oven at 65° for 1 hr. The solvent was removed *in vacuo*, and the residue was taken up in ether–ethyl acetate (1:1). This solution was washed successively with dilute HCl, water, and 5% potassium carbonate solution. The washed extract was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residual solid was recrystallized from acetone–hexane to give pure VIIIa (9.2 g.), m.p. 194–197°, $[\alpha]^{25}D$ −57°.

Anal. Calcd. for $C_{28}H_{45}NO_3$: C, 75.80; H, 10.22; N, 3.16. Found: C, 75.54; H, 10.21; N, 3.13.

3β-Acetoxy-23-nor-5-cholenic Acid Isopropylamide (VIIIb).—Thionyl chloride (1 ml.) was added dropwise with stirring to a solution of 3β-acetoxy-23-nor-5-cholenic acid[23] (2.0 g.) in anhydrous benzene (25 ml.). The solution was refluxed for 90 min., and the solvent was removed under reduced pressure. Traces of thionyl chloride were removed by the repeated addition and distillation of anhydrous benzene. The crude acid chloride was dissolved in anhydrous benzene (15 ml.) and added dropwise with stirring to a cooled solution of isopropylamine (2 ml.) in anhydrous benzene (20 ml.). The mixture was stirred at room temperature for 3 hr. and water (25 ml.) and ether were added (50 ml.). The organic layer was separated, washed with water, and dried over a mixture of Na_2SO_4 and Darco. Removal of the solvent *in vacuo* afforded a white crystalline solid (2.2 g.), m.p. 187–194°. Recrystallization from acetone–heptane gave pure VIIIb, m.p. 197–199°, $[\alpha]^{25}D$ −41°.

Anal. Calcd. for $C_{28}H_{45}NO_3$: C, 75.80; H, 10.22. Found: C, 75.92; H, 10.21.

3β-Acetoxy-5-cholenic Acid Dimethylamide (VIIIc).—The crude acid chloride of 3β-acetoxy-5-cholenic acid (15 g.) was prepared in a manner similar to that described above. This product was dissolved in anhydrous benzene (130 ml.) and a solution of dimethylamine in toluene (26.6% w./w., 30 ml.) was added with stirring and external cooling. Benzene (40 ml.) was used to rinse the addition funnel and this was added to the reaction mixture. The mixture was stirred at room temperature for 2 hr. and ether (200 ml.) was added. The solution was washed successively with water, 2 *N* HCl, and 5% $NaHCO_3$ solution and dried over a mixture of anhydrous potassium carbonate and Darco. Removal of the solvent under reduced pressure gave crude VIIIc (17.3 g.), m.p. 177–183°, which was satisfactory for subsequent use. A sample was purified by adsorption onto silica gel and elution with ethyl acetate–benzene (1:9). Alternate recrystallization from ethyl acetate–heptane and benzene–heptane gave a pure sample, m.p. 184–186.5°, $[\alpha]^{26}D$ −41° (lit.[13] m.p. 189.5–190°, $[\alpha]D$ −40.9°).

Anal. Calcd. for $C_{28}H_{45}NO_3$: C, 75.80; H, 10.22; N, 3.16. Found: C, 76.13; H, 9.90; N, 3.33.

Reduction of Amides. General Method.—A solution of V (4.4 g., 0.01 *M*) in dioxane (75 ml.) was added dropwise with stirring to a suspension of lithium aluminum hydride (3.8 g., 0.1 *M*) in dioxane (75 ml.) at the reflux temperature. The mixture was refluxed with stirring for 18 hr., whereupon the excess hydride was decomposed by the successive dropwise addition of water (4 ml.) in dioxane (50 ml.), 20% NaOH solution (3 ml.), and water (20 ml.). The inorganic salts were removed by filtration and washed with dioxane. The filtrate was concentrated to dryness *in vacuo* and the residue was crystallized from acetone. This gave pure N-isoamyl-20α-aminopregn-5-en-3β-ol (VI, 2.7 g.), m.p. 120–121°, $[\alpha]^{25}D$ −33.5°.

Anal. Calcd. for $C_{26}H_{45}NO$: C, 80.56; H, 11.70; N, 3.61. Found: C, 80.79; H, 11.78; N, 4.04.

Hydrochloride Salts.—The crystalline amines were dissolved in isopropyl alcohol and sufficient 7 *N* HCl in isopropyl alcohol was added dropwise with agitation. The mixture was allowed to stand at room temperature for a few minutes and the precipitate was collected by filtration. The salts were recrystallized from either aqueous isopropyl alcohol or a mixture of methanol and isopropyl alcohol and gave satisfactory elemental analyses.

(23) K. J. Sax and W. Bergmann, *J. Am. Chem. Soc.*, **77**, 1910 (1955).

