rated to give 9.36 g of an amber oil. The analytical sample was obtained by distillation at 253° (1.5 mm).

Anal. Calcd for $C_{20}H_{17}ClN_2$: C, 74.87; H, 5.34; N, 8.73. Found: C, 75.02; H, 5.48; N, 8.85.

Acknowledgments.—The authors are indebted to the following persons for their contributions to this work: Dr. F. J. Saunders and Dr. E. F. Nutting for anti-inflammatory testing, Dr. S. Mizuba and Dr. R. D. Muir for antifungal testing, Mr. B. Heitke for preparation of several intermediates, Dr. R. Bible for nmr interpretations, and Dr. R. T. Dillon and his staff for microanalyses.

Some Steroidal Cyclic Ethers As Antiestrogens[1]

EDWARD A. BROWN

Chemical Research Division of G. D. Searle & Co., Chicago, Illinois 60680

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The synthesis of four-, five-, and six-membered spiroethers at C-17 and a number of cyclic ethers resulting from rearrangement at C-17 is reported. Several of these steroids exhibit potent antiestrogenicity.

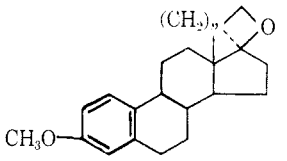
As an extension of work done in these laboratories directed toward the synthesis of steroidal spirolactones as aldosterone antagonists, several steroidal spiroethers were prepared; in addition, some novel cyclic ethers were obtained in a dehydration–rearrangement at C-17. A number of the spiroethers prepared in these laboratories exhibit potent antiestrogenic activity. They have not been found to be of interest as aldosterone antagonists,[2] although Arth and his associates[3] report that the lactone carbonyl is not essential for anti-aldosterone activity.

Steroids containing four-, five-, and six-membered spiroethers at C-17 have been prepared. Reduction of 2′,3′α-tetrahydrofuran-2′-spiro-17-(4-estren-3-one) (**3a**)[3] with lithium aluminum tri-*t*-butoxyhydride gave the 3β-hydroxy-Δ^4 derivative **4a** which was acetylated to give **4c**. Similar treatment of the corresponding compound in the androstane series produced the 3β-hydroxy derivative **4b** and its acetate **4d**.

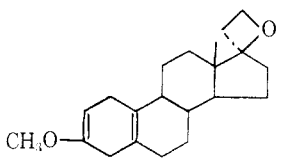
The 19-nor six-membered spiroether was prepared by $LiAlH_4$ reduction of 4-[17β-hydroxy-3-methoxy-1,3,5(10)-estratrien-17α-yl]butanoic acid lactone[4] to give the diol **6e** which was treated with *p*-toluenesulfonyl chloride, and the product cyclized with potassium *t*-butoxide in refluxing *t*-butyl alcohol to give 3′,4′,5′,6′-tetrahydrospiro[3-methoxyestra-1,3,5(10)-triene-17,2′(2′H)-pyran] (**1b**). In a modified Birch reduction[5] using Li–NH_3, **1b** was converted to the 1,4-dihydro enol ether and then *via* acid hydrolysis and rearrangement of the double bond to 3′,4′,5′,6′-tetrahydrospiro[estr-4-ene-17,2′(2′H)-pyran]-3-one (**3b**).

Six-membered spiroethers in the androstane series were made beginning with $LiAlH_4$ reduction of 4-(3β,17β-dihydroxy-5-androsten-17α-yl)butanoic acid lactone[4] to the triol **7b**. Reaction of the triol with *p*-toluenesulfonyl chloride was followed by cyclization of the crude product with potassium *t*-butoxide in refluxing *t*-butyl alcohol; chromatographic separation yielded 3′,4′,5′,6′-tetrahydrospiro[androst-5-ene-17,2′-(2′H)-pyran]-3β-ol (**5**). Oppenauer oxidation then yielded the 3-keto-Δ^4 derivative **3c**.

A four-membered spiroether at C-17 was prepared using ethyl 2-[17β-hydroxy-3-methoxyestra-1,3,5(10)-trien-17α-yl]acetate (**8**), prepared in a Reformatsky



1a, $n = 1$
b, $n = 3$



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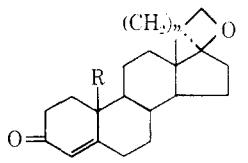
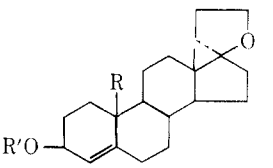
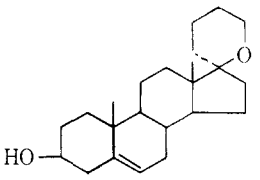


3a, $n = 2$; R = H
b, $n = 3$; R = H
c, $n = 3$; R = CH_3



4a, R = H; R′ = H
b, R = CH_3; R′ = H
c, R = H; R′ = CH_3CO–
d, R = CH_3; R′ = CH_3CO–



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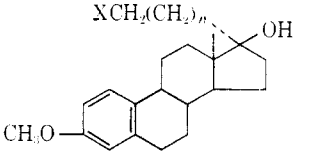
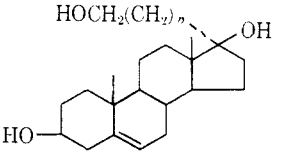
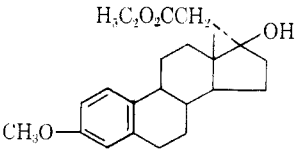


6a, $n = 1$; X = OH
b, $n = 1$; X = Otosyl
c, $n = 1$; X = Cl
d, $n = 2$; X = OH
e, $n = 3$; X = OH



7a, $n = 1$
b, $n = 3$



8

A four-membered spiroether at C-17 was prepared using ethyl 2-[17β-hydroxy-3-methoxyestra-1,3,5(10)-trien-17α-yl]acetate (**8**), prepared in a Reformatsky

(1) Paper X: Steroidal Aldosterone Blockers. For paper IX see W. F. Johns and E. A. Brown, *J. Org. Chem.*, **31**, 2099 (1966).

(2) None of the compounds reported herein were effective at 2.4 mg/rat in producing a 50% block in the effect of 12μg of deoxycorticosterone acetate. For test details see C. M. Kagawa, J. A. Cella, and C. G. Van Arman, *Science*, **126**, 1015 (1957).

