demonstrated by reduction with lithium aluminum hydride to the epimeric 3-methyl-3,17β-androstanediols **9a** and **10a**. These compounds have been reported by Pelc, who obtained them by reaction of methyl Grignard reagent with dihydrotestosterone and assigned stereochemistry by analogy with known examples.[8] Although Pelc's assignment of configuration appeared reasonable, we felt that an unequivocal demonstration was desirable. Therefore monoacetates **9b** and **10b** were subjected to the dehydrating conditions used by Barton in a study of epimeric 3-methylcholestanols.[9] Nmr spectroscopy clearly demonstrated *exo*-methylene structure **11** for the product from **9b** and endocyclic structure **12** for the product from **10b**. Nmr showed that prolonged treatment of *exo*-methylene **11** with trifluoroacetic acid isomerized it to the endocyclic compound **12**. Reasoning analogous to that of Barton[9] confirms Pelc's assignments of structures **9** and **10**[8] and leads to the structures shown for **7a** and **8**.[1d] Wolff, *et al.*,[10] and Lehmann, *et al.*,[3c] have also reported the oxirane isomer of mp 173–175°. Whereas the former assumed structure **7a**, the latter adduced evidence for structure **8** and prepared **7a** by an independent route. Their results are in accord with those presented here.

The epoxides **7a** and **8** were not separable by tlc under the conditions used, but the corresponding diols **9a** and **10a** and monoacetates **9b** and **10b** were. When the crude product from reaction of ketone **6** and sulfonium ylide **1** was reduced with lithium aluminum hydride and the product acetylated, tlc showed the presence of epimeric acetates **9b** and **10b**, which were separated by preparative tlc. The acetates were also separable by gas chromatography. Complete peak separation was not achieved, making quantitative analysis difficult, but comparison with known mixtures showed **9b** and thus β-oxide **7a** to predominate by a 2:1 ratio.

Analogous results were obtained in the reaction of cholestanone (**13**) with sulfonium ylide **1**. The crude mixture of epoxides (shown to be a mixture by tlc) was reduced with lithium aluminum hydride to the methylcholestanols. Separation by preparative tlc gave the epimeric 3-methylcholestanols **16**. Again, gas chromatography on the crude reduction product indicated

(6) Methyl resonances for the other likely impurities, the methyl ethers of estrone and estradiol, occur at 53 and 47 cps.

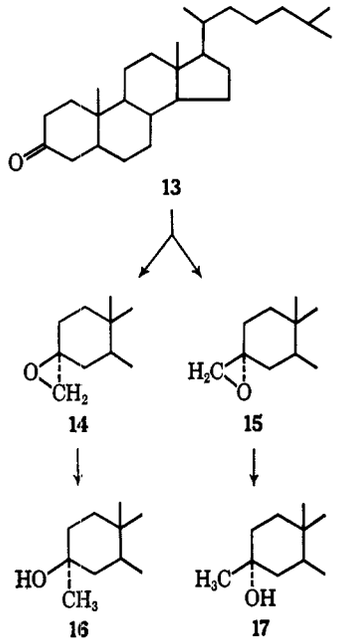
(7) R. Gedeon and V. Gyar, French Patent 1,333,946 (Aug 2, 1963).

(8) B. Pelc, *Collect. Czech. Chem. Commun.*, **25**, 1924 (1960).

(9) D. H. R. Barton, A. da S. Campos-Neves, and R. C. Cookson, *J. Chem. Soc.*, 3500 (1956).

(10) M. E. Wolff, W. Ho, and R. Kwok, *J. Med. Chem.*, **7**, 577 (1964).

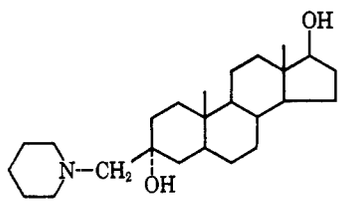
SCHEME II



16 (and thus epoxide 14) to predominate by a 2:1 ratio (Scheme II).