Anabolic Agents. A-Ring Conjugated Enone Androstane Derivatives[1a]

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Various A-ring modified derivatives of testosterone were prepared in the hope of obtaining compounds with high anabolic and minimal androgenic activity. A comparison of the biological activity of these A-ring isomers is discussed. The synthesis of some of these isomers is described in detail.

In a previous publication,[1b] it was noted that shifting the double bond of testosterone and 17α-methyltestosterone from the 4,5- to the 1,2-position enhanced parenteral anabolic and, to a lesser extent, androgenic activity. Moreover, a comparison of oral myotrophic activity of the 4,5- and 1,2-ene systems indicated that the latter had a more favorable anabolic–androgenic ratio. These oral activities (Table I) were much greater than would have been expected from an examination of the original biological parenteral data.[1b]

The potent activity found for the 1-dehydro isomers of testosterone (I) prompted interest in other A-ring isomers (Table II) in which the position of not only the double bond, but also the carbonyl group was altered. This paper will discuss the chemistry and biology of these modifications.

The observation by Wharton and Bohlen[2] that hydrazine caused rearrangement of steroidal α,β-epoxy ketones to allylic alcohols prompted investigation of this reaction when applied to the 1,2α-epoxy-3-keto-

TABLE I
ANABOLIC–ANDROGENIC ACTIVITIES[a]

	I.m.		Oral	
Compd.	Myotrophic	Androgenic	Myotrophic	Androgenic
Testosterone propionate	100	100		
Testosterone	26	35		
Ie	200	100		
Ia	400	100		
IVa	5	1		
VIIIa	4	1		
XIIa	200	25		
17α-Methyltestosterone	26	24	100	100
Ib	50	25	1600	100
IVb	20	10	150	20
VIIIb	≤5	<1	<25	≤20
XIIb	100	10–25	100	15

[a] Potencies are given in terms of per cent of the activity of testosterone propionate and 17α-methyltestosterone and were determined from the lowest levels at which significant increases in seminal vesicle or levator ani muscle weights were obtained.

(1a) Presented in part before the Division of Medicinal Chemistry at the 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 1964. (1b) R. E. Counsell, P. D. Klimstra, and F. B. Colton, *J. Org. Chem.*, **27**, 248 (1962).

(2) P. S. Wharton and D. H. Bohlen, *ibid.*, **26**, 3615 (1961).

