Oxoestrapolyene Ketals as Antilipemic Agents

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Thirty nine ketals of the type named in the title (mostly derivatives of estrone) have been prepared and examined for antilipemic and feminizing activities. A number showed appreciable separations of effects. The activities of various ketals were compared with those of the corresponding ketones.

An estramimetic substance capable of altering blood-lipid composition but lacking feminizing properties would be of potential use in the treatment of atherosclerosis.[2] The high blood-cholesterol depressing and low estrogenic potencies found in these laboratories for (±)-13β-ethyl-17,17-ethylenedioxy-3-methoxygona-1,3,5(10)-triene and its $\Delta^{8,14}$-derivative[3] impelled us to examine a number of related ketals of the estrapolyene series for the desired separation of effects. The structures and biological activities of the ketals investigated are given in Tables I–III.

The ketals were prepared by Salmi ketalization[4] of the corresponding ketones or from appropriate ketal precursors. Preparative details are given in the Experimental section. Notably, ketalization of 16α-chloroestrone and 16α-acetoxyestrone methyl ethers required reaction in refluxing toluene, whereas 16β-acetoxyestrone and 16-methyleneestrone methyl ethers reacted readily in refluxing benzene. In refluxing toluene, 16α-iodoestrone methyl ether decomposed, and 16,16-difluoroestrone methyl ether failed to react. The latter was recovered unchanged after vacuum distillation of its solution for over 6 hr. in ethylene glycol containing toluene-*p*-sulfonic acid.[5] The 16α-bromo ketal **27**[6] was made from estrone methyl ether ethylene ketal with pyridine hydrobromide perbromide, which has previously been used for the 16-bromination of various 17-oxoandrostane ketals.[7]

Biological Activities.—Antilipemic activity was measured by the depression of serum cholesterol produced by 9 days of drug treatment in male rats. "Feminizing" activity was estimated from the depression of testis weights of the same treated rats. Estrogenic activity was obtained from a 3-day mouse uterine weight assay.[8] For certain compounds antilipemic activity was also derived from the alteration in serum cholesterol–phospholipid ratio of cholesterol-fed cockerels after administration of the drug over 4 days.[9] Potencies, where known with sufficient accuracy, are expressed in terms of estrone (100%).

No regular patterns of structure–activity relationships emerge from the biological data. Notably, ketalization of a 17-ketone sometimes depresses the feminizing and estrogenic activities while leaving the antilipemic activity unchanged or even enhanced. The low estrogenic activity of estrone methyl ether ethylene ketal[10a] and estrone hemithioethylene ketal[10b] has been recorded previously. The allyl ether ketal (**7**), having the highest antilipemic activity with the best separation of activities in Table I, is one of the most interesting compounds examined. Whereas ketals **11–13**, **17**, and **18**, with unsaturation in the estrone nucleus at the 6-, 14-, and 15-positions, are inactive, ketals **14–16**, with unsaturation at the 7- and 9(11)-positions, have higher antilipemic activities and better separations of effects than the parent ketones. Interestingly, the (±)-$\Delta^{8,14}$-estrone methyl ether ketal **20**,[3a,b] showed separation of antilipemic and feminizing effects, while its D-homolog **31** was feminizing but not antilipemic. All of the 16-substituted estrone methyl ether ketals, except the inactive 16α-acetoxy member **25**, showed high antilipemic activity with low estrogenicity. The hemithio- and dithioketals (Table II) had lower activity than the corresponding ketals.

Experimental[11]

Ketals 1–**5**, **7–10**, **13**, **16**, **17**, **19–22**, **23**, **25–29**, **31**, **32**, and **37–39** were made by Salmi ketalization[4] of the corresponding ketones. Ketals **6**, **12**, and **15** were prepared by methylation of the corresponding phenolic ketals. Ketals 11 and **24** were obtained by saponification of ketals **13** and **26**, respectively. Ketal **18** was made by dehydrobromination of ketal **27**.[6]

In the preparation of ketals by Salmi's method, the proportions employed were steroid ketone (1 g.)–toluene-*p*-sulfonic acid monohydrate (0.1 g.)–ethylene or other glycol (10 ml.)–benzene (100 ml.), and the reaction mixture was refluxed for 15–30 hr. (Dean–Stark apparatus). Solvents used for recrystallization were methanol, ethyl acetate, acetone, and diethyl ether. The hemithioketals were prepared similarly, substituting 2-mercaptoethanol for the glycol. The dithioketals were made by the previously described method.[12] Necessary experimental details for new compounds are given in the sequel.

