with 30% H_2SO_4, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O and saturated NaCl and dried over Na_2SO_4. Removal of the $CHCl_3$ gave 36 g of brown oil which was partially purified by dissolving in MeOH and treating with charcoal. Concentration gave a light yellow residue. Crystallization from C_6H_{14}–C_6H_6 gave 21 g (61%) of **8**, mp 104–106°. *Anal.* ($C_{34}H_{40}O_7$) C, H.

2-[10(*R*)-Hydroxy-6-oxo-*trans*-1-undecenyl]-4,6-bis(benzyloxy)benzoic Acid (9). To a solution of **8** (20 g, 35.7 mmol) in 150 ml of THF was added, with cooling, 100 ml of 2.2 *N* $HClO_4$ and the mixture was stirred at room temperature for 6 hr. The mixture was poured into H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O and saturated NaCl and dried over Na_2SO_4. Removal of the solvents gave 17.8 g (96%) of crude **9** as an oil. Crystallization of a small portion from C_6H_{14}–C_6H_6 gave pure **9** as a white amorphous solid, mp 82–84°.

2-[10(*R*)-Hydroxy-6-oxo-*trans*-1-undecenyl]-4,6-bis(benzyloxy)benzoic Acid μ-Lactone (10). A solution of **9** (10 g, 19.4 mmol) in anhydrous C_6H_6 was cooled to 5°, trifluoroacetic anhydride (4.2 g, 20 mmol) was slowly added over a 30-min period under N_2, and the mixture was stirred at 5° for 24 hr. The reaction mixture was washed with 5% KOH (aqueous), H_2O, and saturated NaCl and dried over Na_2SO_4. Removal of the C_6H_6 gave 6.3 g of brown residue which was recrystallized several times from *i*-PrOH to give 1.8 g (19%) of pure **10** as white crystals, mp 128.5–129.5°. *Anal.* ($C_{32}H_{34}O_5$) C, H.

(*R*)-Zearalanone (11). A portion of **10** (1.0 g, 2 mmol) was dissolved in 140 ml of EtOH–EtOAc (2.5:1) and hydrogenated under atmospheric pressure and room temperature with 5% Pd/C (0.3 g). Filtration of the catalyst and removal of the solvents gave 0.60 g (94%) of white solid. Recrystallization from MeOH gave pure (*R*)-zearalanone (**11**) as white crystals: mp 190–191°; $[\alpha]^{25}D$ (MeOH) +36.8°. (The physical properties of (*S*)-zearalanone are mp 190–191°; $[\alpha]^{25}D$ (MeOH) −34°.) *Anal.* ($C_{18}H_{24}O_5$) C, H.

Uterotropic Assay. Samples were administered orally (in sesame oil) to ten adult castrate female mice for 3 days at levels of 50, 100, and 300 μg/mouse/day. On day 4 the animals were sacrificed, and the uteri were removed and weighed.

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Synthesis and Biological Properties of 17α-Furylestradiol and Dihydroequilin Derivatives

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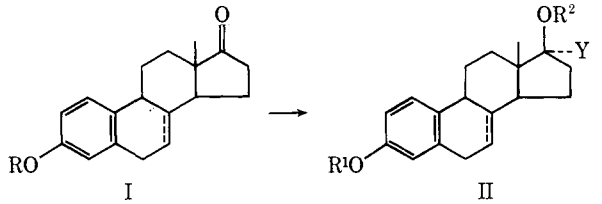
A series of 17α-furylestradiol and dihydroequilin derivatives was synthesized by reacting the appropriate 3-substituted estrone and equilin with 2- or 3-furyllithium. The oral estrogenic activity of the compounds was compared with that of mestranol. In the Allen–Doisy test, the 17α-(3-furyl) analogs were 4–19 times as potent orally as the standard in rats but they were less active in mice. Acetylation of the 17-alcohol or replacement of the 3-furyl by a 2-furyl group produced a decrease in activity. In the mouse uterotrophic assay in mice the compounds were less effective than mestranol and exhibited very shallow dose–response curves.

As part of an extensive program concerning the oxidation of furans,[1,2] a series of 17α-(3-furyl)estradiol and dihydroequilin derivatives was synthesized. As evidenced by the detailed pharmacology of estrofurate[3] [17α-(3-furyl)-estra-1,3,5(10),7-tetraene-3,17-diol 3-acetate, compound **13**], these constitute a new class of potent oral estrogens with a profile of activity in animals different from the one exhibited by mestranol. This paper deals with the synthesis and biological properties of these compounds as well as those of the related 17α-(2-furyl) and 17α-(3-tetrahydrofuryl) analogs.