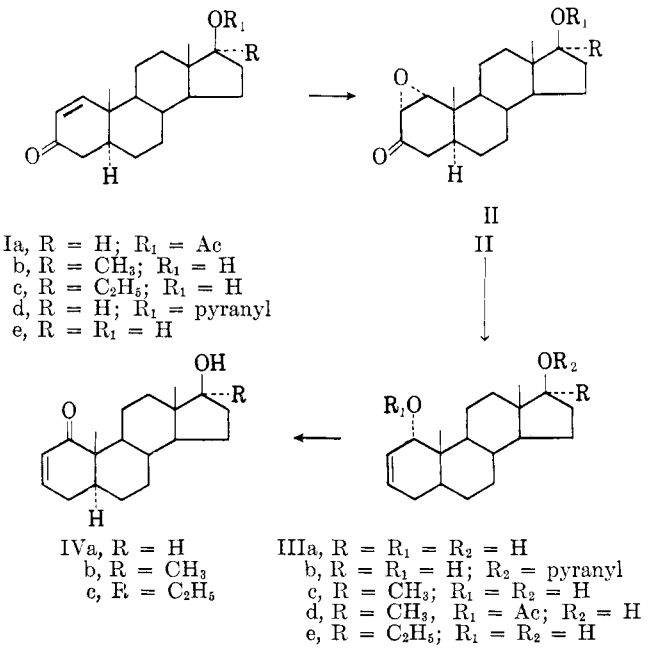
TABLE II

A-RING MODIFIED ANDROSTANE DERIVATIVES

Compd.	Recrystn. media	Yield, %	M.p., °C.	$[\alpha]^{26}D$, deg.	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
IIIa	Me_2CO–hexane	89.2	140–143	+116	$C_{19}H_{30}O_2$	78.57	10.41	78.35	10.42
c	MeOH–H_2O	87.7[a]	128–130	+109	$C_{20}H_{32}O_2$	78.89	10.59	78.81	10.46
d	MeOH–H_2O	64.5	61.5–64	+195	$C_{22}H_{34}O_3$	76.26	9.89	75.95	9.77
e	[b]	85.1		+104.5	$C_{21}H_{34}O_2$	79.19	10.76	78.72	10.44
IVa	Me_2CO–hexane	62.4	179–181	+138.5	$C_{19}H_{28}O_2$	79.12	9.79	79.36	9.62
b	MeOH–H_2O	70	153–155	+96	$C_{20}H_{30}O_2$	79.42	10.00	79.69	10.13
c	MeOH–H_2O	65.4	170–172	+113	$C_{21}H_{32}O_2$	79.70	10.19	79.41	10.14
VIIa	MeOH	52	167–169	+184.5	$C_{21}H_{31}BrO_3$	61.31	7.60	60.91	7.60
b	Me_2CO	56	154–156	+190	$C_{20}H_{31}BrO_2$	62.65	8.15	62.96	8.09
VIIIa	MeOH–H_2O	48	87–90	+8	$C_{21}H_{30}O_3$	76.32	9.15	76.47	9.21
b	Me_2CO	39.2	221–224	−119	$C_{20}H_{30}O_2$	79.42	10.00	79.68	10.16
IXb	MeOH–H_2O	76.5	139.5–140	+30	$C_{20}H_{32}O$	83.27	11.18	82.96	10.87
XIa	MeOH–H_2O	83	130–132	−79.5	$C_{21}H_{31}BrO_3 \cdot 0.5H_2O$	60.00	7.44	60.30	7.70
b	MeOH–H_2O	51.5	130.5–133	−141	$C_{20}H_{31}BrO_2$	62.66	8.15	62.17	8.23
XIIa[c]	MeOH–H_2O	36.4	182–184	+7.5	$C_{21}H_{30}O_3$	76.32	9.15	76.02	9.34
b	Me_2CO–hexane	70.5	116–118	−4.5	$C_{20}H_{30}O_2$	79.42	10.00	79.69	10.26

[a] Yield based on crude material, suitable for further reactions. [b] Could not be recrystallized from a variety of solvents. [c] λ_{max} 226 mμ (log ε 3.87).

5α-androstane system. Epoxidation of the 1-dehydro-3-keto steroids (I) with alkaline hydrogen peroxide according to Hoehn[3] afforded the intermediate 1,2α-epoxy-3-keto steroids (II) in excellent yield. The crude epoxides were of sufficient purity for direct conversion to 1α-hydroxy-5α-androst-2-ene derivatives (III) by heating with hydrazine hydrate in a heterogeneous mixture. The α-configuration of the C-1 axial hydroxyl group was previously established for this rearrangement product by chemical means in the cholestane series.[4] An n.m.r. spectrum of 17α-methyl-5α-androst-2-ene-1α,17β-diol (IIIc)[5] indicated the presence of a fairly narrow unresolved multiplet from 217–223 c.p.s. which was assigned to the C-1 equatorial proton.



Ia, R = H; R_1 = Ac
b, R = CH_3; R_1 = H
c, R = C_2H_5; R_1 = H
d, R = H; R_1 = pyranyl
e, R = R_1 = H

IVa, R = H
b, R = CH_3
c, R = C_2H_5

IIIa, R = R_1 = R_2 = H
b, R = R_1 = H; R_2 = pyranyl
c, R = CH_3; R_1 = R_2 = H
d, R = CH_3, R_1 = Ac; R_2 = H
e, R = C_2H_5; R_1 = R_2 = H

A split peak at 344 and 347 c.p.s. was assigned to the C-2 and C-3 protons on the double bond.[6,7] More recently, Djerassi, *et al.*,[4] applied the hydrazine rearrangement to 1,2α-epoxy-5α-androstan-17β-ol-3-one (IIa) and likewise obtained the 1α-hydroxy-2-ene system.

Usual methods employed to oxidize III with manganese dioxide failed. Similarly, the use of dicyanodichlorobenzoquinone proved unsuccessful, a result also observed by Djerassi and co-workers,[4] indicating that this system is not typically allylic.[8] On the other hand, oxidation of III with chromium trioxide in acetone[9] gave a good yield of the 2-dehydro-1-keto system (IV).

Preparation of the 2-dehydro-1-keto isomer of testosterone (IVa) began with the preparation of the tetrahydropyranyl ether of 17β-hydroxy-5α-androst-1-en-3-one (Id). Epoxidation followed by hydrazine hydrate rearrangement gave 5α-androst-2-ene-1α,17β-diol 17-tetrahydropyranyl ether (IIIb). Chromic acid oxidation in acetone[9] followed by acid hydrolysis of the protecting ether group afforded 17β-hydroxy-5α-androst-2-en-1-one (IVa). In our hands, the reaction of 100% hydrazine hydrate with 1,2α-epoxy-5α-androstan-17β-ol-3-one acetate (IIa) gave cleavage of the acetate to the diol IIIa making selective oxidation to IVa impossible.[10] Djerassi, *et al.*,[4] however, did obtain 5α-androst-2-ene-1α,17β-diol 17-acetate by using isopropyl alcohol as a solvent and heating the reaction only at steam bath temperature.