(1) To whom inquiries should be addressed.

(2) (a) G. P. Mueller, W. F. Johns, D. L. Cook, and R. A. Edgren, *J. Am. Chem. Soc.*, **80**, 1769 (1958); (b) L. F. and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 478.

(3) (a) H. Smith and G. A. Hughes, Belgian Patent 600,759 (1961); (b) H. Smith and G. A. Hughes, Belgian Patent 614,337 (1962); (c) H. Smith, *et al.*, *Experientia*, **19**, 394 (1963).

(4) E. Salmi, *Ber.*, **71**, 1803 (1938); E. Salmi and V. Ranniko, *ibid.*, **72**, 600 (1939).

(5) W. S. Allen, S. Bernstein, and R. Littell, *J. Am. Chem. Soc.*, **76**, 6116 (1954).

(6) W. S. Johnson and W. F. Johns, *ibid.*, **79**, 2005 (1957).

(7) A. Marquet, M. Dvolaitzky, H. B. Kagan, L. Mamlok, C. Ouannes, and J. Jacques, *Bull. soc. chim. France*, 1822 (1961); A. Marquet and J. Jacques, *ibid.*, 90 (1962).

(8) R. A. Edgren, *Proc. Soc. Exptl. Biol. Med.*, **92**, 569 (1956).

(9) *Cf.* D. L. Cook, D. W. Calhoun, and R. A. Edgren, *Arch. Intern. Pharmacodyn.*, **135**, 91 (1962).

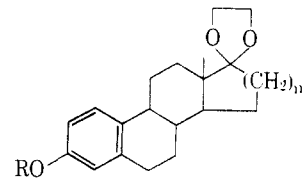
(10) (a) W. S. Allen, H. M. Kissman, S. Mauer, I. Ringler, and M. J. Weiss, *J. Med. Pharm. Chem.*, **5**, 133 (1962); (b) J. Romo, G. Rosenkranz and C. Djerassi, *J. Am. Chem. Soc.*, **73**, 4961 (1951).

(11) Corrected melting points were determined in capillary tubes (Thomas–Hoover apparatus). Optical rotations were determined on 0.5–1% solutions in chloroform except where stated otherwise. Ultraviolet absorption spectra were recorded in 95% ethanol.

(12) C. Djerassi, H. J. Ringold, and G. Rosenkranz, *J. Am. Chem. Soc.* **76**, 5533 (1954).