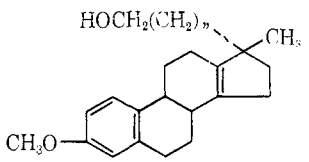
(3) G. E. Arth, H. Schwam, L. H. Sarett, and M. Glitzer, *J. Med. Chem.*, **6**, 617 (1963).

(4) J. A. Cella, E. A. Brown, and R. R. Burtner, *J. Org. Chem.*, **24**, 743 (1959).

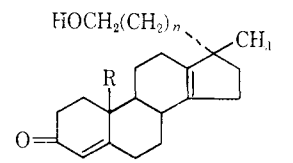
(5) H. L. Dryden, Jr., G. M. Webber, R. R. Burtner, and J. A. Cella, *ibid.*, **26**, 3237 (1961).

reaction of estrone methyl ether with ethyl bromoacetate. $LiAlH_4$ reduction provided the diol **6a** which when treated with *p*-toluenesulfonyl chloride in pyridine yielded a mixture of primary tosylate **6b** and primary chloride **6c** separated by column chromatography. The crude mixed product of tosylation was cyclized as in the six-membered series with potassium *t*-butoxide in refluxing *t*-butyl alcohol to give 3′,4′-dihydro-3-methoxyestra-1,3,5(10)-trien-17,2′(2′H)-oxete (**1a**). When subjected to the modified Birch reduction with Li–NH_3, **1a** was converted to the 1,4-dihydro enol ether **2**. However, all attempts at acid hydrolysis of **2** to obtain the 3-keto-Δ^4 or 3-keto-$\Delta^{5(10)}$ derivative with retention of the strained four-membered spiro ring at C-17 failed. Work-up of an HCl–aqueous methanol hydrolysis of **2** yielded a rearrangement product assigned as 17α-(2-hydroxyethyl)-17β-methylgona-4,13-dien-3-one (**10a**) on the basis of infrared and nmr spectra.

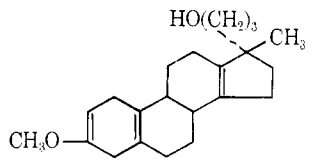
It appeared of interest to prepare additional steroid structures having the Δ^{13}-17α-hydroxyalkyl-17β-methyl moiety and, since in the presence of acids 17β-hydroxy-17α-alkyl steroids are known to dehydrate with migration of the 13-methyl group,[6] the aromatic A-ring diol



9a, $n=1$
b, $n=2$



10a, $n=1$; R = H
b, $n=2$; R = H
c, $n=2$; R = CH_3



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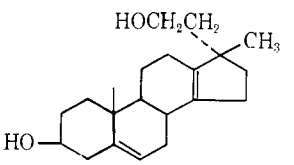

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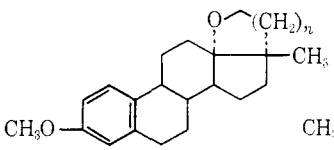
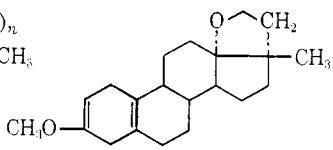


13a, $n=1$
b, $n=2$



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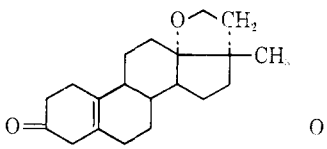

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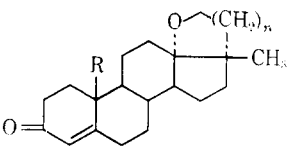
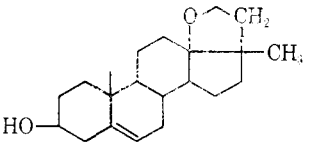


16a, $n=1$; R = H
b, $n=1$; R = CH_3
c, $n=2$; R = CH_3

6a was subjected to reaction with HCl in refluxing ethanol. From this reaction, in addition to the expected 17α-(2-hydroxyethyl)-3-methoxy-17β-methylgona-1,3,5(10),13-tetraene (**9a**), column chromatography yielded two other products which have been assigned as 14,17-epoxy-17α-ethyl-3-methoxy-17β-methyl-13ξ-gona-1,3,5(10)-triene (**18**) and 13,17[2]-epoxy-17α-ethyl-3-methoxy-17β-methyl-13α-gona-1,3,5(10)-triene (**13a**). Cyclization to C-13 or C-14 might reasonably be expected since an intermediate carbonium ion center would be generated at either of these positions.



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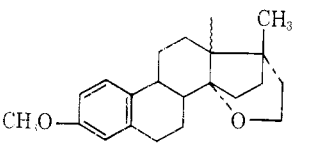
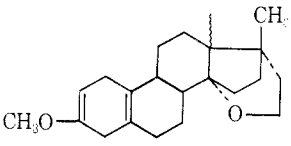


18



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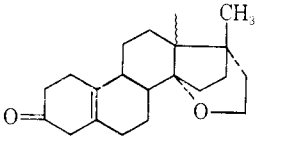

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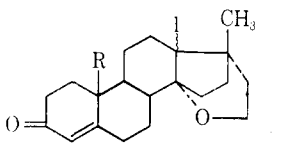
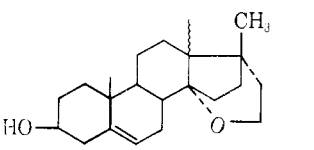


21a, R = H
b, R = CH_3



22

In addition, both **18** and **13a** lacked hydroxyl absorption in the infrared. The nmr spectrum for the five-membered cyclic ether **13a** had a multiplet centered at 225 cps (partially obscured by the methoxyl peak)[7] for the protons next to the ether oxygen and the C-17 methyl protons peak at 68 cps. The six-membered cyclic ether **18** had a less symmetrical multiplet centered at 217 cps and the C-17 methyl peak was at 58 cps. Evidence for the assignment of **18** as a six-membered ring ether came from the fact that when it was oxidized with chromium trioxide–acetic acid the crude product had an infrared absorption band at 5.77 μ, characteristic of a δ-lactone. Li–NH_3 reduction of **18** produced the enol ether **19** which when hydrolyzed with 90% acetic acid gave the 3-keto-$\Delta^{5(10)}$ derivative **20** and when hydrolyzed and then isomerized with dilute HCl in methanol gave 14,17[2]-epoxy-17α-ethyl-17β-methyl-13ξ-gon-4-en-3-one (**21a**). Similarly, Li–NH_3 reduction of **13a** gave the enol ether **14**, hydrolyzed to **15**, and hydrolyzed and isomerized to 13,17[2]-epoxy-17α-ethyl-17β-methyl-13α-gon-4-en-3-one (**16a**).