Reduction with lithium tri(*t*-butoxy)aluminum hydride or lithium aluminum hydride converted the ketone IVb into the C-1 axial alcohol IIIc in good yield. Chromatography of the crude product indicated an absence of any of the C-1 equatorial hydroxyl isomer.

(3) W. M. Hoehn, *J. Org. Chem.*, **23**, 1929 (1958).

(4) C. Djerassi, D. H. Williams, and B. Berkoz, *ibid.*, **27**, 2205 (1962).

(5) The 1957 IUPAC rules on steroid nomenclature as set forth in *J. Am. Chem. Soc.*, **82**, 5577 (1960), have been followed.

(6) The peak positions and relative intensities seem to fit an A–B–X system not unlike that calculated for this type of allylic alcohol: R. H. Bible, "The Interpretation of NMR Spectra—An Empirical Approach," Plenum Press, New York N. Y., 1964.

(7) We are grateful to Dr. R. H. Bible of our laboratories for his interpretation of the n.m.r. data.

(8) It may be possible that the allylic character of the 2-dehydro-1α-hydroxy system is distorted because of the proximity of the C-10 methyl group and the C-11 protons interfering with the proper approach of some reagents.

(9) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

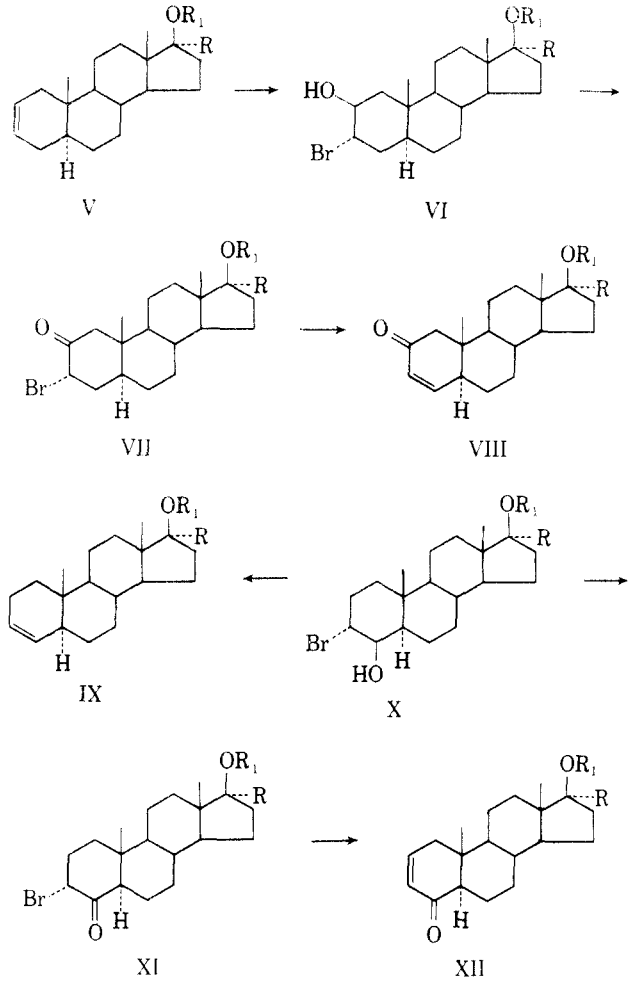
(10) It was subsequently found that the use of 95% hydrazine hydrate in place of 100% hydrazine hydrate caused minimal hydrolysis of the 17-acetate.

Several investigators,[11,12] have been concerned with the preparation of the 3-dehydro-2-keto system. Addition of hypobromous acid to 5α-androst-2-en-17β-ol derivatives (V) gave the intermediate bromohydrins (VI) which upon oxidation with either chromic acid in acetone[9] or preferably with chromic acid in acetic acid afforded the 3α-bromo-2-keto derivatives (VII). In the sapogenin series, Wendler and Slates[13] were unable to dehydrohalogenate the 3α-bromo-2-keto system with boiling pyridine or collidine. Even with lithium chloride in dimethylformamide at 100° they obtained displacement of the bromine with chlorine, but no 3-dehydro 2-ketone.

In the androstane series we were successful in eliminating HBr from compounds VI using lithium chloride and dimethylformamide at reflux temperature to give the 3-dehydro-2-keto derivatives (VIII) in fair yield.