In contrast, cholestanone reacted with the oxosulfonium ylide 2 to give a single epoxide shown to be 15 by direct reduction with lithium aluminum hydride to 3β-methylcholestan-3α-ol (17). None of epimer 16 was observed on thin layer chromatography. These stereochemical results are consistent with those reported by Corey and Chaykovsky.[2b]

Epoxide 8 upon treatment with piperidine and phenol smoothly reacted to form the β-amino alcohol 18. In



all of the ring-opening reactions of the epoxides described, we expected attack of the nucleophile on the least hindered carbon of the oxirane ring to yield a tertiary alcohol. That this was the case was readily demonstrated by the nmr technique of Chapman and King.[11] The amino alcohol 18 in dimethyl sulfoxide-d_6 exhibited a doublet (J = 5 cps) centered at 260 cps for the 17-OH and a singlet at 214 cps for the tertiary 3-OH. Also there was a singlet (2 H) at 127.5 cps for the NCH_2CO protons. The stereochemistry of 18 follows from that of 8 and the mode of attack. Similarly, the hydroxynitrile 5e gave a singlet in dimethyl sulfoxide-d_6 at 293 cps (exchangeable with D_2O) for the tertiary 17-OH and a singlet at 158 cps for the $OCCH_2CN$ group. There were no peaks in the OCH_2 region. Structures of the amino alcohols 5c and 5d were assigned by analogy.

Experimental Section[4]

All reactions involving ylides were carried out under nitrogen in oven-dried apparatus. Tetrahydrofuran was distilled from lithium aluminum hydride just before use. Dimethyl sulfoxide was distilled from calcium hydride at reduced pressure and stored over molecular sieve. Melting points were taken on a Kofler apparatus. Unless otherwise noted optical rotations were obtained in chloroform solution (c approximately 1–2). Analyses were carried out by Micro-Tech Laboratories, Skokie, Ill.

Spiro-17β-oxiranylestra-1,3,5(10)-trien-3-ol (4a).—A 50.2% suspension of sodium hydride in oil (19.2 g, 0.40 mol) was washed with tetrahydrofuran by decantation. Dry dimethyl sulfoxide (300 ml) was added and the sodium salt prepared by stirring and heating for *ca.* 0.75 hr at 70–75° under nitrogen.[2] Tetrahydrofuran (300 ml) was added and the mixture cooled to −5°. Then a solution of 82 g (0.40 mol) of trimethylsulfonium iodide in 700 ml of dimethyl sulfoxide was added rapidly with stirring. During this addition the reaction mixture solidified, and another 400 ml of tetrahydrofuran was added. Next, a solution of 27.0 g (0.1 mol) of estrone in 800 ml of tetrahydrofuran was added. After 2 hr at 0 to −5°, the mixture was allowed to warm to room temperature, poured into 2000 ml of water, and extracted with three 1000-ml portions of chloroform. The combined chloroform layers were dried over sodium sulfate overnight and evaporated. The product was sometimes contaminated with 5–10% of estrone, and the melting point was 170–177° after one recrystallization from methylcyclohexane. The estrone could be removed by crystallization from benzene to yield oxirane 4a: mp 181–183°; $[\alpha]D$ +61°; nmr peaks at 56 (singlet, 18-CH_3) and 172 cps (quartet, J = 5 cps, oxirane CH_2).

Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.04; H, 8.59.

17α-Methyl-3,17β-estradiol (5a). A.—Epoxide 4a (0.5 g) was refluxed for 5 hr with excess $LiAlH_4$ in 50 ml of tetrahydrofuran. Ethyl acetate (50 ml) was slowly added to the reaction mixture and then it was poured into 200 ml of 5% HCl. After two extractions with 100-ml portions of benzene, the organic layers were combined, washed with water, dried over Na_2SO_4, and evaporated. The white residue weighed 0.51 g: mp 187–190°; nmr peaks at 54 and 77 cps (singlets, 18- and 17-CH_3).

B.[5a]—In a dry flask under nitrogen, 0.5 g of estrone in 50 ml of tetrahydrofuran was slowly added to excess methyllithium in tetrahydrofuran–ether solution (55 ml). The solution was stirred 1.5 hr at room temperature and refluxed for 5 hr. Excess reagent was decomposed by addition of 10 ml of methanol followed by 10 ml of water. The mixture was poured into 200 ml of 5% HCl and extracted with benzene. From the benzene, after washing with water, drying over Na_2SO_4, and evaporation, there was obtained 0.56 g of off-white solid, mp 174–183°. Purification of 0.25 g by preparative thin layer chromatography (silica gel HF_{254}, 20% ethyl acetate in benzene) gave 45 mg of estrone (mp and mmp 254–258°) and 144 mg of diol 5a, mp 188–190°, undepressed in a mixture with the substance prepared by method A.