Surprisingly, when 8, having the ethyl acetate side chain at C-17, was subjected to reaction with HCl in refluxing ethanol, no dehydration involving the 17β-hydroxyl group occurred. The starting material was totally recovered. No explanation for this anomaly is immediately apparent but Magrath, *et al.*,[8] reported difficulty in dehydrating the analogous ethyl 2-(3β-acetoxy-17β-hydroxyandrost-5-en-17α-yl)-acetate. To disprove the hypothesis that successful dehydration–rearrangement using the conditions reported herein required the presence of the terminal hydroxyl group on the alkyl side chain at C-17, 17α-

(6) V. Tortorella, G. Lucente, and A. Romeo, *Ann. Chim.* (Rome), **50**, 1198 (1960).

(7) The position is clearly evident in the derivative **16a** which does not have a methoxyl group.

(8) D. Magrath, D. S. Morris, V. Petrow, and R. Royer, *J. Chem. Soc.*, 2393 (1950).

ethylestradiol 3-methyl ether[9] was treated with HCl in refluxing ethanol for 45 min. Dehydration was complete and 17α-ethyl-3-methoxy-17β-methylgona-1,3,5(10),13-tetraene, previously prepared by Kirdani and Dorfman[10] was obtained.

The rearrangement reaction was run in the androstane series by dehydrating 3β,17β-dihydroxy-17α-(2-hydroxyethyl)androst-5-ene (**7a**)[8] in ethanol with HCl. In addition to 17α-(2-hydroxyethyl)-10,17β-dimethylgona-5,13-dien-3β-ol (**12**) which could be obtained directly from the reaction mixture, chromatography yielded 14,17²-epoxy-17α-ethyl-10,17β-dimethyl-13ξ-gon-5-en-3β-ol (**22**) and 13,17²-epoxy-17α-ethyl-10,17β-dimethyl-13α-gon-5-en-3β-ol (**17**). Compounds **17** and **22** when subjected to Oppenauer oxidation yielded the 3-keto-Δ^4 derivatives **16b** and **21b**, respectively.

Rearrangement was then carried out on the homologous 17α-(3-hydroxypropyl)-3-methoxy-1,3,5(10)-estratrien-17β-ol (**6d**),[11] the major product being 17α-(3-hydroxypropyl)-3-methoxy-17β-methylgona-1,3,5-(10),13-tetraene (**9b**). Chromatography yielded another product having no hydroxyl function and an nmr spectrum which led to its assignment as 13,17³-epoxy-3-methoxy-17β-methyl-17α-propyl-13α-gona-1,-3,5(10)-triene (**13b**). Li–NH_3 reduction of **9b** yielded the 1,4-dihydro enol ether **11** and this was converted to the 3-keto-Δ^4 derivative **10b** with HCl in methanol.

The acid rearrangement was also successfully extended to 17α-(3-hydroxypropyl)-4-androsten-17β-ol-3-one,[3] yielding after chromatography 13,17³-epoxy-10,17β-dimethyl-17α-propyl-13α-gon-4-en-3-one (**16c**) as the minor product; the major product of chromatography was 17α-(3-hydroxypropyl)-10,17β-dimethylgona-4,13-dien-3-one (**10c**).

The antiestrogenic potency of some of the steroidal ethers is reported in Table I. Although clinical utility for antiestrogens has not as yet been demonstrated, a variety of applications for mammalian use might be suggested. Bialy, Merrill, and Pincus[12] have reported on the ability of **3a** to inhibit estrogen-stimulated carbonic anhydrase activity as well as uterine weight. The values herein reported are a measure of the potency of the compounds in blocking estrogen-stimulated uterine weight increase relative to progesterone as the standard. Both **4a** and **4c**, the 3β-hydroxy-Δ^5 derivative of **3a** and its acetate, respectively, have suffered some loss of potency. Compound **3b**, a six-membered spiroether and a homolog of **3a**, shows good activity, and the novel 14,17-epoxy steroids **20**, **21a**, and **21b** are active.

TABLE I

Compd	Antiestrogenic potency[a]
Progesterone	1
3a	100
3b	10
4a	10
4b	0.1
4c	3.3
14	0.05
16a	0.05
20	0.4
21a	4.0
21b	0.4

[a] Determined by the procedure of R. A. Edgren, D. W. Calhoun, R. L. Elton, and F. B. Colton, *Endocrinology*, **65**, 265 (1959). The test compound along with 0.3 μg of estrone was administered in three equal subcutaneous injections over three successive days to intact, immature mice. The animals were autopsied 24 hr after the third injection; uteri were weighed and compared with controls. These tests were under the direction of Dr. E. F. Nutting and Mr. Roger Bergstrom of the Division of Biological Research.

Experimental Section

The microanalyses and optical determinations were carried out by Dr. Robert T. Dillon and his associates of these laboratories. Nmr spectra were recorded on a Varian A-60 instrument in $CDCl_3$ with Me_4Si as internal standard and peaks are reported in cycles per second downfield. Ultraviolet spectra were determined in methanol. Melting points are reported as observed on a Fisher-Johns block. Chromatograms were run on silica gel columns (60 × the weight of steroid used) by Dr. E. G. Daskalakis and his staff.

2′,3′α-Tetrahydrofuran-2′-spiro-17-(estr-4-en-3β-ol) (4a).—To a cold (0°) stirred suspension of 10.0 g of lithium aluminum tri-*t*-butoxyhydride in 100 ml of tetrahydrofuran (THF) under N_2 was added over 15 min a solution of 10.0 g of 2′,3′α-tetrahydrofuran-2′-spiro-17-(4-estren-3-one) (**3a**)[3] in 100 ml of THF. The reaction mixture was stirred at 0° for 60 min and then at room temperature for 90 min. It was then transferred into 2.0 l. of 0.6% acetic acid in water. The separated oil solidified and the collected solid was washed with water, dried, and recrystallized from ethyl acetate containing 1 drop of pyridine to yield 2.9 g of **4a**: mp 130–132°; λ_{max}^{KBr} 2.91, 6.00 μ.

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.81; H, 10.12.