The preparation of compounds where the carbonyl group was shifted to the C-4 position was accomplished starting with the 3-dehydro analogs (IX). At the present time, the 3-dehydro-5α-androstane derivatives (IX) are prepared only with great difficulty. The method of McKenna and co-workers,[14a] which involves treating the 4-dehydro-3-keto system with an enormous excess of zinc dust and acetic acid, is practical only for very small quantities of material. Another method employed in these laboratories involved dehydrotosylating 3β-tosyloxy-5α-androstane derivatives to give a mixture of the corresponding 2- and 3-dehydro-5α-androstanes.[14b] This mixture was not separable by presently available physical means.[15] Treatment of the olefin mixture with hypobromous acid, however, afforded a mixture of bromohydrins from which the less soluble 3α-bromo-2β-hydroxy isomer separated upon crystallization from methanol. The mother liquors were chromatographed on silica gel using at least a 100:1 ratio of adsorbant to steroid. From the benzene–ethyl acetate eluate was obtained the 3α-bromo-4β-hydroxy isomers (X). A portion of the bromohydrins was converted in good yield to the 3-dehydro derivatives (IX)[16] by a brief treatment with zinc and acetic acid at reflux temperature. The remaining portion was oxidized with chromic acid in acetic acid to give the bromo ketones XI. Dehydrohalogenation with lithium chloride and dimethylformamide gave the desired 2-dehydro-4-keto derivatives (XII) in good yield.

Biological Activity.[17]—The assay used to determine androgenic and myotrophic activities was an adaptation[18] of that used by Eisenberg and Gordan.[19] The



a, R = H; R1 = Ac
b, R = CH3; R1 = H

compounds were injected intramuscularly or given orally to castrated male rats. The potencies are given in terms of per cent activity of testosterone propionate (i.m.) or 17α-methyltestosterone (oral) and were determined from the minimal levels at which significant increases in seminal vesicle or levator ani muscle weights were obtained. Table I shows the estimates of the androgenic and myotrophic potencies obtained in these assays.

Comparison of the parenteral potency of the various A-ring modifications of testosterone showed that 17β-hydroxy-5α-androst-2-en-4-one acetate (XIIa) had 2.0 times the anabolic and 0.25 times the androgenic activity of testosterone parenterally and approximated the potency of the previously reported[1b] 17β-hydroxy-5α-androst-1-en-3-one derivatives (Ia and Ie). The other two isomers, IVa and VIIIa, showed minimal activity.[11]

Recently, emphasis has been placed on oral assays for assessment of myotrophic activity. The current method for effecting oral activity is by 17α-alkylation. A comparison of the 17α-methyl compounds in Table I reveals a somewhat specific structural requirement for high oral activity. 17β-Hydroxy-17α-methyl-5α-androst-1-en-3-one (Ib) was much more potent than any of the other A-ring isomers. This compound also possessed a good anabolic–androgenic ratio. Isomers IVb

(11) R. R. Engel and C. Djerassi, Abstracts, 134th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 1958, p. 15-O.

(12) C. Djerassi and T. Nakano, *Chem. Ind.* (London), **45**, 1385 (1960).

(13) N. L. Wendler and H. L. Slates, *J. Org. Chem.*, **26**, 4738 (1961).

(14) (a) J. McKenna, J. K. Norymberski, and R. D. Stubbs, *J. Chem. Soc.*, 2502 (1959). (b) Since completion of this work, L. Caglioti, G. Cainelli, G. Maina, and A. Selva [*Gazz. chim. ital.*, **92**, 309 (1962); *Tetrahedron*, **20**, 957 (1964)] have reported what appears to be an improved procedure for the preparation of the 3-dehydro-5α-androstanes.

(15) J. Fajkos and F. Sorm [*Collection Czech. Chem. Commun.*, **24**, 3115 (1959)] also were unable to separate these isomers by crystallization or chromatography.

(16) The physical constants of 5α-androst-3-en-17β-ol acetate compared favorably with those reported previously by A. Bowers, A. D. Cross, J. A. Edwards, H. Carpio, M. C. Calzada, and E. Denot, *J. Med. Chem.*, **6**, 156 (1963).

(17) We are grateful to Drs. F. J. Saunders, H. D. Lennon, and E. F. Nutting of our Endocrinology Division for furnishing us with this information.

(18) F. J. Saunders and V. A. Drill, *Proc. Soc. Exptl. Biol. Med.*, **94**, 646 (1957).

(19) E. Eisenberg and G. S. Gordan, *J. Pharmacol. Exptl. Therap.*, **99** 38 (1950).

and XIIb, the 2-dehydro-1-keto and 2-dehydro-4-keto derivatives, respectively, were approximately equal to 17α,methyltestosterone myotrophically, but were much less androgenic. Compound VIIIb, the 3-dehydro-2-keto derivative, was essentially devoid of oral activity. Similarly, the 17α-ethyl homolog (IVc) showed low parenteral and oral activity as was previously observed for the 17α-ethyl analog of Ib.[1b]

Some of the intermediates also displayed significant physiological activity. For example, the 17α-methyl-1α, 17β-diol (IIIb) was equal to 17α-methyltestosterone myotrophically and only 1/10 as androgenic. In addition, all of the compounds in Table I possessed some degree of antiestrogenic activity. Specifically, XIIa, XIIb, IIIc, and IVb were between 100 and 600% the activity of progesterone in the mouse uterine growth assay.[20] Because of the relatively high antiestrogenic response of IIIc, studies are in progress to evaluate it as an inhibitor of mammary fibroadenoma.