Spiro-17β-oxiranyl-3-methoxyestra-1,3,5(10)-triene (4b).—The 3-methyl ether of estrone (5.0 g, 17.6 mmol) was allowed to react with dimethylsulfonium methylide (63 mmol) in the manner described for estrone. After 1.5 hr the mixture was poured into water and the product obtained by extraction with chloroform. The product was crystallized from aqueous methanol: mp 97–107°. Chromatography on alumina (50 g, activity III) and elution with benzene yielded 4.7 g (90%) of white solid which showed no carbonyl absorption in the infrared, but contained trace impurities (tlc). These were removed from a 300-mg sample by preparative tlc and recrystallization from ethyl acetate to yield the analytical sample: mp 103–105°; nmr peaks at 55.5 (singlet, 18-CH_3) and 167 cps (quartet, J = 5 cps, oxirane CH_2); $[\alpha]D$ +56°.

Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.46; H, 8.95.

When the reaction was repeated on a 100-mg scale (using NaH washed free of oil), and the total product (94 mg) examined by nmr spectroscopy, the 18-CH_3 peak at 55.5 cps was accompanied by a trace peak at 50.5 cps. Separate integration was not possible, but the small peak was 3.5% of the height of the main peak.

Reduction of a homogeneous aliquot of the crude epoxide (70 mg) with $LiAlH_4$ gave 60 mg of crude 3-methoxy-17α-methylestra-1,3,5(10)-trien-17β-ol. The nmr peak at 54 cps (singlet, 18-CH_3) was accompanied by a trace peak at 43 cps about 3% as intense as the major peak, and tlc showed a trace of impurity slightly faster moving than the main spot.

(11) O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, **86**, 1256 (1964).

17α-N-Piperidinomethyl-3,17β-estradiol (5c).—Oxirane **4a** (10 g, 35.2 mmol) containing a small percentage of estrone was dissolved in 100 ml of piperidine, and 3 g of phenol[7] was added. After a 24-hr reflux period, tlc showed the reaction to be complete. The mixture was poured into 500 ml of water and extracted with two 200-ml portions of ether. The combined ether layers were washed with two 100-ml portions of water and 100 ml of saturated sodium chloride solution. Evaporation left a yellow gum. Crystallization from methanol yielded 7.5 g of pale yellow crystals, mp 191–195°. Recrystallization from benzene gave 5.7 g (44%) of **5c**, mp 196.5–198°. One more recrystallization gave the analytical sample: mp 197–198°; $[\alpha]_D$ +41°.

Anal. Calcd for $C_{24}H_{35}NO_2$: C, 78.00; H, 9.55; N, 3.79. Found: C, 78.05; H, 9.51; N, 4.07.

17α-N-Benzylaminomethyl-3,17β-estradiol (5d).—Oxirane **4a** (14 g, 49 mmol) was refluxed with 50 ml of benzylamine and 3 g of phenol.[7] The reaction was followed by gas chromatography (on SE-30) until starting material had almost completely disappeared (29 hr). The cooled solution was poured into 300 ml of water and extracted with ether. The ether was washed with water, dried (sodium sulfate), and evaporated, leaving an oily residue. After several triturations with water to remove benzylamine, the residue was a sticky gum. Trituration of this with methanol yielded 4 g of crystals, mp 189–196°. The filtrate was evaporated and the residue triturated with benzene to yield 4.5 g, mp 192–197°. Chromatography of the filtrate from this crop on 150 g of alumina (Woelm, activity III) gave more product. Recrystallization of the various crops from methanol–methylene chloride gave a total of 11.2 g (58%) of **5d**, mp 193–196°. Three more recrystallizations gave the analytical sample: mp 199–201°; $[\alpha]_D$ +30° (in methanol); nmr peak at 50 cps (singlet, 18-CH_3) in dimethyl sulfoxide-d_6.

Anal. Calcd for $C_{26}H_{33}NO_2$: C, 79.75; H, 8.50; N, 3.58. Found: C, 80.01; H, 8.60; N, 3.51.

