mum dioxide and 200 ml. of methanol. After shaking with hydrogen at room temperature and 1 atm. for 48 hr., the calculated amount of hydrogen was consumed. Filtration, evaporation of the filtrate, and crystallization from CCl_4 gave 3.61 g. (61%) of white solid, m.p. 84–88°. The analytical sample was recrystallized from CCl_4 and dried at 45° (30 μ), m.p. 98–98.5°.

Anal. Calcd. for $C_{12}H_{20}O_6$: C, 55.37; H, 7.75. Found: C, 55.39; H, 8.06.

2,5-Dihydroxycyclohexane-1,4-dimethanol (4).—A mixture of 28.0 g. of lithium tri-*t*-butoxyaluminohydride, 2.08 g. of vacuum-dried 1,4-dicarbethoxy-2,5-dihydroxycyclohexane, and 88 ml. of tetrahydrofuran was refluxed with stirring for 22 hr. After cooling, there was added 36 ml. of water (hydrogen evolution), 200 ml. of MeOH, 32.4 g. of NaF, and gradually, with ice bath cooling so that the temperature did not exceed 20° during the addition, 36.6 ml. of 38% HCl. The resulting slurry was filtered and the filtrate was evaporated. The filtration residue was evaporatively distilled at 210° (15 μ) overnight. Crystallization of the distillate from methanol–acetone gave 0.70 g., m.p. 141–142°. The analytical sample was crystallized from isopropyl alcohol and dried at 100° (50 μ).

Anal. Calcd. for $C_8H_{16}O_4$: C, 54.53; H, 9.15. Found: C, 54.36; H, 8.85.

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The Preparation and Some Biological Properties of 17α-Ethyl-17β-methyl-$\Delta^{4,13}$-gonadien-3-one

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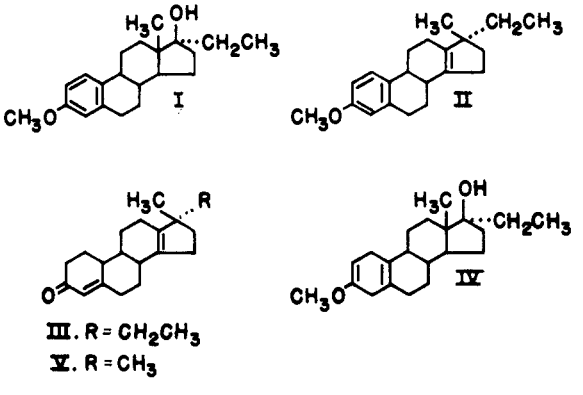
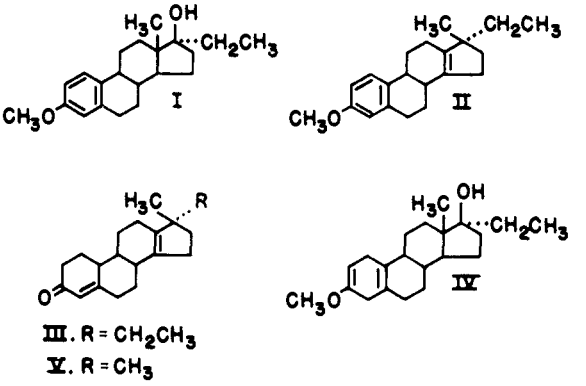
The preparation, proof of structure, and antiestrogenic and antiandrogenic activities of the novel 17,17-dimethyl-4,13-gonadien-3-one (V) have been described.[1] Since this suggested competitive inhibition at the site of action with the parent hormones, it was of interest to examine the biological effect of varying the 17α-substituent. The preparation of 3-methoxy-17α-ethyl-17β-methyl-1,3,5(10),13-gonatetraene (II) and 17α-ethyl-17β-methyl-4,13-gonadien-3-one (III) by acid-catalyzed rearrangement of 17α-ethylestradiol 3-methyl ether (I) and of 3-methoxy-17α-ethyl-2,5(10)-estradien-17β-ol (IV), respectively, is presented. The antiestrogenic and antiandrogenic activities of III are also reported.



(1) R. Kirdani, R. I. Dorfman, and W. R. Nes, *Steroids* **1**, 219 (1963).



Proof of structure for the *gem*-ethylmethyl compounds reported in the present work follows: (a) by analogy to the preparation of the *gem*-dimethyl analogs,[1] (b) from the ultraviolet and infrared spectra indicating that ring A is intact in both the estrogen methyl ether and the Δ^4-3-ketone, and (c) from the n.m.r. spectra in which strong singlets due to the methyl groups at 17 are present at τ 9.00 close to the multiplets of the 17α-groups.