2′,3′α-Tetrahydrofuran-2′-spiro-17-(3β-acetoxyestr-4-ene) (4c).—A solution of 330 mg of **4a**, 3.5 ml of pyridine, and 2.7 ml of acetic anhydride was held at room temperature for 19 hr and then transferred into 100 ml of ice water. The precipitate was collected, washed with water, dried, and recrystallized twice from hexane to yield 270 mg of **4c**: mp 117–120°; λ_{max}^{KBr} 5.78, 5.98 μ.

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.17; H, 9.33.

2′,3′α-Tetrahydrofuran-2′-spiro-17-(4-androsten-3β-ol) (4b).—To a cold (0°) stirred suspension of 5.5 g of lithium aluminum tri-*t*-butoxyhydride in 50 ml of THF under N_2 was added over 10 min a solution of 6.57 g of 2′,3′α-tetrahydrofuran-2′-spiro-17-(4-androsten-3-one)[3] in 50 ml of THF. The reaction mixture was stirred at 0° for 60 min and then at room temperature for 60 min following which it was transferred into 800 ml of 2.5% aqueous acetic acid. After 1 hr at 5° the precipitate was collected, washed with water, dried, and recrystallized from benzene–hexane and then again from benzene to yield 2.0 g of **4b**: mp 166–170°; $\lambda_{max}^{CHCl_3}$ 2.75, 6.02 μ; $[\alpha]D$ +9° (MeOH); nmr, 53 (18-CH_3), 63 (19-CH_3), 224 (multiplet, 22-CH_2), 248 (axial 3-H), 318 (4-H) cps.

Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.81; H, 10.07.

2′,3′-Tetrahydrofuran-2′-spiro-17-(3β-acetoxyandrost-4-ene) (4d).—A solution of 750 mg of **4b**, 8 ml of pyridine, and 6 ml of acetic anhydride was held at room temperature for 20 hr and then transferred into 100 ml of ice water. After the precipitate had solidified it was collected, washed with water, dried, and recrystallized from hexane to yield 500 mg of **4d**: mp 102–103°; $\lambda_{max}^{CHCl_3}$ 5.76, 5.99 μ.

Anal. Calcd for $C_{23}H_{36}O_3$: C, 77.37; H, 9.74. Found: C, 77.59; H, 9.54.

17β-Hydroxy-17α-(4-hydroxybutyl)-3-methoxyestra-1,3,5-(10)-triene (6e).—A suspension of 1.1 g of $LiAlH_4$ in 100 ml of anhydrous ethyl ether was stirred and refluxed for 90 min. A

(9) F. B. Colton, L. N. Nysted, B. Riegel, and A. L. Raymond, *J. Am. Chem. Soc.*, **79**, 1123 (1957).

(10) R. Y. Kirdani and R. I. Dorfman, *J. Med. Chem.*, **8**, 268 (1965).

(11) R. Pappo, U. S. Patent 2,913,467 (1959).

(12) G. Bialy, A. P. Merrill, and G. Pincus, *Endocrinology*, **79**, 125 (1966).

solution of 2.15 g of 4-[17β-hydroxy-3-methoxy-1,3,5(10)-estratrien-17α-yl]butanoic acid lactone[4] in 12 ml of dioxane was then added over a 10-min period. An additional 50 ml of anhydrous ethyl ether was added and then reflux with stirring was maintained for 4 hr. The cautious addition of 4 ml of water was followed by dilute HCl until an acid reaction was achieved. The solution was decanted from the pasty residue, washed twice with water, and dried (Na_2SO_4). Evaporation of solvent left an oily residue which crystallized when ethyl acetate was added. Recrystallization from ethyl acetate yielded 2.0 g of **6e**, mp 127–128°, liquified at 88° and resolidified.

3′,4′,5′,6′-Tetrahydrospiro[3-methoxyestra-1,3,5(10)-triene-17,2′(2′H)-pyran] (1b).—A solution of 3.0 g of **6e** and 3.0 g of *p*-toluenesulfonyl chloride in 30 ml of pyridine was held at room temperature for 90 hr and then transferred into 150 ml of ice water. The precipitated gum was extracted with ethyl acetate and the solution was washed twice with water and twice with dilute acetic acid. After it was dried (Na_2SO_4), the solution was evaporated to 1.5 g of oily residue. This residue, together with 1.5 g of potassium *t*-butoxide, was dissolved in 75 ml of *t*-butyl alcohol and the solution was refluxed for 2 hr. After standing 4 days at room temperature it was diluted with 100 ml of ethyl ether and extracted with four 25-ml portions of water. The combined aqueous washings were extracted with 50 ml of ether and the ether extract was washed twice with water. The nonaqueous solutions were then combined and dried (Na_2SO_4). Evaporation of solvents afforded an oily residue which crystallized overnight and was recrystallized from ethyl acetate to yield 700 mg of **1b**: mp 108–110°; $\lambda_{max}^{CHCl_3}$ 6.21, 6.33, 6.62, 9.26, 9.62 μ; λ_{max} 278 mμ (ε 2110); nmr, 52 (18-CH_3), *ca.* 225 (multiplet, 23-CH_2), 227 (OCH_3) cps.

Anal. Calcd for $C_{23}H_{32}O_2$: C, 81.13; H, 9.47. Found: C, 81.31; H, 9.54.

3′,4′,5′,6′-Tetrahydrospiro[estr-4-ene-17,2′(2′H)-pyran]-3-one (3b).—Lithium wire (1.2 g) was added over a 10-min period to a stirred solution of 1.75 g of **1b** in 60 ml of THF, 60 ml of *t*-butyl alcohol, and 120 ml of liquid NH_3. After 2.5 hr the reaction mixture had decolorized and 5 ml of methanol was added. Ammonia was allowed to evaporate for 2 hr and 100 ml of H_2O was added. Nonaqueous solvents were removed by vacuum distillation and the residual aqueous suspension was filtered. The solid product was washed with H_2O and dried to yield 1.7 g of crude 1,4-dihydro product, 1.0 g of which was stirred in 10 ml of methanol with 0.5 ml of H_2O and 0.6 ml of concentrated HCl. Stirring was continued for 1 hr and the resulting solution was transferred into 100 ml of H_2O. The aqueous suspension was extracted with ethyl acetate and the ethyl acetate layer was washed with H_2O and dried (Na_2SO_4). Evaporation of solvent afforded an oil which crystallized slowly. Recrystallization from ethyl acetate–hexane provided 230 mg of **3b**: mp 126–130°; $\lambda_{max}^{CHCl_3}$ 5.99, 6.16 μ; λ_{max} 240 mμ (ε 15,550).