Estrone.—A mixture of 0.5 g (1.75 mmol) of oxirane **4a**, 0.45 g (9 mmol) of sodium cyanide, and 2.5 ml of N,N-dimethylformamide (DMF) was heated for 22 hr at 110° under a reflux condenser. The liquid which had condensed on the inside of the condenser was rinsed into a flask with more DMF and examined by gas chromatography (12-ft SE-30 column at 50°, flame ionization detector). A small peak of retention time 1.3 min was observed before the large DMF peak at 2.4 min. This result was identical with that given by a solution of acetonitrile in DMF (2.9 mg/ml). Varying the concentration of acetonitrile caused the size of this peak to change. The dark reaction mixture was poured into water (300 ml) and extracted with benzene (three 100-ml portions). The combined benzene extracts were washed thoroughly with water, dried (sodium sulfate), and evaporated. The crude residue (0.53 g) melted at 245–251°. Recrystallization from benzene gave 0.32 g of estrone, mp 249–254°, and a third recrystallization raised the melting point to 252–255°. The product was identified as estrone by melting point, mixture melting point, and comparison of infrared spectra.

When 100 mg of oxirane **4a** was heated at 120–130° for 24 hr with 4 ml of ethylene glycol and 200 mg of sodium cyanide, and the reaction worked up by pouring into water and extracting with ether, the product consisted mainly of estrone (*ca.* 40% by gas chromatography) and an unidentified product more polar than either estrone or the β-hydroxynitrile **5e**.

17α-Cyanomethyl-3,17β-estradiol (5e).—Oxirane **4a** (0.5 g, 1.75 mmol) was dissolved in 20 ml of ethylene glycol and 1 g of sodium cyanide added. After 2 hr on a steam bath, all the starting material had reacted. The mixture was poured into water and the solid which formed (203 mg) was filtered off. Extraction of the filtrate with ether gave another 276 mg of product. Thin layer chromatography indicated one major product plus a small amount of estrone. The product **5e** (69% yield) was isolated by preparative tlc on silica gel HF_{254} (30% ethyl acetate in benzene). A second chromatography followed by crystallization from benzene gave the analytical sample: mp 227–228°; $[\alpha]_D$ +32° (in methanol); nmr peaks (DMSO-d_6) at 49 (singlet, 18-CH_3), 158 (broad singlet, $-CH_2CN$), 293 (singlet, exchanges with D_2O, 17-OH), and 535 cps (singlet, exchanges with D_2O, ArOH).

Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.13; H, 8.09; N, 4.50. Found: C, 76.77; H, 8.14; N, 4.43.

Spiro-3β-oxiranyl-5α-androstan-17β-ol (7a) and 17β-Methoxyspiro-3β-oxiranyl-5α-androstane (7b).—A solution of dimethylsulfonium methylide (prepared as described for **4a**) was treated with 29 g (0.10 mol) of dihydrotestosterone (**6**) in 500 ml of tetrahydrofuran. Tlc showed that the reaction required 2.5 hr at 0–5° for completion. The mixture was then allowed to warm to room temperature and poured into water (1500 ml) containing 25 ml of acetic acid. Extraction with chloroform yielded a white solid which was recrystallized from benzene. Four crops weighing 5.2, 7.0, 5.6, and 12.5 g were obtained. The third crop was used for further reactions. A portion of the remainder (20 g) was chromatographed on 400 g of alumina (activity III). Elution with benzene gave three fractions. The first (1.4 g, mp 160–161°, $[\alpha]_D$ +8°) was assigned the ether structure **7b** on the basis of analysis, infrared spectrum (oxirane CH_2 at 3035 cm^{-1}, no OH), and nmr peaks at 46 (18-CH_3), 53 (19-CH_3) 154 (oxirane CH_2), and 202 cps (singlet, OCH_3).

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.35; H, 10.89.

The second fraction, a mixture, upon rechromatography yielded 0.1 g of the ether and 4.0 g of **7a**, and the third fraction (14.4 g) upon recrystallization from benzene yielded 11.4 g of **7a**: mp 193–196°; $[\alpha]_D$ +6° (*cf.* ref 3c); nmr peaks at 154 (singlet, CH_2 of oxirane), 53 (19-CH_3), and 45 cps (18-CH_3).

Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59. Found: C, 78.86; H, 10.58.