TABLE I

17,17-ETHYLENEDIOXYESTRAPOLYENES



No.	R	Additional substn.	n	M.p., °C.	[α]D, degrees	λmax, mμ (ε)	Formula
1	H	...	1	182–185	+26.2	281 (2280), 289 (2090)	$C_{20}H_{26}O_3$
2[d]	CH_3	...	1	101–104	+26.6	280 (2390), 288 (2150)	$C_{21}H_{28}O_3$
3	C_2H_5	...	1	92–93	+57.4[f]	280 (1710), 288 (1520)	$C_{22}H_{30}O_3$
4	n-C_3H_7	...	1	64–65	+26.6	281 (2130), 288 (2130)	$C_{23}H_{32}O_3$
5	n-C_4H_9	...	1	Oil	+8.9	281 (2110), 288 (1940)	$C_{24}H_{34}O_3$
6	n-C_7H_{15}	...	1	Oil	+15.5	281 (1890), 288 (1890)	$C_{27}H_{40}O_3$
7	CH_2=$CHCH_2$	...	1	71–72	+25	280 (2000), 288 (1810)	$C_{23}H_{30}O_3$
8	CH_2=$CH(CH_2)_2$	...	1	Oil	+13.2	281 (1230), 288 (1250)	$C_{24}H_{32}O_3$
9	HC≡CCH_2	...	1	99–101	+25.8	280 (1530), 288 (1590)	$C_{23}H_{28}O_3$
10	Cyclopentyl	...	1	101–102.5	+22.7	281 (2000), 289 (1780)	$C_{25}H_{34}O_3$
11[a]	H	Δ^6	1	187–189	...	262 (6740), 303 (2320)	$C_{20}H_{24}O_3$
12	CH_3	Δ^6	1	75–76	−227	261 (6780), 301 (2320)	$C_{21}H_{26}O_3$
13[n]	CH_3CO	Δ^6	1	119–120	−213[o]	262 (8500)	$C_{22}H_{26}O_4$
14	H	Δ^7	1	155–156	+158	280 (1920)	$C_{20}H_{24}O_3$
15	CH_3	Δ^7	1	148–150	+145	280 (1710)	$C_{21}H_{26}O_3$
16	CH_3	$\Delta^{9(11)}$	1	130–131.5	p	264 (18000)	$C_{21}H_{26}O_3$
17[r]	CH_3	Δ^{14}	1	121–122	+80.6	277 (2070)	$C_{21}H_{26}O_3$
18	CH_3	Δ^{15}	1	122–125	...	277 (1880)	$C_{21}H_{26}O_3$
19	CH_3	$\Delta^{6,8}$	1	141–145	−47.1	...	$C_{21}H_{24}O_3$
20	CH_3	$\Delta^{8,14}$	1	94–97.5	p	311 (31000)	$C_{21}H_{24}O_3$
21	H	1-CH_3	1	173–175	+103.1	281–289 (2150)	$C_{21}H_{28}O_3$
22	CH_3	1-CH_3	1	76.5–77.5	...	...	$C_{22}H_{36}O_3$
23	CH_3	16α-HO	1	161–163	+10.5	280 (1500), 288 (1500)	$C_{21}H_{28}O_4$
24	CH_3	16β-HO	1	142–144	+34.5	...	$C_{21}H_{28}O_4$
25	CH_3	16α-AcO	1	114–115	−23	280 (2050), 288 (2050)	$C_{23}H_{30}O_5$
26	CH_3	16β-AcO	1	161–163	+1.7	281 (1510), 287 (1510)	$C_{23}H_{30}O_5$
27[r]	CH_3	16α-Br	1	195–197	...	278 (1725)	$C_{21}H_{27}BrO_3$
28	CH_3	16α-Cl	1	207–210	+40.3	279 (1750), 287 (1630)	$C_{21}H_{27}ClO_3$
29	CH_3	16-CH_2=	1	123–125	0	278 (2140), 288 (2000)	$C_{22}H_{28}O_3$
30	CH_3	16-O=	1	158–160	−93.8	281 (1600), 288 (1740)	$C_{21}H_{26}O_4$
31	CH_3	$\Delta^{8,14}$	2	123–126	p	...	$C_{22}H_{26}O_3$
32	CH_3	...	2	99–100	+28.5	279 (2120), 287 (1950)	$C_{22}H_{30}O_3$

[a] Rat test; potencies expressed relative to estrone (100%); A = active, I = inactive, and Q = questionable. [b] Most of the parent ketones used in the preparation of ketals are old; literature references, where deemed necessary, are given in the final column. [c] Mouse uterine weight assay; potency expressed relative to estrone (100%), see ref. 8. [d] P. DeRuggieri, *Gazz. chim. ital.*, **87**, 795 (1957). [e] Antilipemic activity in cockerel test (see ref. 9), 25% (estrone = 100% as standard). [f] In ethanol. [g] R. Courrier, L. Velluz, J. J. Alloiteau, and G. Rousseau, *Compt. rend. Soc. biol.*, **139**, 128 (1945). [h] Cockerel test, 17%. [i] A. Ercoli and R. Gardi, *Chem. Ind.* (London), 1037 (1961); A. Ercoli, F. Galletti, and G. Falconi, *Endocrinology*, **71**, 593 (1962). [j] Cockerel test, 25%. [k] K. Miescher

3-(3′-Butenyl)oxyestra-1,3,5(10)-trien-17-one.—A mixture of 5.0 g. of estrone, 6 ml. of 4-bromo-1-butene, 1.95 g. of potassium hydroxide, and 85 ml. of methanol was refluxed for 16 hr. The mixture was adjusted to pH 10, 3 ml. of 4-bromo-1-butene was added, and the mixture was refluxed for 24 hr., 5 ml. of 4-bromo-1-butene and alkali (to pH 10) being added every 2 hr. The precipitate was filtered off and dissolved in methanol, the methanol was evaporated, and the residue, in benzene, was washed with water. The benzene solution was evaporated to an oil which was triturated with petroleum ether (b.p. 40–60°), yielding 5.05 g. of crystals, m.p. 70–85°. After several recrystallizations from methanol, the pure butenyl ether was obtained; m.p. 84–85°; $[\alpha]_D$ +137°; λ_{max}^{KBr} 5.77, 6.08, 6.20, 6.36, and 6.65 μ.