Experimental

Melting points are uncorrected and were taken on a Fisher-Johns melting point apparatus. Ultraviolet spectra were determined on a Cary Model 14 recording spectrophotometer. Infrared spectra were determined on a Perkin-Elmer Infracord and a Beckman IR-7 infrared spectrophotometer. Rotations were measured in a Hilger Mark III standard polarimeter. N.m.r. spectra were determined on a Varian Associates instrument Model V 4302. Combustion analyses were performed by Schwarzkopf Microanalytical Laboratories. 17α-Ethylestradiol 3-methyl ether was purchased from Steraloids, Inc.

17α-Ethyl-3-methoxy-17β-methyl-1,3,5(10),13-gonatetraene (II).—A solution of 500 mg. of 17α-ethylestradiol 3-methyl ether in 50 ml. of 1 *M* HCl in methanol was refluxed for 18 hr. The mixture was then diluted with water and extracted with ether, and the ether extract was washed with saturated $NaHCO_3$ and dried (Na_2SO_4). The residue remaining on evaporation of solvent was applied in hexane to a column of silica gel (50 g., Grace, Davidson Chemical). After washing the column with 300 ml. of hexane the product (400 mg.) was eluted with 20% benzene in hexane. The analytical sample melted at 55–56°; λ_{max}^{EtOH} 287 mμ (ϵ 1975) and 278 mμ (ϵ 2180); $\lambda_{max}^{CS_2}$ 1272, 1240, and 1050 cm.$^{-1}$; n.m.r. maxima (τ): 2.74 and 3.38 (multiplets, aromatic protons), 6.29 (OCH_3), 8.71 (quartet, CH_2CH_3), 9.04 (17β-CH_3), and 9.23 (triplet, 17α-CH_2CH_3, J = 7.0 c.p.s.); $[\alpha]D$ −38° (chloroform).

Anal. Calcd. for $C_{21}H_{28}O$: C, 85.08; H, 9.52. Found: C, 84.92; H, 9.57.

17α-Ethyl-3-methoxy-2,5(10)-estradien-17β-ol (IV) was prepared by Birch reduction of 17α-ethylestradiol 3-methyl ether as described by Colton, *et al.*[2] The melting point was 126.5–128° (lit.[2] m.p. 126–128°); no selective absorption in the ultraviolet; $\lambda_{max}^{CS_2}$ 3575, 1660, and 1220 cm.$^{-1}$.

17α-Ethyl-17β-methyl-4,13-gonadien-3-one (III).—IV was treated as described above for the preparation of II. The product was chromatographed on silica gel, eluted with 2% ether in benzene, and crystallized twice from aqueous methanol. The yield from 17α-ethylestradiol 3-methyl ether for the two steps was 35%. The analytical sample melted at 82–83°; λ_{max}^{EtOH} 239 mμ (ϵ 15,900); $\lambda_{max}^{CS_2}$ 1675 and 1617 cm.$^{-1}$; peaks in the n.m.r. spectrum in τ values: 4.12 (C-4 proton), 8.63–8.88 (quartet, CH_2CH_3), 9.03 (17β-CH_3), and 9.25 (triplet, 17α-CH_2CH_3, J = 6.7 c.p.s.); $[\alpha]D$ −52° (chloroform).

Anal. Calcd. for $C_{20}H_{28}O$: C, 84.45; H, 9.92. Found: C, 84.67; H, 9.86.

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

TABLE I

THE ANTIANDROGENIC ACTIVITY OF 17α-ETHYL-17β-METHYL-$\Delta^{4,13}$-GONADIEN-3-ONE (III)

Expt.	Test compd. designation	Total dose, mg. s.c.	Total dose of testosterone, mg.	No. of mice	Mean body wt., g.	Tissue ratio ± S. E. Prostate	Tissue ratio ± S. E. Seminal vesicles
A	0	0	0	8	17	0.02 ± 0.005	0.17 ± 0.016
		0	0.8	10	17	0.19 ± 0.014	1.24 ± 0.153
	Progesterone	5	0.8	9	17	0.14 ± 0.016	0.83 ± 0.059
		10	0.8	9	17	0.15 ± 0.012	0.68 ± 0.125
		20	0.8	8	15	0.12 ± 0.013	0.42 ± 0.032
	III	17	0.8	10	16	0.13 ± 0.009	0.53 ± 0.026
B	0	0	0	9	18	0.06 ± 0.015	0.23 ± 0.018
		0	0.8	10	16	0.23 ± 0.020	0.94 ± 0.133
	Progesterone	5	0.8	9	16	0.16 ± 0.022	0.84 ± 0.100
		10	0.8	9	16	0.11 ± 0.021	0.55 ± 0.076
		20	0.8	10	16	0.12 ± 0.010	0.43 ± 0.040
	III	5	0.8	7	18	0.15 ± 0.015	0.59 ± 0.045
		10	0.8	8	15	0.15 ± 0.021	0.62 ± 0.048