3α-Methyl-5α-androstane-3β-diol (9a) and 3α-Methyl-17β-acetoxy-5α-androstan-3β-ol (9b).—**7a** (1.00 g) was treated with 0.40 g of lithium aluminum hydride in 200 ml of tetrahydrofuran. The mixture, which contained much solid, was refluxed for 5 hr. Excess hydride was decomposed with ethyl acetate. The reaction mixture was added to 5% HCl and extracted with ether. The ether was washed with $NaHCO_3$ solution and saturated NaCl solution and dried (Na_2SO_4). Evaporation left 0.88 g of solid, which was recrystallized from methanol to yield four crops: 150 mg, mp 193–195°; 360 mg, mp 193–195°; 220 mg, mp 192–195°; and 125 mg, mp 190–195°. There were nmr peaks at 74 (3-CH_3), 49 (19-CH_3), and 44 cps (18-CH_3), and $[\alpha]_D$ was +19° (lit.[8] mp 186–188°; $[\alpha]_D$ +12°). Acetylation of diol **9a** (pyridine–acetic anhydride at room temperature) yielded monoacetate **9b**: mp 207.5–208° (from ether); $[\alpha]_D$ +10° (lit.[8] mp 194–195°; $[\alpha]_D$ +12°); nmr peaks at 122 (CH_3COO), 75 (3α-CH_3), 49 (19-CH_3), and 47.5 cps (18-CH_3).

Dehydration of 3α-Methyl-17β-acetoxy-5α-androstan-3β-ol.—The tertiary alcohol **9b** (70 mg) was dissolved in 10 ml of dry pyridine and cooled to 0°. Then 0.2 ml of phosphorus oxychloride was added and the solution allowed to warm slowly to room temperature.[9] It was then poured into 250 ml of water and extracted with ethyl acetate (three 100-ml portions). The combined ethyl acetate solution was washed thoroughly with water, dried, and evaporated, leaving 54 mg of pale yellow gum (crude **11**) which exhibited infrared bands at 3070, 1645, and 890 cm^{-1} (*exo*-methylene) and nmr peaks at 276 (=CH_2), 122 (CH_3COO), 53 (19-CH_3), and 48 cps (18-CH_3).

To the nmr sample was added 5 drops of trifluoroacetic acid, and the solution was heated in a sealed vial on a steam bath for 24 hr. The solvents were evaporated and the nmr spectrum was rerun. The olefinic proton peak had shifted to 219 cps and the 19-CH_3 to 44 cps. The 3-CH_3 protons of **12** appeared at 98 cps and the acetate and 18-CH_3 protons were unchanged.[12]

Spiro-3α-oxiranyl-5α-androstan-17β-ol (8).[10]—A mixture of 8.24 g (0.192 mol) of 50.2% sodium hydride in oil, 42.6 g of trimethyloxosulfonium iodide (0.194 mol), and 888 ml of dry dimethyl sulfoxide was stirred under nitrogen at room temperature until gas evolution ceased. Solid dihydrotestosterone (27.53 g, 0.095 mol) was added and the solution stirred for 16 hr at room temperature and then for 2 hr at 50°. The solution was poured into 2 l. of water, and the solid which precipitated was filtered off and recrystallized from acetonitrile. Four crops were obtained: 6.5 g, mp 172–175°; 10.0 g, mp 172–175°; 4.7 g, mp 172–175°; and 1.8 g, mp 170–174°. Total yield was 79%. The filtrate from the last crop showed only traces of epoxide on tlc, the bulk of the material consisting of more polar substances. Recrystallization of part of the first crop from acetonitrile gave prisms which changed to needles at *ca.* 160° and melted at 173–174°. Recrystallization of another portion from methanol gave plates which changed to needles at *ca.* 168° and melted at 174–176°: mmp 141–160° with isomer **7a**; $[\alpha]_D$ +7° (lit.[10] mp 173–175°; $[\alpha]_D$ +3°); nmr peaks at 157 (singlet, oxirane CH_2), 52 (19-CH_3), and 45 cps (18-CH_3).

(12) L. M. Jackman, "Nuclear Magnetic Resonance Spectroscopy," Pergamon Press Inc., New York, N. Y., 1959, p 61. Compare, *e.g.*, α-pinene (340 cps) and β-pinene (294 cps).

3β-Methyl-5α-androstane-3α,17β-diol (10a) and 3β-Methyl-17β-acetoxy-5α-androstan-3α-ol (10b).—The oxirane **8** (3.00 g) was reduced with lithium aluminum hydride as described for **7a**. The reaction was worked up by addition of excess ethyl acetate, followed by slow addition of water until all gray material became white. Filtration and evaporation left 2.59 g (86%) of white solid, mp 167–170°. Recrystallization from methanol gave white needles of diol **10a**: mp 169–171° after drying *in vacuo* over refluxing toluene; $[\alpha]D$ +8°; nmr peaks at 82 (3-CH_3) and 44 cps (19-CH_3) (lit.[8] mp 168–170°; $[\alpha]D$ +8°).