Anal. Calcd. for $C_{22}H_{28}O_2$: C, 81.44; H, 8.70. Found: C, 81.58; H, 8.76.

3-Propargyloxyestra-1,3,5(10)-trien-17-one.—A solution of 4.0 g. of estrone in 75 ml. of hot methanol containing 3.3 g. of potassium hydroxide was treated with 3.6 ml. of propargyl bromide over 8 min. The mixture was refluxed overnight, after which time 2 ml. of propargyl bromide was added, and the solution was adjusted to pH 10 with alkali. The mixture was refluxed for 24 hr., 1 ml. of propargyl bromide and alkali (to pH 10) being added every 2 hr. Work-up as in the previous experiment gave a crystalline residue which was recrystallized from methanol, yielding 3.4 g. of ketal, m.p. 146–149°. Recrystallization from methanol afforded the analytical sample, m.p. 146–149°; $[\alpha]_D$ +144.5°; λ_{max}^{KBr} 3.06, 4.73, 5.75, 6.23, 6.33, 6.67, and 8.18 μ.

Anal. Calcd. for $C_{21}H_{24}O_2$: C, 81.78; H, 7.84. Found: C, 81.64; H, 7.57.

16β-Acetoxy-3-methoxyestra-1,3,5(10)-trien-17-one.—To a solution of 7.0 g. of 17-acetoxy-3-methoxyestra-1,3,5(10),16-tetraene[6] in 150 ml. of glacial acetic acid and 3 ml. of acetic anhydride was added 9.53 g. of lead tetraacetate.[13] The mixture was shaken occasionally during the day and allowed to stand overnight at room temperature. It was concentrated to *ca.* 70 ml., diluted with benzene, and washed with water. Evaporation of the dried benzene solution rendered a residue which was crystallized from methanol to give 5.75 g. of crude product.

(13) *Cf.* W. R. Biggerstaff and T. F. Gallagher, *J. Org. Chem.*, **22**, 719 (1957).

Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Antilipemic biological test[a] % Ketal Lipid,	Ketal Feminization,	Parent ketone[b] Lipid,	Parent ketone[b] Feminization,	Ketal, estrogenicity %[c]	Ketone ref.
76.40	76.70	8.34	8.60	100	20	100	100	5–10	...
76.79	76.83	8.59	8.79	100[e]	10	100	30–100	6	...
77.15	77.30	8.83	8.94	100	10	200	55	1	*g*
77.49	77.62	9.05	8.87	100[h]	A	100	100	8	*i*
77.80	77.90	9.25	9.35	100	100	100	A	...	*i*
78.59	78.90	9.77	10.20	30	100	...	...	...	...
77.93	77.91	8.53	8.45	1000[j]	10	100	10	1–2	*k*
78.22	77.89	8.75	8.93	[l]		100	120	...	*m*
78.37	78.28	8.01	7.98	100	100	300	100	...	*m*
78.49	78.97	8.96	8.90	100	10	100	10	3–10	*i*
76.89	...	7.74	...	I	I	...	...	A	...
77.27	77.53	8.03	7.92	I	I	...	...	A	...
74.55	74.38	7.39	7.30	I	I	...	...	>0.01	...
76.89	76.72	7.74	7.42	300	100	200	300	>1	...
77.27	76.91	8.03	7.90	300	A	...	...	1	...
77.27	77.26	8.03	8.03	100	5	...	...	0.3	*q*
77.27	77.42	8.03	8.18	I	I	...	...	...	...
77.27	...	8.03	...	I	I	30	Q	>1	*r*
77.75	78.06	7.46	7.76	100	100	200	300	0.3	...
77.75	77.79	7.46	7.39	30	10	50	10	0.03–0.1	*q*
76.79	76.95	8.59	8.45	40	Q	I	I	...	*s*
77.15	77.07	8.83	8.72	I	I	...	...	...	*t*
73.22	73.35	8.19	7.98	100	I	30	Q	...	*u*
73.22	73.48	8.19	8.24	100	Q	...	...	...	*m*
71.48	71.78	7.82	7.89	I	I	300	Q	...	*u*
71.48	71.61	7.82	8.03	100	I	300–1000	Q	...	*m*
61.92	...	6.68	...	300	Q	100	Q	...	*r*
69.50	69.63	7.49	7.38	200	I	300	1–10	1–3	*v*
77.61	77.53	8.29	8.00	I	I	I	I	...	*w*
73.66	73.56	7.66	7.68	I	I	...	...	...	...
78.0	77.8	7.75	7.5	I	I	I	I	...	*p*
77.15	77.12	8.83	8.52	I	A	300	I	...	*x*