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found: C, 80.24; H, 9.77.

17α-(4-Hydroxybutyl)-5-androstene-3β,17β-diol (7b).—To a stirred suspension of 3.3 g of $LiAlH_4$ in 150 ml of THF was added over a 10-min period a solution of 9.8 g of 4-(3β,17β-dihydroxy-5-androsten-17α-yl)butanoic acid lactone[4] in 250 ml of THF. Reflux with stirring was maintained for 2 hr and then a solution of 2 ml of H_2O in 28 ml of THF was added dropwise, followed by 15 ml of H_2O dropwise. The reaction mixture was filtered and the filtrate was evaporated to a residual volume of 250 ml and cooled to 5° producing 3.4 g of **7b**. Further evaporation of solvent yielded 1.9 g of a second crop. Recrystallization from a large volume of ethyl acetate provided an analytical sample: mp 224–227°; λ_{max}^{KBr} 3.02, 5.98 μ.

Anal. Calcd for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57. Found: C, 75.92; H, 10.27.

3′,4′,5′,6′-Tetrahydrospiro[androst-5-ene-17,2′(2′H)-pyran]-3β-ol (5).—A solution of 3.4 g of **7b** and 3.4 g of *p*-toluenesulfonyl chloride in 60 ml of pyridine was held at room temperature for 18 hr and then transferred into 500 ml of ice water. The solid precipitate was collected, washed with H_2O, dried, and, together with 3.0 g of potassium *t*-butoxide, dissolved in 115 ml of *t*-butyl alcohol. The solution was refluxed for 2 hr, cooled, diluted with 300 ml of ethyl ether, and washed in a separatory funnel with H_2O five times and then finally with saturated NaCl. After it was dried (Na_2SO_4) the solvent was evaporated to a 2.9-g residue which was subjected to chromatographic separation. The fractions eluted with 10% ethyl acetate–benzene were combined and recrystallized from *n*-hexane to yield 510 mg of **5**, mp 144–149°; nmr, 50 (18-CH_3), 61 (19-CH_3), *ca.* 220 (multiplet, 23-CH_2 and 3αH), 320 (6-H) cps.

Anal. Calcd for $C_{23}H_{36}O_2$: C, 80.16; H, 10.53. Found: C, 80.01; H, 10.40.

3′,4′,5′,6′-Tetrahydrospiro[androst-4-ene-17,2′(2′H)-pyran]-3-one (3c).—A reaction mixture of 350 mg of **5**, 350 mg of aluminum isopropoxide, 3 ml of cyclohexanone, and 20 ml of toluene was stirred at reflux under N_2 for 30 min. The solution was cooled, 1.3 ml of saturated aqueous Rochelle salt solution was added, and then it was steam distilled for 30 min. The granular precipitate which formed on cooling was collected, washed with H_2O, dried, and recrystallized from ethyl acetate to yield 200 mg of **3c**: mp 170° (after prior sublimation); $\lambda_{max}^{CHCl_3}$ 5.98, 6.19 μ; λ_{max} 241 mμ (ε 14,450).

Anal. Calcd for $C_{23}H_{34}O_2$: C, 80.65; H, 10.01. Found: C, 80.98; H, 10.03.

Ethyl 2-[17β-Hydroxy-3-methoxyestra-1,3,5(10)-trien-17α-yl] acetate (8).—A reaction mixture of 10 g of estrone 3-methyl ether, 22 g of ethyl bromoacetate, 14 g of 20-mesh zinc (pretreated successively with dilute HCl, H_2O, methanol, dry ethyl ether, and dry benzene), and 100 ml of dry benzene was stirred and heated to reflux whereupon an exothermic reaction began and continued under control for 15 min without external heat. Heat was then applied to maintain reflux for 2 hr after which the reaction mixture was decanted from the unreacted zinc and into 500 ml of cold 2% HCl. The benzene layer was separated and combined with an ether extract of the aqueous layer. The combined ether and benzene solutions were washed with water, dried (Na_2SO_4), and evaporated. The oily residue was dissolved in 80 ml of ethanol, 8 g of trimethylaminoacetohydrazide chloride (Girard's reagent) and 8.0 ml of acetic acid were added, and the solution was refluxed for 30 min and then transferred into a solution of 12 g of $NaHCO_3$ in 400 ml of H_2O. After 18 hr at 5° the precipitate was collected, washed with H_2O, dried, and recrystallized from methanol to yield 5.75 g of **8**: mp 102–104°; $\lambda_{max}^{CHCl_3}$ 2.88, 5.83 μ.

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 73.83; H, 8.85.

17β-Hydroxy-17α-(2-hydroxyethyl)-3-methoxyestra-1,3,5(10)-triene (6a).—A suspension of 2.5 g $LiAlH_4$ in 100 ml of anhydrous ethyl ether was stirred and refluxed for 30 min. A solution of 5.0 g of **8** in 110 ml of anhydrous ethyl ether was added over 10 min and then refluxing and stirring were resumed for 3 hr. After 10 ml of ethyl ether saturated with H_2O was added dropwise, 3 ml of H_2O was added cautiously and the slurry was filtered. Concentration of the filtrate provided 280 mg of **6a**, mp 158–160°. The insolubles were stirred for 3 hr with 200 ml of H_2O, 25 ml of concentrated HCl, and 100 ml of $CHCl_3$. The $CHCl_3$ layer was separated, washed with H_2O, dried, and evaporated to yield 3.9 g of **6a**, mp 162–163°.

17β-Hydroxy-17α-(2-chloroethyl)-3-methoxyestra-1,3,5(10)-triene (6c) and 17β-Hydroxy-17α-(2-*p*-toluenesulfonyloxyethyl)-3-methoxyestra-1,3,5(10)-triene (6b).—A solution of 800 mg of **6a**, 800 mg of *p*-toluenesulfonyl chloride, and 8 ml of pyridine was held at room temperature for 18 hr and then transferred into 100 ml of ice water. The precipitate was collected, washed with H_2O, dried, and chromatographed. The first peak fraction eluted with 2% ethyl acetate–benzene was recrystallized from benzene to yield 100 mg of **6c**, mp 168–170°, λ_{max}^{KBr} 2.80 μ.

Anal. Calcd for $C_{21}H_{29}ClO_2$: C, 72.40; H, 8.38. Found: C, 72.17; H, 8.27.