I II

R = CH_3, cyclopentyl, and tetrahydropyranyl
R^1 = H, CH_3, cyclopentyl, and acetyl
R^2 = H and acetyl
Y = 2-furyl, 3-furyl, and 3-tetrahydrofuryl

Chemistry. The 17α-(3-furyl)-17-hydroxy and 17α-(2-furyl)-17-hydroxy moieties in II were introduced conventionally by reacting the appropriate estrone and equilin derivatives I with 3- and 2-furyllithium. The phenolic alcohols were usually protected as tetrahydropyranyl ethers prior to the reaction and removal of the protecting group could be achieved under mildly acidic conditions without concomitant dehydration.

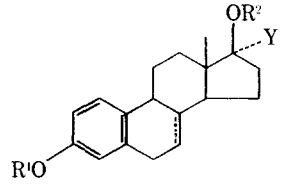
Acetylation of the 3-phenols was accomplished with acetic anhydride and pyridine at room temperature. In order to acetylate the 17-alcohol, more drastic conditions were required such as heating the pyridine–acetic anhydride solution at 100° for 24 hr. The compounds prepared are listed in Table I.

Biology. 1. Methods. The oral estrogenicity of the compounds was determined in two standard assays.

(a) Allen–Doisy test[4a] with a slight modification.[4b] Cornification of the vaginal epithelial cells in ovariectomized rats or mice was the end point of the experiment. The results are expressed as the dose necessary to induce cornification in 50% of the animals (ED_{50}). The ED_{50} was calculated by using an average of 40 (20–100) animals per compound. Dose–response curves were used to determine the ED_{50} graphically.[5] There were at least four dose levels for the determination of the ED_{50} for each compound.

(b) Uterotrophic assay in immature intact mice.[6] This test was done at a minimum of five doses for each compound. Five to ten animals were used at each dose level. The results are expressed as the minimum effective dose

Table I. Physical and Biological Properties of 17α-Furylestradiol and Dihydroequilin Derivatives II



No.	R^1	R^2	Δ^7	Y	Mol formula[g]	$[\alpha]_D$[a]	Mp, °C	Solvents of crystn[b]	Yield, %	Activity po, Allen–Doisy: Rat ED_{50}, μg	Rat: Rel potency	Mouse ED_{50}, μg	Mouse: Rel potency	Uterotrophic mouse, μg po
1	CH_3	H	–	C≡CH		Mestranol				46	1	1.8	1	0.5
2	H	H	–	3-Furyl	$C_{22}H_{26}O_3$	+68.5[c]	185–190	M–E	72[d,e]	11	4.2			32
3	CH_3	H	–	3-Furyl	$C_{23}H_{28}O_3$	+24.0	161–162	E	67	10	4.6	2.7	0.66	50
4	CH_3	$COCH_3$	–	3-Furyl	$C_{25}H_{30}O_4$	+80.6	154–155	A–H	63	80	0.56	740	0.002	>512
5	$COCH_3$	H	–	3-Furyl	$C_{24}H_{28}O_4$	+46.1	132–134	E–H	62[e]	9.4	4.9			32
6	$COCH_3$	$COCH_3$	–	3-Furyl	$C_{26}H_{30}O_5$	+76.2	155–158	I	48	140	0.32			>512
7	c-C_5H_{10}	H	–	3-Furyl	$C_{27}H_{34}O_3$	+44.1	Amorphous		67[d]	25	1.8			3
8	c-C_5H_{10}	$COCH_3$	–	3-Furyl	$C_{29}H_{36}O_4$	+64.7	165–168	M	40	140	0.32			8
9	CH_3	H	–	3-Tetrahydrofuryl	$C_{23}H_{32}O_3$	+43.3	127–128	A–H	57	>1152	<0.04			64
10	CH_3	H	–	2-Furyl	$C_{23}H_{28}O_3$	+54.6	117–118	A–H	65	70	0.66			16
11	CH_3	H	+	3-Furyl	$C_{23}H_{26}O_3$	+152.0	124–126	E–H	43	2.8	16.4	2.5	0.7	256
12	CH_3	$COCH_3$	+	3-Furyl	$C_{25}H_{28}O_4$	+158.9	188–189	Mc–H	59	15	3	80	0.02	512
13	$COCH_3$	H	+	3-Furyl	$C_{24}H_{26}O_4$	+140.4	166–168	M	43[f]	2.4	19.2	5	0.35	32
14	$COCH_3$	$COCH_3$	+	3-Furyl	$C_{26}H_{28}O_5$	+184.2	199–200	Mc–M	44	12	3.83	90	0.02	>512
15	c-C_5H_{10}	H	+	3-Furyl	$C_{27}H_{32}O_3$	+134.2	Amorphous		59	5.4	8.5			4
16	c-C_5H_{10}	$COCH_3$	+	3-Furyl	$C_{29}H_{34}O_4$	+161.1	159–161	Mc–M	50	26	1.7			32
17	$COCH_3$	H	+	2-Furyl	$C_{24}H_{26}O_4$	+156.2	182–183	A–H	34[f]	30	1.5	5.6	0.32	32
18	Estriol									76	0.6	9.6	0.19	64