and C. Scholz, *Helv. Chim. Acta*, **20**, 1237 (1937). [l] Cockerel test, 6%. [m] See Experimental. [n] J. Iriarte, H. J. Ringold, and C. Djerassi, *J. Am. Chem. Soc.*, **80**, 6105 (1958). [o] In dioxane. [p] Racemic. [q] G. H. Douglas, J. M. H. Graves, D. Hartley, G. A. Hughes, B. J. McLoughlin, and H. Smith, *J. Chem. Soc.*, 5072 (1963). [r] See ref. 6. [s] C. Djerassi, G. Rosenkranz, J. Romo, J. Pataki, and S. Kaufmann, *J. Am. Chem. Soc.*, **72**, 4540 (1950). [t] H. J. Ringold, G. Rosenkranz, and F. Sondheimer, *ibid.*, **78**, 2477 (1956). [u] J. G. D. Carpenter and A. E. Kellie, *Biochem. J.*, **84**, 303 (1962). [v] See ref. 2a. [w] F. Kincl and M. Garcia, *Ber.*, **92**, 595 (1959). [x] H. Heusser, P. T. Herzig, A. Furst, and P. A. Plattner, *Helv. Chim. Acta*, **33**, 1093 (1950).

Two recrystallizations from methanol yielded the pure 16β-acetoxy 17-ketone, m.p. 153–156°; $[\alpha]_D$ +96.6°; λ_{max}^{KBr} 5.74, 6.22, 6.36, and 6.68 μ.

Anal. Calcd. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66. Found: C, 73.70; H, 7.59.

17,17-Ethylenedioxy-3-heptyloxyestra-1,3,5(10)-triene (6).—A solution of 3.14 g. of estrone ethylene ketal in 85 ml. of methanol containing 0.66 g. of KOH was stirred and heated to reflux and 3.58 g. of 1-bromoheptane was added slowly. After 6 hr. the pH was adjusted to 9–10 with alkali, 1.0 ml. of 1-bromoheptane was added, and the mixture was refluxed for 4 hr. The oily product, which was approximately 90% 3-heptyl ether by thin layer chromatography,[14] was triturated with petroleum ether, and the unchanged estrone ketal, 0.45 g., m.p. 160–170°, was filtered off. The filtrate was chromatographed on basic alumina (Woelm) and eluted with petroleum ether, yielding 3.0 g. of the ketal as a colorless oil; λ_{max}^{film} 6.20, 6.35, and 6.67 μ, devoid of hydroxyl or ketone absorption bands.

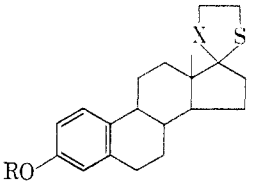
17,17-Ethylenedioxyestra-1,3,5(10),7-tetraen-3-ol (14).—A well-stirred mixture of 900 mg. of equilin, 100 mg. of *p*-toluenesulfonic acid monohydrate, and 160 ml. of ethylene glycol was distilled at 6 mm. for 1 hr.[5] An additional 100 ml. of ethylene glycol was added and distillation was continued for 1 hr., a total of 230 ml. of distillate having been collected. The solution was cooled, saturated $NaHCO_3$ solution was added, and the resulting gum, in ether, was washed with water, dried over anhydrous magnesium sulfate, and evaporated. The residue was triturated with petroleum ether, yielding 1.0 g. of crude product. Recrystallization from acetonitrile gave 570 mg. of product, m.p. 122–132°, which was recrystallized three times from acetonitrile to give the analytical sample, m.p. 155–156°; λ_{max}^{KBr} 2.95, 6.17, 6.33, and 6.67 μ (see Table I).

16α-Bromo-17,17-ethylenedioxy-3-methoxyestra-1,3,5(10)-triene (27).—To 100 mg. of estrone-3-methyl ether ethylene ketal in 10 ml. of anhydrous tetrahydrofuran was added 0.134 g. of pyridinium hydrobromide perbromide. After stirring for 2.5 hr. at room temperature, the mixture was poured into 25 ml. of 5% aqueous sodium bicarbonate solution and extracted with chloroform. The crude product was recrystallized from methanol, yielding 91 mg. of **27**, m.p. 180–188°; the infrared spectrum

(14) L. L. Smith and T. Foell, *J. Chromatog.*, **9**, 339 (1962).