Experimental[21]

17β-Hydroxy-5α-androst-1-en-3-one Tetrahydropyranyl Ether (Id).—A solution of Ie (20 g.) and dihydropyran (24 ml.) in methylene chloride (160 ml.) containing *p*-toluenesulfonic acid monohydrate (10 mg.) was allowed to stand at room temperature for 72 hr. The solution was washed successively with water and 5% $NaHCO_3$ solution, and dried over anhydrous K_2CO_3 containing Darco. Solvent removal *in vacuo* left an oil which was crystallized from methanol–water to give Id (18.0 g., 69.6%), m.p. 94–96°, λ_{max} 229.5 mμ (log ε 4.01).

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.36; H, 9.62.

1,2α-Epoxy-5α-androstan-17β-ol-3-one Tetrahydropyranyl Ether (IId).—To a solution of Id (5.0 g.) in methanol (85 ml.) cooled to 5° was added a solution of 30% hydrogen peroxide (5.7 ml.) and 10% NaOH in methanol (1.5 ml.). The reaction was stirred for 20 min. at room temperature and poured into ice and water. The resulting mixture was extracted with chloroform–methanol (4:1). The extract was washed with water and dried over anhydrous K_2CO_3 containing Darco. The solvent was removed by distillation and the residue crystallized from methanol–water to give pure IId (4.5 g., 86.5%), m.p. 123–125°, $[\alpha]^{26}D$ +90°.

Anal. Calcd. for $C_{23}H_{35}O_4$: C, 74.19; H, 9.34. Found: C, 74.45; H, 9.19.

17β-Hydroxy-5α-androst-2-en-1-one (IVa).—A heterogeneous mixture of IId (4.0 g.) and 100% hydrazine hydrate (60 ml.) was heated at about 90° for 5 min. and then refluxed for 20 min. Cooling caused two layers to form. The upper layer was discarded and the residual semisolid dissolved in methanol (50 ml.) and was poured into cold water. The precipitate was collected, washed with water, and air-dried to give crude IIIb (3.5 g.), identified by its infrared spectrum. This crude product was suitable for the following reaction.

A solution of crude IIIb (0.5 g.) in acetone (20 ml.) was treated with standard chromic acid solution[9] dropwise until the color of the reagent persisted. The excess chromic acid was decomposed by adding a drop of isopropyl alcohol. The organic layer was decanted from its inorganic salts. To the acetone solution (25 ml.) was added methanol (10 ml.) and *p*-toluenesulfonic acid monohydrate (0.5 g.). The solution was refluxed 15 min. and allowed to stand 64 hr. at room temperature. The reaction was poured into water and extracted with ether. The extract was washed with 5% $NaHCO_3$ solution and dried over anhydrous K_2CO_3 containing Darco. The solvent was removed *in vacuo*, the residue was dissolved in benzene, and the solution was adsorbed onto silica gel (65 g.). Elution with benzene–ethyl acetate (9:1) gave pure IVa (234 mg.), λ_{max} 224.5 mμ (log ε 3.88).

17α-Methyl-5α-androst-2-ene-1α,17β-diol (IIIc). General Method.—A heterogeneous mixture of IIb[22] (8.0 g.) and 100% hydrazine hydrate (120 ml.) was allowed to stand 0.5 hr. at room temperature. The mixture was heated at 90–100° for 15 min. and refluxed for the same period of time. The reaction was cooled resulting in separation into two layers. The supernatant liquid was poured into water and the precipitate was collected, washed with water, and air-dried (0.5 g.). The residual semisolid was dissolved in methanol (50 ml.) and poured into ice and water, and the precipitate was collected. The combined precipitates were washed with 2% aqueous HCl solution, 5% $NaHCO_3$ solution, and water. After air drying, the product weighed 7.2 g. and was suitable for subsequent reactions. Recrystallization from methanol–water afforded pure IIIc (3.7 g.).

17α-Methyl-5α-androst-2-ene-1α,17β-diol 1-Acetate (IIId).—A solution of IIIc (1.5 g.) in pyridine (22 ml.) and acetic anhydride (11 ml.) was allowed to stand overnight at about 40°. The reaction was poured into water and extracted with ether. The extract was washed with water, 10% HCl, and 5% $NaHCO_3$ solution and dried over anhydrous K_2CO_3 containing Darco. Solvent removal *in vacuo* left an oil which was crystallized from methanol–water to give IIId (1.1 g.).