[a] $[\alpha]_D$ were determined in 1% $CHCl_3$ solutions at 24-25°. [b] Solvents of crystallization are A, Me_2CO; E, Et_2O; H, *n*-hexane; I, *i*-PrOH; M, MeOH; Mc, CH_2Cl_2. [c] $[\alpha]_D$ determined in MeOH. [d] 3-Furyllithium prepared from 3-bromofuran. [e] Overall yield calculated from estrone THP ether. [f] Overall yield calculated from equilin THP ether. [g] All the compounds were analyzed for C and H and the results were all within 0.4% of the calculated values.

at which a threefold increase in uterine weight over that of the controls was obtained.

2. Results. In the rat Allen-Doisy assay, the 17α-(3-furyl)-17-hydroxy derivatives were found to be 4-19 times as potent as mestranol (**1**), compounds **11**, **13**, and **15** in the dihydroequilin series being more active than the corresponding estradiol analogs **3**, **5**, and **7**. On the other hand, since mestranol is much more potent in mice than in rats in this assay, a few 3-furyl derivatives were also tested in mice. Compounds **3**, **11**, and **13** retained their high degree of activity, but they were all less active than the standard. Acetylation of the 17-alcohol or replacement of the 3-furyl by a 2-furyl group produced a sharp decrease in efficacy. Finally, hydrogenation of the 3-furyl to the 3-tetrahydrofuryl group (**9**) destroyed the activity.

In the mouse uterotrophic assay the furyl steroids proved to be very weak agents with shallow dose-response curves. For this reason their relative potency to mestranol could not be calculated since the standard gives a very steep dose-response curve.

In conclusion, the introduction of a 3-furyl group in the 17α position of estradiol and dihydroequilin appears to confer to the compounds a selectivity of action on the target organs. They are highly active on the vaginal epithelium in both rats and mice. However, similarly to estriol[7] (**18**), in the uterotrophic assay in mice they behave like "impeded estrogens"[8] giving shallow dose-response curves.

Experimental Section

The compounds had satisfactory analyses for C and H. In addition the nmr, ir, and uv spectra were in agreement with the proposed structures. The melting points are uncorrected.

Starting Materials (I). The appropriate starting materials I were obtained from estrone and equilin according to described procedures: the 3-cyclopentyl ethers by the method of Ercoli and Gardi[9] and the 3-THP ethers by the method of Cross.[10]

17α-(3-Furyl)-17-hydroxy Steroids. In most cases of 3-furyllithium was prepared *in situ* by reacting 3-iodofuran with *n*-BuLi according to the procedure of Gronowitz and Sörlin.[11] In turn 3-iodofuran was obtained from 2-furoic acid by the modified procedure of Gilman and Wright[12] described therein. Freshly prepared (in ether) or commercially available (22% in hexane) *n*-BuLi was used.

The general procedure for the preparation of 17α-(3-furyl)-17-hydroxy steroids may be illustrated as follows. A solution of 3-iodofuran (10 g), Et_2O (200 ml), and *n*-BuLi in Et_2O (1.67 *N*, 27 ml) was stirred for 30 min at −60°. A solution of estrone methyl ether (10 g) in toluene (40 ml) was added and the mixture stirred at room temperature for 16 hr. After the addition of Et_2O, the mixture was washed to neutrality (H_2O), dried ($MgSO_4$), and evaporated. The residue was boiled with Et_2O, affording pure **3** (8.3 g).