The monoacetate **10b** was prepared (acetic anhydride in pyridine) and recrystallized from aqueous acetone. White needles were obtained: mp 207–209° (214–215° after drying *in vacuo* over refluxing toluene); $[\alpha]D$ +6° (lit.[8] mp 205–207°; $[\alpha]D$ +5°); nmr peaks at 122 (CH_3COO), 72 (3β-CH_3), 46 (19-CH_3) and 47.5 cps (18-CH_3).

Dehydration of 10b.—By the procedure used for dehydration of **9b**, 300 mg of acetate **10b** yielded 258 mg of a pale yellow solid (crude **12**): nmr peaks at 122 (CH_3COO), 98 (CH_3C=), 48 (18-CH_3), and 44 cps (19-CH_3).[12]

Reaction of Dimethylsulfonium Methylide with Cholestan-3-one and Reduction of Crude Product.—The sodium salt of dimethyl sulfoxide was prepared from 208 mg (4.3 mmol) of 50% sodium hydride in oil and 12 ml of dimethyl sulfoxide. Tetrahydrofuran (5 ml) was added and the mixture cooled to −5°. A solution of 880 mg of trimethylsulfonium iodide in 7 ml of dimethyl sulfoxide was added rapidly with stirring, followed by 500 mg (1.3 mmol) of cholestan-3-one in 7 ml of tetrahydrofuran. The mixture was stirred for 0.5 hr at −5°, allowed to warm to room temperature, and poured into water. Extraction with hexane yielded 424 mg (82%) of crude epoxide mixture (infrared band at 3040 cm^{-1}, no carbonyl band). On tlc using 10% acetone–hexane, it showed a single spot different from starting material. On continuous tlc using benzene as eluent, two spots were observed, the less polar of which corresponded in R_f to the epoxide obtained from cholestan-3-one and dimethyloxosulfonium ylide.

The crude epoxide was dissolved in 50 ml of tetrahydrofuran. Half of the solution was transferred to a flask and stirred for 1 hr with 300 mg of lithium aluminum hydride. After addition of a few drops of ethyl acetate, the mixture was poured into 100 ml of 1 *N* HCl, and the mixture was extracted with ether. The ether was washed with water, sodium bicarbonate solution, and saturated sodium chloride, and dried over Drierite. Evaporation left 226 mg of a gum. The total sample was dissolved in benzene and an aliquot submitted to preparative tlc (10% acetone–hexane on silica gel H, visualized with Morin dye). The two major bands were removed and eluted with ethyl acetate. After two crystallizations from methanol, the more polar product, 3α-methylcholestan-3β-ol (**16**), melted at 147–149° (lit.[9] mp 147–149°). The less polar 3β-methylcholestan-3α-ol (**17**) melted at 126–127° (lit.[9] mp 126–127°).

An aliquot of the benzene solution of the crude reduction product was analyzed by gas chromatography on a 12-ft column of 1% SE-30 at 240°. The two cholestanols were not completely separated under these conditions, but by comparison with standard mixtures, the 3α-methylcholestan-3β-ol was shown to predominate by a ratio of 2:1. When ether solutions of the pure isomers were stirred for 20 min with 1 *N* HCl, gas chromatography showed that no isomerization occurred.

Reaction of Dimethyloxosulfonium Methylide with Cholestan-3-one and Reduction of the Crude Product.—The reaction was carried out using 208 mg of 50% NaH in oil, 950 mg of trimethyloxosulfonium iodide, and 500 mg of cholestan-3-one in 15 ml of dimethyl sulfoxide and 7.5 ml of tetrahydrofuran. After being stirred for 16 hr at room temperature, the solution was heated at 50° for 2 hr and poured into 50 ml of distilled water. The mixture was extracted with hexane (yield 253 mg) and then with ethyl acetate (yield 163 mg). Both crops were shown by tlc (benzene on silica gel H, continuous flow) to consist of a single product with an R_f equal to that of the less polar epoxide from the preceding reaction.