A secondary peak from elution with 2% ethyl acetate–benzene was recrystallized from ethyl acetate to yield 50 mg of **6b**, mp 147–148°. *Anal.* Calcd for $C_{28}H_{36}O_5S$: C, 69.39; H, 7.49. Found: C, 69.54; H, 7.58.

3′,4′-Dihydro-3-methoxyestra-1,3,5(10)-trien-17,2′(2′H)-oxete (1a).—To a solution of 7.5 g of the crude reaction product from the treatment of **6a** with *p*-toluenesulfonyl chloride (see **6b** and **6c**) in 350 ml of *t*-butyl alcohol was added 7.5 g of potassium *t*-butoxide. After 3.5 hr of stirring at reflux the cooled reaction mixture was diluted with 500 ml of ethyl ether. The upper layer was separated and washed with four 250-ml portions of water. The combined water washes were extracted with 200 ml of ethyl ether. The combined nonaqueous solvent layer was dried (Na_2SO_4) and evaporated and the solid residue was recrystallized from benzene–hexane to yield 3.55 g of **1a**: mp 109–110°; nmr, 48 (18-CH_3), 227 (OCH_3), 265 (multiplet, 21-CH_2) cps.

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.82; H, 8.96.

3′,4′-Dihydro-3-methoxyestra-2,5(10)-dien-17,2′(2′H)-oxete (2).—Lithium wire (3.6 g) was added over a 10-min period to a stirred solution of 6.0 g of **1a** in 180 ml of THF, 180 ml of *t*-butyl alcohol, and 360 ml of liquid NH_3. After 2 hr, 15 ml of methanol was added dropwise over a 20-min period. The reaction mixture decolorized 10 min later. NH_3 was allowed to evaporate for 16 hr and then 300 ml of H_2O was added. Nonaqueous solvents were removed by vacuum distillation and the precipitate was collected, washed with H_2O, and dried to yield 6.0 g of **2**. Recrystallization from cyclohexane provided a sample for analysis: mp 112–118°; $\lambda_{max}^{CHCl_3}$ 5.88, 5.99 μ; $\lambda_{max}^{CH_3OH-HCl}$ 240 mμ (ε 15,600).

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 79.79; H, 9.30.

17α-(2-Hydroxyethyl)-17β-methylgona-4,13-dien-3-one (10a).—A reaction mixture of 3.2 g of **2**, 20 ml of methanol, 5 ml of H_2O, and 1 ml of concentrated HCl was stirred at room temperature with solution complete in 15 min. After 2 hr it was diluted with 500 ml of H_2O and extracted with ethyl acetate. The ethyl acetate solution was washed with H_2O, dried (Na_2SO_4), and evaporated to an oily residue: $\lambda_{max}^{CHCl_3}$ 2.71, 2.83, 5.80, 5.90, 6.15 μ, indicating the presence of both 3-keto-Δ^4 and 3-keto-$\Delta^{5(10)}$ systems. When subjected to chromatography the 30% ethyl acetate–benzene fractions yielded **10a**, recrystallized once from ethyl acetate–hexane and finally from benzene–hexane to give 300 mg: mp 110–115°; $\lambda_{max}^{CHCl_3}$ 2.72, 2.80, 5.99, 6.16 μ; λ_{max} 238 mμ (ε 16,500); nmr, 61 (17-CH_3), 216 (triplet, 21-CH_2), 351 (4-H) cps.

Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.99; H, 9.67.

17α-(2-Hydroxyethyl)-3-methoxy-17β-methylgona-1,3,5(10),-13-tetraene (9a), 14,17²-Epoxy-17α-ethyl-3-methoxy-17β-methyl-13ξ-gona-1,3,5(10)-triene (18), and 13,17²-Epoxy-17α-ethyl-3-methoxy-17β-methyl-13α-gona-1,3,5(10)-triene (13a).—A reaction mixture of 8.8 g of **6a**, 35 ml of ethanol, and 8.8 ml of concentrated HCl was stirred and refluxed for 45 min with solution of the steroid complete after 15 min. Benzene (150 ml) was added and the benzene layer was washed with H_2O, dried, and evaporated to 7.9 g of oily residue which was chromatographed. The ethyl acetate–benzene (10:90) fractions were crystallized from ethyl acetate–hexane to yield 180 mg of **9a**, mp 87–94°. A sample was recrystallized from ethyl acetate–hexane for analysis: mp 95–97°; $\lambda_{max}^{CHCl_3}$ 2.88 μ; nmr, 62 (17-CH_3), 216 (triplet, 21-CH_2), 229 (OCH_3) cps.

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 81.00; H, 9.10.

The first 5% ethyl acetate–benzene fraction (2.41 g) was impure **18**, crystallized from hexane: mp 76–80°; nmr, 58 (17-CH_3), 217 (multiplet, 21-CH_2), 224 (OCH_3) cps.

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.74; H, 9.17.

The second 5% ethyl acetate–benzene fraction (2.19 g) was impure **13a** (an oil) which was induced to crystallize and recrystallized from hexane: mp 60–61°; nmr, 68 (17-CH_2), 225 (multiplet, 21-CH_2), 225 (OCH_3) cps.

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.93; H, 9.03.

14,17²-Epoxy-17α-ethyl-3-methoxy-17β-methyl-13ξ-gona-2,5-(10)-diene (19).—Lithium wire (1.8 g) was added over a 10-min period to a stirred solution of 3.0 g of **18** in 90 ml of THF, 90 ml of *t*-butyl alcohol, and 180 ml of liquid NH_3. After 3 hr, 6 ml of methanol was added dropwise and the reaction mixture decolorized after 3.5 hr. NH_3 was allowed to evaporate for 18 hr and then 180 ml of H_2O was added. Nonaqueous solvents were removed by vacuum distillation and the oil which precipitated from the aqueous residue was separated, washed with H_2O, and dried to yield 3.0 g of **19**: $\lambda_{max}^{CHCl_3}$ 5.88, 5.98 μ.

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.48; H, 9.88.

14,17²-Epoxy-17α-ethyl-17β-methyl-13ξ-gon-5(10)-en-3-one (20) and 14,17²-Epoxy-17α-ethyl-17β-methyl-13ξ-gon-4-en-3-one (21a).—A suspension of 2.75 g of **19** in 55 ml of 90% acetic acid was stirred until solution was complete (2–3 min), held at room temperature for 90 min, diluted with 250 ml of H_2O, and cooled to 10°. The precipitate was collected, washed with H_2O, dried, and recrystallized from hexane to yield 1.2 g of **20**, mp 123–128°, $\lambda_{max}^{CHCl_3}$ 5.80 μ.

Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 80.13; H, 9.20.

A suspension of 900 mg of **20** in 12 ml of methanol, with 0.7 ml of concentrated HCl and 0.7 ml of H_2O was stirred for 60 min during which time the steroid dissolved and a new substance precipitated from the solution. After standing 60 min, 500 mg of precipitate was collected. Addition of water (*ca.* 75 ml) produced a second crop of 200 mg. The two crops were combined and recrystallized from 25 ml of methanol containing a drop of pyridine to yield 500 mg of **21a**: mp 181–186°; λ_{max} 240 mμ (ε 17,250); nmr, 58 (18-CH_3), 217 (multiplet, 21-CH_2), 347 (4-H) cps.

Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 80.28; H, 9.31.

13,17²-Epoxy-17α-ethyl-3-methoxy-17β-methyl-13α-gona-2,5(10)-diene (14).—Lithium wire (1.6 g) was added over a 10-min period to a stirred solution of 2.4 g of **13a** in 75 ml of THF, 75 ml of *t*-butyl alcohol, and 150 ml of liquid NH_3. After 2 hr, 8 ml of methanol was added dropwise over 45 min and the reaction mixture decolorized after 3 hr. Ammonia was allowed to evaporate for 2 hr, 300 ml of H_2O was added, and the nonaqueous solvents were removed by vacuum distillation. The separated oil was extracted with ethyl acetate and the extract solution was washed with H_2O, dried (Na_2SO_4), and evaporated to yield 2.35 g of **14**: $\lambda_{max}^{CHCl_3}$ 5.90, 6.00 μ.

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.45; H, 9.56.

13,17²-Epoxy-17α-ethyl-17β-methyl-13α-gona-5(10)-en-3-one (15) and 13,17²-Epoxy-17α-ethyl-17β-methyl-13α-gona-4-en-3-one (16a).—A suspension of 2.3 g of **14** in 50 ml of 90% acetic acid was stirred until solution was complete (5 min), held at room temperature for 90 min, diluted with 250 ml of H_2O, and then extracted twice with hexane (200 ml). The hexane solution was washed with water, dried (Na_2SO_4), and evaporated to yield 1.5 as an oil, $\lambda_{max}^{CHCl_3}$ 5.78 μ.

Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.78; H, 9.72.

A suspension of 2.0 g of **14** in 20 ml of methanol with 1.4 ml of concentrated HCl and 1.4 ml of H_2O was stirred to complete solution (30 min), held for another 2 hr, and then diluted with 150 ml of ice water. After 2 hr at 0° the precipitate was collected, washed with H_2O, dried, and recrystallized from hexane to yield 1.1 g of **16a**: mp 83–87°; $\lambda_{max}^{CHCl_3}$ 5.99, 6.15 μ; nmr, 70 (17-CH_3), 225 (multiplet, 21-CH_2), 350 (4-H) cps.

Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 80.17; H, 9.45.

17α-(2-Hydroxyethyl)-10,17β-dimethylgona-5,13-dien-3β-ol (12), 14,17²-Epoxy-17α-ethyl-10,17β-dimethyl-13ξ-gon-5-en-3β-ol (22), and 13,17²-Epoxy-17α-ethyl-10,17β-dimethyl-13α-gon-5-en-3β-ol (17).—A reaction mixture of 15.5 g of 3β,17β-dihydroxy-17α-(2-hydroxyethyl)androst-5-ene (**7a**),[8] 60 ml of ethanol, and 15 ml of concentrated HCl was stirred and refluxed for 100 min with complete solution of the steroid after 80 min. Water was added (150 ml) and after 18 hr at 0° the tacky precipitate was collected, washed with H_2O, dried, and digested with 50 ml of boiling ethyl acetate. The portion remaining insoluble after cooling to 25° was recrystallized from ethyl acetate to yield 3.2 g of **12**: mp 163–168°; $\lambda_{max}^{CHCl_3}$ 2.75 μ; nmr (pyridine), 60 (17-CH_3), 66 (19-CH_3), 233 (multiplet, 21-CH_2 + 3H), 325 (6-H) cps.

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.68; H, 10.19. Found: C, 79.73; H, 10.05.

The ethyl acetate mother liquor was chromatographed and the peak fraction eluted with 10% ethyl acetate–benzene was recrystallized from ethyl acetate and then from ethanol to yield 310 mg of **22**: mp 212–215°; nmr, 57 (17-CH_3), 59 (19-CH_3), 200–230 (multiplet, 21-CH_3 + 3H), 325 (6-H) cps.

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.68; H, 10.19. Found: C, 79.54; H, 9.97.

The fractions eluted with 15% ethyl acetate–benzene were again subjected to chromatography and the peak fractions eluted with 10% ethyl acetate–benzene were combined and recrystallized from ethyl acetate–hexane to give 520 mg of **17**: mp 48–53°; nmr, 58 (19-CH_3), 69 (17-CH_3), *ca.* 210 (multiplet, 3-H), 225 (triplet, 21-CH_2), 322 (6-H) cps.

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.68; H, 10.19. Found: C, 79.66; H, 10.24.

14,17²-Epoxy-17α-ethyl-10,17β-dimethyl-13ξ-gon-4-en-3-one (21b), and 13,17²-Epoxy-17α-ethyl-10,17β-dimethyl-13α-gon-4-en-3-one (16b).—A solution of 950 mg of **22**, 6.5 ml of cyclohexanone, and 40 ml of toluene was stirred and heated to reflux under N_2. A solution of 950 mg of aluminum isopropoxide in 15 ml of toluene was added rapidly and the reaction mixture was brought to reflux for 30 min. The solution was cooled, 3.6 ml

of saturated aqueous Rochelle salt solution was added, and the mixture was steam distilled to remove nonaqueous solvents. The solid precipitate was collected, washed with water, dried, and recrystallized from ethyl acetate to yield 620 mg of **21b**: mp 129–134°; $\lambda_{max}^{CHCl_3}$ 6.00, 6.19 μ.

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.15; H, 9.48.

Following the above procedure identically, 1.0 g of **17** was oxidized and the crude reaction product was recrystallized from ethyl acetate to yield 480 mg of **16b**: mp 144–150°; nmr, 68 (17-CH_3), 72 (19-CH_3), 225 (multiplet, 21-CH_2), 344 (4-H) cps.