Since Gronowitz and Sörlin have shown that the 3-iodofuran contained up to 5% of 2-iodofuran, variable quantities of 17α-(2-furyl)-17-hydroxy isomers may be present in the products. In later work the presence of this isomer was avoided by replacing 3-iodofuran with 3-bromofuran.[13] This may be illustrated as follows. A solution of freshly distilled 3-bromofuran (5 ml), Et_2O (110 ml), and commercial *n*-BuLi in *n*-hexane (22%, 15 ml) was stirred at −60° for 60 min. A solution of estrone cyclopentyl ether (5 g) in toluene (90 ml) was added and the reaction allowed to proceed as above. Work-up gave an oily residue which was purified by chromatography on neutral Al_2O_3 (activity III). Elution with C_6H_6–hexane (1:1) afforded pure **7** as an amorphous solid (4.0 g).

17α-(2-Furyl)-17-hydroxy Steroids. 2-Furyllithium was prepared *in situ* according to the modified method of Ramanathan and Levine.[14] The following example will illustrate the method. A solution of freshly distilled furan (6 g), Et_2O (120 ml), and *n*-BuLi in Et_2O (2.35 *N*, 42.5 ml) was stirred at room temperature for 1 hr. A solution of estrone methyl ether (6 g) in toluene (240 ml) was added and the mixture was stirred overnight at room temperature. The reaction was worked up as above. The residue was chromatographed on basic Al_2O_3 (activity III; ratio 1:100). The fractions eluted with C_6H_6–hexane (1:1) and C_6H_6 were combined and crystallized from acetone–hexane affording pure **10** (4.88 g).

17α-(2- or 3-Furyl)-3,17-dihydroxy Steroids. The following example will illustrate the general procedure. A solution of 3-iodofuran (5 g), Et_2O (100 ml), and *n*-BuLi in Et_2O (1.37 *N*, 14.6 ml) was stirred for 30 min at −60°. A solution of equilin 3-THP ether (5 g) in toluene (200 ml) was added and the reaction was allowed to proceed at room temperature for 16 hr. The reaction product was isolated as above yielding crude 17α-(3-furyl)dihydroequilin 3-THP ether (6.15 g). A solution of the latter in MeOH (246 ml) was stirred for 1 hr with 0.1 *N* HCl (61.5 ml). H_2O was added and the precipitate filtered and washed. The solid was dissolved in EtOAc–MeOH, washed to neutrality ($NaHCO_3$–H_2O), dried ($MgSO_4$), and evaporated affording 17α-(3-furyl)dihydroequilin (4.9 g) of sufficient purity for further use (acetylation).

With the exception of 17α-(3-furyl)estradiol (**2**), the 17α-(furyl)-3,17-dihydroxy steroids were very difficult to purify; satisfactory analyses could not be obtained, the samples always retaining solvents of crystallization. Extensive heating resulted in decomposition.

3-Acetates of 17α-(2- or 3-Furyl)-3,17-dihydroxy Steroids. The general procedure may be illustrated as follows. A solution of 17α-(3-furyl)dihydroequilin obtained above (4.9 g), pyridine (49 ml), and Ac_2O (49 ml) was left overnight at room temperature. The mixture was poured on ice and extracted with Et_2O. The solution was washed to neutrality (aqueous H_2SO_4, aqueous $NaHCO_3$, H_2O), dried, and evaporated. Crystallization from MeOH afforded pure **13** (2.3 g).

3,17-Diacetates of 17α-(3-Furyl)-3,17-dihydroxy Steroids. The following example will illustrate the procedure. A solution of 17α-(3-furyl)dihydroequilin (5.1 g), pyridine (51 ml), and Ac_2O (51 ml) was heated on a steam bath for 24 hr. The reaction was worked up as above. The residue was chromatographed on neutral Al_2O_3 (activity III, ratio 1:50). The fractions eluted with C_6H_6–hexane (1:1) were combined and crystallized from CH_2Cl_2–MeOH to give pure **14** (2.8 g).

A similar procedure was used to obtain the 17-acetates **4**, **6**, **8**, **12**, and **16**. Attempts to acetylate 17α-(2-furyl)-17-hydroxy steroids by this method were unsuccessful; the only products isolated were the corresponding 16-dehydro derivatives.

3-Methoxy-17α-(3-tetrahydrofuryl)estra-1,3,5(10)-trien-17-ol (9). The hydrogenation of **3** (10 g) was carried out in EtOAc (200 ml) in the presence of preactivated 5% Pd/$CaCO_3$ (10 g) at room temperature and at normal pressure for 20 hr. The catalyst was filtered and the filtrate evaporated to dryness. The residue was chromatographed on neutral Al_2O_3 (activity III, ratio 1:30). Elution with C_6H_6–hexane and C_6H_6 and further purification by crystallization from Me_2CO–hexane afforded pure **9** (5.73 g).

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