TABLE II

ESTRONE THIOKETALS



No.	R	X	M.p., °C.	$[\alpha]_D$, degrees	λ_{max}, mμ (ε)	Formula	Carbon, % Caled.	Carbon, % Found	Hydrogen, % Caled.	Hydrogen, % Found	Sulfur, % Caled.	Sulfur, % Found	Antilipemic biological test,[a] % Lipid	Antilipemic biological test,[a] % Femi-nization	Antilipemic biological test,[a] % Estro-genicity[b]
33[c]	H	O	162–163	−1.8	280 (1875)	$C_{20}H_{26}O_2S$	72.69	72.17	7.93	7.72	9.70	9.60	10[d]	I	...
34	CH_3	O	109–111	−2.6	280 (2020)	$C_{21}H_{28}O_2S$	73.21	72.91	8.19	8.03	9.30	9.10	A	A	2
35	H	S	165–167	0	280 (1880)	$C_{20}H_{26}OS_2$	69.32	69.33	7.56	7.73	18.51	18.40	40	5	A
36	CH_3	S	138–139	0	280 (1910)	$C_{21}H_{28}OS_2$	69.95	70.15	7.83	7.82	17.79	17.70	50[e]	1	2–3

[a] See Table I, footnote *a*. [b] See Table I, footnote *c*. [c] See ref. 10b. [d] Cockerel test, 25%. [e] Cockerel test, 3%.

TABLE III

MISCELLANEOUS KETALS

No.	Compd.	M.p., °C.	$[\alpha]_D$, degrees	λ_{max}, mμ (ε)	Formula	Carbon, % Caled.	Carbon, % Found	Hydrogen, % Caled.	Hydrogen, % Found	Antilipemic biological test,[a] % Lipid	Antilipemic biological test,[a] % Femini-zation
37[b]	3-Methoxy-16,16-ethylenedioxy-estra-1,3,5(10)-triene	132.5–134.0	...	...	$C_{21}H_{28}O_3$	76.79	76.78	8.59	8.58	100	1
38[c]	17,17-Ethylenedioxy-1-hydroxy-4-methylestra-1,3,5(10)-triene	240–240.5	+138.3	282 (2300)	$C_{20}H_{28}O_2$	76.79	76.82	8.59	8.52	1	0
39[d]	3-Methoxy-17,17-trimethylene-dioxyestra-1,3,5(10),8,14-pentaene	136–141	[e]	310 (27,900)	$C_{22}H_{26}O_3$	78.07	78.02	7.79	7.73	A	1[f]

[a] See Table I, footnote *a*. [b] For parent ketone see M. N. Huffmann, M. H. Lott, and A. Tillotson, *J. Biol. Chem.*, **217**, 107 (1955). [c] For parent ketone see A. S. Dreiding and A. Voltman, *J. Am. Chem. Soc.*, **76**, 537 (1954). [d] For parent ketone see Table I, footnote *q*. [e] Racemic. [f] Mouse uterine assay (see Table I, footnote *c*), 0.06% estrogenic.

and thin layer chromatographic behavior were identical with a sample of **27**, m.p. 195–197°, prepared by Johnson and Johns' method.[6]

17,17-Ethylenedioxy-3-methoxyestra-1,3,5(10)-trien-16β-ol (24).—A solution of 440 mg. of **26** in 100 ml. of methanol was refluxed under nitrogen with 450 mg. of potassium hydroxide in 7 ml. of water. The solution was neutralized with acetic acid, diluted with ether, and washed with water. The crude product was recrystallized from methanol, yielding 270 mg., m.p. 142–144°; λ_{max}^{KBr} 2.86, 6.22, 6.34, and 6.66 μ.

17,17-Ethylenedioxy-3-methoxyestra-1,3,5(10)-trien-16-one (30).—A solution of 1.0 g. of 17,17-ethylenedioxy-3-methoxyestra-1,3,5(10)-trien-16α-ol (**23**) in 10 ml. of dry pyridine was added to a solution of 500 mg. of chromium trioxide in 25 ml. of dry pyridine at 15–20°. After 18 hr. at room temperature the reaction mixture was poured into 600 ml. of water, and the mixture was extracted with ethyl acetate. The sirupy product was crystallized from methanol, 400 mg., m.p. 151–155°. Several recrystallizations from methanol gave the pure product, m.p. 158–160°; λ_{max}^{KBr} 5.70, 6.22, 6.37, and 6.67 μ.

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