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.21; H, 9.37.

17α-(3-Hydroxypropyl)-3-methoxy-17β-methylgona-1,3,5(10),-13-tetraene (9b) and 13,17[3]-Epoxy-3-methoxy-17β-methyl-17α-propyl-13α-gona-1,3,5(10)-triene (13b).—A reaction mixture of 25 g of 17α-(3-hydroxypropyl)-3-methoxy-1,3,5(10)-estratrien-17β-ol (**6d**),[11] 100 ml of ethanol, and 25 ml of concentrated HCl was stirred and refluxed for 45 min with solution being complete after 10 min. It was cooled and stirred, and 350 ml of cold H_2O was added producing an oil which congealed when cooled to 5°. The oil was collected, washed with H_2O, dried, and recrystallized from ethyl acetate to give 8.0 g of **9b**. A sample was recrystallized from acetone for analysis: mp 85–90°; $\lambda_{max}^{CHCl_3}$ 2.76 μ; nmr, 61 (17-CH_3), 216 (triplet, 22-CH_2), 226 (OCH_3) cps.

Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26. Found: C, 80.74; H, 8.92.

The mother liquors from **9b** were chromatographed and the first fractions eluted with 1% ethyl acetate–benzene were combined and recrystallized twice from ethyl acetate to yield 1.1 g of **13b**: mp 93–95°; nmr, 44 (17-CH_3), *ca.* 225 (multiplet, 22-CH_2), 227 (OCH_3) cps.

Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26. Found: C, 81.23; H, 9.22.

17α-(3-Hydroxypropyl)-3-methoxy-17β-methylgona-2,5(10),-13-triene (11) and 17α-(3)-Hydroxypropyl)-17β-methylgona-4,-13-dien-3-one (10b).—Lithium wire (1.6 g) was added over a 10-min period to a stirred solution of 2.5 g of **9b** in 75 ml of THF, 75 ml of *t*-butyl alcohol, and 150 ml of liquid NH_3. After 2.5 hr, 6 ml of methanol was added dropwise over 15 min with decolorization of solution after 3 hr. NH_3 was allowed to evaporate for 2 hr and then 150 ml of H_2O was added. Nonaqueous solvents were removed by vacuum distillation and the precipitate was collected, washed with H_2O, dried, and recrystallized from ethyl acetate containing 1 drop of pyridine to yield 1.3 g of **11**: mp 83–89°; $\lambda_{max}^{CHCl_3}$ 2.74, 5.88, 6.00 μ.

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found: C, 80.69; H, 10.00.

A solution of 800 mg of **11** in 8 ml of methanol with 0.6 ml of concentrated HCl, and 0.6 ml of H_2O was held at room temperature for 2 hr and then diluted with 40 ml of H_2O. The precipitate was collected, washed with H_2O, dried, and recrystallized from ethyl acetate to yield **10b** (550 mg): mp 135–141°; $\lambda_{max}^{CHCl_3}$ 2.74, 6.00, 6.18 μ; λ_{max} 238.5 mμ (ε 16,000).

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.15; H, 9.59.

13,17[3]-Epoxy-10,17β-dimethyl-17α-propyl-13α-gon-4-en-3-one (16c) and 17α-(3-Hydroxypropyl)-10,17β-dimethylgona-4,3-dien-3-one (10c).—A reaction mixture of 15 g of 17α-(3-hydroxypropyl)-4-androsten-17β-ol-3-one,[3] 60 ml of ethanol, and 15 ml of concentrated HCl was stirred and refluxed for 50 min during which time solution became complete. Water (300 ml) was added and the precipitate was extracted with benzene and chromatographed. The fraction eluted with 15% ethyl acetate–benzene was recrystallized from hexane to yield 2.35 g of **16c**. An analytical sample was obtained by a second recrystallization from hexane; mp 100–105°; $\lambda_{max}^{CHCl_3}$ 5.98, 6.18 μ; nmr, 45 (17-CH_3), 72 (19-CH_3), 222 (multiplet, 22-CH_2), 343 (4-H) cps.

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found: C, 80.63; H, 9.89.

The oily peak fractions eluted with 40% ethyl acetate–benzene (8.44 g) were crude **10c** contaminated with a small amount of the acetate ester of the C-22 hydroxyl group (from transesterification with ethyl acetate). A 2-g sample was dissolved in 20 ml of warm methanol, 5 ml of 2% aqueous $KHCO_3$ was added, and after 5 hr at room temperature 100 ml of H_2O was added. The separated oil was extracted with ether and the ether solution was washed with H_2O, dried (Na_2SO_4), and evaporated to yield 1.7 g of **10c**: $\lambda_{max}^{CHCl_3}$ 2.73, 2.88, 5.98, 6.18 μ; λ_{max} 239 mμ (ε 17,100); nmr, 49 (17-CH_3), 59 (19-CH_3), 216 (triplet 22-CH_2), 345 (4-H) cps.

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found: C, 80.33; H, 9.72.

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6-Chloro-6-dehydro-A-nor Steroids with Progestational Activity. 7α-Chloro-A-nor Steroids

PATRICK A. DIASSI, SEYMOUR D. LEVINE, AND RAYMOND M. PALMERE

The Squibb Institute for Medical Research, New Brunswick, New Jersey

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The synthesis of several 6-chloro-6-dehydro-A-nor steroids is described. Two of these compounds, 6-chloro-6-dehydro-17α-acetoxy-A-norprogesterone (**16**) and 6-chloro-6-dehydro-16α,17α-dimethylmethylenedioxy-A-norprogesterone (**14**), are potent progestational agents. These represent the first examples of A-nor steroids having this hormonal activity. Reaction of Δ^3-2-keto-A-nor steroids with 2,3-dichloro-5,6-dicyanobenzoquinone and HCl results in the formation of 7α-chloro compounds as well as the 6-dehydro derivatives. The mechanism of this reaction is discussed.

Previously reported A-nor analogs of sterodial hormones have shown little or none of the biological properties of the parent hormones. Thus A-norprogesterone (**1**)[1] does not exhibit progestational properties but is a potent antiandrogenic compound;[2] A-nortestosterone (**2**)[1] is weakly androgenic,[3] and A-norhydrocortisone and A-norcortisone[4] do not show the glucocorticoid or antiinflammatory properties of hydrocortisone or cortisone.

The chemical modification of steroid structures designed to enhance progestational activity has been the subject of much interest in recent years. In certain

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