Biological Activity. Methods.—Antiestrogenic activity was assessed by the method of Dorfman, *et al.*[3] This test measures the ability of a compound to inhibit the uterotrophic activity of estrone. Antiandrogenic activity was determined in the testosterone-stimulated castrated mouse.[4] The end points were the weights of the seminal vesicles and prostate. The compound was also tested for possible antitumor activity using a transplantable rat fibroadenoma system.[5]

Results and Conclusion

The antiandrogenic activity of III is illustrated in Table I. The compound was assayed twice in parallel with the standard progesterone at 5, 10, and 20 mg. total doses. Statistically significant decreases in the seminal vesicles' response were observed after giving III at total doses of 5, 10, and 17 mg. The dimethyl derivative (V) was active at the 20 and 40 mg. dose levels (Table II).

As indicated in Table III, antiestrogenic activity was demonstrated at all three total doses studied, 50, 125, and 500 γ. The maximum inhibition was 56% at the highest doses. This compares (Table II) with the antiestrogenic activity of V which showed a maximum activity of 49%, and 160 γ was the minimum effective dose. It is apparent from Table I and III that no meaningful dose–response curves can be drawn for III in either the antiandrogenic or antiestrogenic assay. At 14 mg. total dose, the compound did not inhibit the mammary tumor weight nor the glycine-2-C^{14} incorporation into the tumor proteins.

The 17-ethyl derivative (III) is perhaps more active as an antiandrogen than the 17-methyl compound (V) under the conditions studied. Antiestrogenic activity of the two compounds is of the same order.

TABLE II

COMPARATIVE BIOLOGICAL ACTIVITY OF THE 17,17-DIMETHYL (V) AND 17α-ETHYL-17β-METHYL (III) DERIVATIVES OF $\Delta^{4,13}$-GONADIEN-3-ONE

Compd.	Test	Result, s.c. injection	Ref.
III	Antiandrogen	+ at 5, 10, 17, and 20 mg.	This report
V	Antiandrogen	+ at 20 and 40 mg.	1
III	Antiestrogen	+ at 50, 125, and 500 γ Maximum inhibition, 56%	This report
V	Antiestrogen	+ at 160–1500 γ Maximum inhibition, 49%	1
III	Antimammary tumor assay	− at 14 mg.	5

TABLE III

THE ANTIESTROGENIC ACTIVITY OF 17α-ETHYL-17β-METHYL-$\Delta^{4,13}$-GONADIEN-3-ONE (III)

Test compd. designation	Total dose, γ s.c.	Total dose of estrone, γ	No. of mice	Mean uterine ratio ± S. E.
0	0		10	0.97 ± 0.053
	0	0.4	10	5.09 ± 0.354
III	50	0.4	10	3.64 ± 0.281
	125	0.4	10	4.74 ± 0.322
	500	0.4	10	2.76 ± 0.240

(3) R. I. Dorfman, F. A. Kincl, and H. J. Ringold, *Endocrinology*, **68**, 17 (1961).
(4) R. I. Dorfman, *Proc. Soc. Exptl. Biol. Med.*, **111**, 441 (1962).
(5) O. Abe, A. Herranen, and R. I. Dorfman, *ibid.*, **111**, 706 (1962).

Hydroxy-, Nitro-, Amino-, and Methoxy-4-(4-dimethylaminostyryl)quinolines[1]

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In view of the fact that *in vivo* hydroxylation of aromatic rings is one of the possible metabolic changes in drugs,[2] we have prepared a series of hydroxy derivatives of 4-(4-dimethylaminostyryl)quinolines (Table I) in order to learn whether the toxicity of these compounds and their antitumor action are greater or less than

(1) This work was supported in part by grants from the American Cancer Society and Public Health Service Research Grants CA 03717-01 through 03717-07 from the National Cancer Institute.
(2) R. T. Williams, "Detoxication Mechanisms," John Wiley and Sons, Inc., New York, N. Y., 1959, pp. 190, 430, 456.