Reduction of the crude epoxide was carried out as in the preceding case. The product, 3β-methylcholestan-3α-ol (**17**), melted at 126–127° (lit.[9] mp 126–127°) after crystallization from methanol.

Reaction of Dihydrotestosterone with Dimethylsulfonium Methylide and Reduction of the Crude Product.—Sodium hydride (575 mg of 56% suspension in oil, 13.4 mmol) was washed with two 5-ml portions of tetrahydrofuran (by stirring, allowing to settle, and pipetting off the supernatant liquid) and dried in the reaction flask in a stream of nitrogen. Dimethyl sulfoxide (15 ml) was added and the sodium salt formed by stirring at 60–70° for 0.75 hr. After addition of 25 ml of tetrahydrofuran the mixture was cooled below −5° and trimethylsulfonium iodide (2.80 g, 13.7 mmol) in 10 ml of dimethyl sulfoxide was added. After 5 min of stirring, the mixture (*ca.* −10°) was treated with 30 ml of tetrahydrofuran containing 1.00 g (3.45 mmol) of dihydrotestosterone (**6**). A flocculent white precipitate formed immediately. The mixture was allowed to warm to −5° and maintained at −6 to −4°. The reaction was monitored by tlc and was complete in 3 hr. The mixture was then allowed to warm to 15°, poured into 500 ml of water, allowed to stand overnight, and filtered to yield 967 mg of white solid.

The crude product was dissolved in 50 ml of tetrahydrofuran. Half of the solution was treated with 25 ml of tetrahydrofuran and 600 mg of lithium aluminum hydride. The mixture was refluxed for 3 hr, ethyl acetate and water were added, and the mixtue was poured into 200 ml of 1 *N* HCl. Extraction with three 50-ml portions of ethyl acetate, followed by washing of the combined organic layers with water, 5% $NaHCO_3$, and saturated NaCl, drying over Drierite, and evaporation, left a foam. Acetylation (acetic anhydride–pyridine) yielded 521 mg of a mixture. Of several tlc solvents tried, 40% ethyl acetate–hexane gave the best separation. The mixture was dissolved in benzene and an 80-mg aliquot chromatographed on silica gel H using the above solvent system. The purified substances obtained were recrystallized from hexane to yield 3α-methyl-17β-acetoxyandrostan-3β-ol (**9b**), mp 206.5–207.5°, and 3β-methyl-17β-acetoxyandrostan-3α-ol (**10b**), mp 213.5–215° (see above).

A sample of the crude acetate mixture was analyzed by gas chromatography on a 6-ft column of 1% QF-1 at 190°. Comparison with a standard mixture showed that **9b** predominated by a ratio of 2:1.

3β-(N-Piperidinomethyl)androstane-3α,17β-diol (18).—Oxirane **8** (4.5 g, 14.8 mmol) in 50 ml of piperidine was treated with 3 g of phenol and refluxed for 48 hr. The solution was poured into water, and an amorphous solid which formed was filtered off and recrystallized from aqueous methanol to yield a white solid, mp 168–172° (4.7 g, 81%). Further recrystallization from aqueous methanol, benzene, and aqueous methanol again gave prisms which changed to needles at *ca.* 160° and melted at 178–179°. The compound showed singlet nmr peaks in dimethyl sulfoxide-d_6 at 49 (18-CH_3), 54 (19-CH_3), and 127.5 cps (N-CH_2) (ratio 3:3:2), a doublet centered at 260 cps (J = 5 cps), and a singlet at 214 cps, both exchangeable with D_2O.

Anal. Calcd for $C_{25}H_{43}O_2N$: C, 77.07; H, 11.13; N, 3.60. Found: C, 76.71; H, 11.33; N, 3.48.

Registry No.—**4a,** 16669-01-5; **4b,** 16669-02-6; **5a,** 302-76-1; **5c,** 16669-04-8; **5d,** 16669-05-9; **5e,** 16669-06-0; **7a,** 2066-43-5; **7b,** 16669-08-2; **8,** 2384-24-9; **9a,** 2066-31-1; **9b,** 2066-32-2; **10a,** 2233-69-4; **10b,** 2611-37-2; **11,** 16669-14-0; **18,** 16669-15-1.

Acknowledgment.—We thank Mrs. Beverly Turner and Mrs. Ingeborg Harper for experimental assistance with the preparation of nitrile **7** and the experiments on stereoselectivity of reactions of **1** with the steroidal 3-ketones.