17β-Hydroxy-17α-methyl-5α-androst-2-en-1-one (IVb).—A solution of IIIc (10.0 g.) in acetone (250 ml.) was treated with standard chromic acid solution[9] dropwise until the color of the reagent persisted. The excess chromic acid was decomposed by adding a drop of isopropyl alcohol. The organic layer was decanted from its inorganic salts and poured into ice and water. The precipitate was collected, washed with water, and air-dried. Recrystallization from methanol–water gave pure IVb (7.0 g.), λ_{max} 224.5 mμ (log ε 3.84).

Reduction of 17β-Hydroxy-17α-methyl-5α-androst-2-en-1-one (IVb).—A solution of IVb (1.9 g.) in dry tetrahydrofuran[23] (20 ml.) under nitrogen was cooled in ice and treated with a previously cooled solution of lithium tri(*t*-butoxy)aluminum hydride[24] (6.0 g.) in dry tetrahydrofuran (20 ml.). The reaction was stirred at ice bath temperature for 2 hr. and poured into an ice-cold solution of 5% aqueous acetic acid. The mixture was extracted with ether, washed with a 5% $NaHCO_3$ solution, and dried over anhydrous Na_2SO_4 containing Darco. Solvent removal *in vacuo* left an oil which was chromatographed over alumina (Woelms, neutral). Elution with benzene–ethyl acetate (9:1) gave 1.2 g. of 17α-methyl-5α-androst-2-ene-1α,17β-diol (IIIc), identical with that prepared from the hydrazine hydrate treatment of IIb. None of the 1β-hydroxy isomer of IIIc was observed.[25]

3α-Bromo-5α-androstane-2β,17β-diol 17-Acetate (VIa).—To a cooled solution of Va (containing an undeterminable small amount of the $\Delta^{3,4}$-isomer) (10.0 g.) in purified dioxane (200 ml.) was added dropwise a mixture of N-bromosuccinimide (7.0 g.), perchloric acid (3.8 g.), and water (80 ml.) during 10 min. The reaction was stirred for 4 hr. at room temperature. The solution was poured into ice and water (1.5 l.). The product was collected, washed with water, and air-dried. Recrystallization from acetone–hexane gave pure VIa (6.0 g.), m.p. 145–147°, $[\alpha]^{25}D$ +46.5°.

Anal. Calcd. for $C_{21}H_{33}BrO_3$: C, 61.01; H, 8.05. Found: C, 61.30; H, 8.45.

The mother liquors were chromatographed over silica gel. Elution with benzene–ethyl acetate (9:1) gave additional VIa (1.4 g., 56.4% total) followed by compound Xa (0.3 g.) which was recrystallized from methanol, m.p. 166–168°, $[\alpha]^{25}D$ −4.5°.[26]

5α-Androst-3-en-17β-ol Acetate (IXa). General Method.—A stirred solution of Xa (8.9 g.) in glacial acetic acid (300 ml.)

(20) E. F. Nutting and D. Calhoun, private communication.

(21) Optical rotations, spectra, and analytical data were furnished by Dr. R. T. Dillon, Mr. E. Zelinski, and Mr. J. Damascus of our Analytical department. The optical rotations and infrared spectra were obtained in chloroform and the ultraviolet spectra in methanol. The n.m.r. spectra were obtained with a Varian A-60 spectrophotometer and are reported in c.p.s. downfield from tetramethylsilane which was used as an internal standard. Deuteriochloroform was used as the solvent unless otherwise specified. The melting points were obtained on a Fisher-Johns apparatus and are corrected.

(22) R. E. Counsell and P. D. Klimstra, *J. Med. Pharm. Chem.*, **5**, 477 (1962).

(23) Freshly distilled from methylmagnesium bromide.

(24) Obtained from Metal Hydrides Inc.

(25) Similarly, treatment of IVb with lithium aluminum hydride gave only the 1α-hydroxy isomer IIIc upon chromatography.

(26) The reaction of hypobromous acid with olefins proceeds *via* diaxial addition. Hence, with the presence of both the $\Delta^{2,3}$- and $\Delta^{3,4}$-isomers in the starting material, a total of four products is theoretically possible. In practice, four isomers have been isolated by careful chromatography two of which (the 2β-bromo-3α-hydroxy- and the 4β-bromo-3α-hydroxy-) were present in only trace amounts and tentatively identified by infrared analysis.

was refluxed with zinc dust (27 g.) for 15 min. The solution was filtered and the filtrate was diluted with cold water. The precipitate was collected, washed with water, and air-dried to give IXa (6.5 g.), m.p. 119–119.5° (lit.[16] m.p. 119–120°). The n.m.r. showed a triplet at 312, 323, and 331 c.p.s.

3α-Bromo-17α-methyl-5α-androstane-2β,17β-diol (VIb).—A cooled solution of Vb (containing an undeterminable small amount of the $\Delta^{3,4}$-isomer) (32.0 g.) treated as above gave the crude bromohydrin. Recrystallization from methanol gave VIb (15 g.), m.p. 164–167°, $[\alpha]^{25}D$ +38.5°.

Anal. Calcd. for $C_{20}H_{33}BrO_2$: C, 62.33; H, 8.63. Found: C, 62.46; H, 8.59.

Crystallization of the first portion of the benzene eluate from methanol gave additional VIb (5.2 g., 47.2% total), while the latter portion gave pure 3α-bromo-17α-methyl-5α-androstane-4β,17β-diol (Xb, 0.7 g.), m.p. 182–184° dec., $[\alpha]^{25}D$ −22.5°.

Anal. Calcd. for $C_{20}H_{33}BrO_2$: C, 62.33; H, 8.62. Found: C, 62.14; H, 8.44.

3α-Bromo-17α-methyl-5α-androstan-17β-ol-2-one (VIIb).—Treatment of VIb (1.0 g.) with standard chromic acid solution[9] as described above gave a crude product. Recrystallization from acetone–hexane gave VIIb (550 mg.).

17β-Hydroxy-17α-methyl-5α-androst-3-en-2-one (VIIIb). General Method.—Freshly prepared VIIb (14.8 g.) was refluxed with lithium chloride (4.0 g.) and lithium carbonate (3.2 g.) in dimethylformamide (200 ml.) for 5.5 hr. and allowed to stand at room temperature overnight. Water (150 ml.) was added and the solution was extracted with ether. The ether extract was washed with 10% HCl solution, 5% $NaHCO_3$ solution, and water. The extract was dried over anhydrous Na_2SO_4 containing Darco, and the solvent was removed *in vacuo* to give a solid, λ_{max} 229.5 mμ (log ε 3.65). The product was purified by chromatography on silica gel. Crystallization of the benzene–ethyl acetate (17:3) eluates from acetone gave pure VIIIb (4.5 g.), λ_{max} 232 mμ (log ε 3.80).

3α-Bromo-17α-methyl-5α-androstan-17β-ol-4-one (XIb). General Method.—To a stirred solution of Xb (2.35 g.) in glacial acetic acid (35 ml.) was added with cooling chromic anhydride (1.05 g.) in glacial acetic acid (15 ml.) and water (1.1 ml.). The addition required 15 min. The reaction was stirred at room temperature overnight and poured into ice and water. The precipitate was collected, washed with water, and air-dried. The crude product was dissolved in methanol and treated with Darco. The solvent was removed *in vacuo*, and the residue was recrystallized from methanol–water to give XIb (1.2 g.).

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Mammalian Antifertility Agents. I. Derivatives of 2,3-Diphenylindenes[1]

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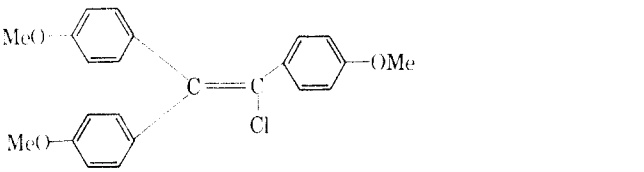
A series of basic ethers of 2,3-diphenylindenes was prepared by the reaction of substituted 2-phenyl-1-indanones. Methods are given for the preparation of the latter. Several of the agents were found to be highly potent antifertility agents in the rat. Structure–activity relations in this series are discussed.

Reproduction of the species is known to be an intricate process dependent at several stages on subtle balances of naturally occurring hormones. Thus, it has been demonstrated that in animals the processes of ovulation, egg transport, and nidation can all be altered by varying the relative hormonal balances.[2] By introducing an exogenous antagonist to a hormone upon which the reproductive process is dependent, it may prove possible to interrupt the chain of events which normally leads to the implantation of a fertilized ovum in the uterus.

Along these lines it has been shown that some basic ethers of compounds related to the synthetic estrogen **1** such as **2** and **3**[3] will exhibit antifertility activity in laboratory animals.[4,5]

It is of particular interest that while some of these agents show weak estrogenic properties, they will antagonize the effects of concurrently administered estrogen.[6,7] Although such lines of evidence can seldom be relied upon, we nevertheless decided to investigate basic ethers of synthetic estrogens. The report[8,9] that indenes such as **4** are relatively potent estrogens made these molecules, which possess a rigid



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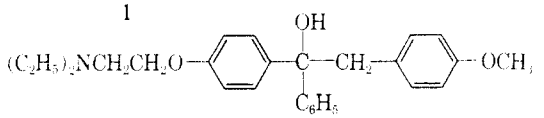

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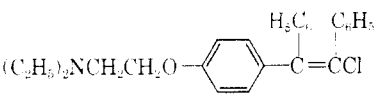

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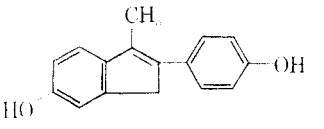

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