N=CHN imidazole), 10.27 (br, 1, NH); UV λ_{max} (pH 1) 206 nm (ϵ 18800), 286 (13650), 315 sh (6210); UV λ_{max} (pH 7) 206 (20700), 270–271 (10980), 300 (8220); UV λ_{max} (pH 11) 205 (25000), 271–272 (10120), 300 sh (7900). Anal. ($C_{11}H_{14}N_4O_5$) C, H, N.

9-(α-D-Arabinofuranosyl)-3-deazaguanine (13): yield of the hydrochloride salt 91% and that of the free arabinoside 63%; isolated as colorless hemihydrate; mp 183–185 °C; NMR (Me_2SO-d_6) δ 3.55 (br, 2, 5′-CH_2), 4.03 (br, 2′-, 3′-, and 4′-CH), 4.32 (br, 1, 2′-CH), 4.89 (br, 1, OH), 5.49 (s, 1, –CH=CNH_2), 5.52 (due to overlap of the 1′-CH signal with olefinic proton and NH or one hydroxyl signal, the multiplicity and coupling constant could not be determined, 3 protons), 5.65 (br, 2, NH_2), 5.81 (br, 1, OH), 7.80 (s, 1, NCH=N imidazole); UV λ_{max} (pH 1) 207 nm (ϵ 19840), 286 (12380), 310 (6700); UV λ_{max} (pH 7) 205 (27200), 272 (11610), 300 (8640); UV λ_{max} (pH 11) 206 (25700), 273 (11400), 300 (8200). Anal. ($C_{11}H_{14}N_4O_5 \cdot 0.5H_2O$) C, H, N.

7-(β-D-Arabinofuranosyl)-3-deazaguanine (11). The recovery of the free nucleoside after passage through the DEAE-cellulose column was 62%. However, this material was contaminated with a blue fluorescent impurity. On further chromatography on a high performance silica column (Waters Associates, prep LC/500, using 2-propanol with 2% concentrated NH_4OH as eluent) pure material was obtained. Recrystallization from water gave a light-tan crystalline product: yield 17.4%; mp 178–180 °C; NMR (Me_2SO-d_6) δ 3.5–3.8 (m, 3, 5′-CH_2 and 4′-CH), 3.9–4.1 (m, 2, 2′- and 3′-CH), 5.04 (m, 1, OH), 5.24 (br, 2, NH_2), 5.41 and 5.47 (br, 2, 2 × OH), 5.50 (s, 1, –CH=CN), 6.66 (d, 1′-CH, $J_{1'-2'}$ = 4 Hz), 8.03 (s, 1, NCH=N imidazole), 10.46 (br, 1, NH); UV λ_{max} (pH 1) 207 nm (ϵ 20550), 278 (10920), 317 (5650); UV λ_{max} (pH 7) 216 (24200), 259–260 (5750), 318–319 (6900); UV λ_{max} (pH 11) 216–217 (24350), 259–260 (5620), 314–315 (5620). Anal. ($C_{11}H_{14}N_4O_5$) C, H, N.

7-(α-D-Arabinofuranosyl)-3-deazaguanine (15). In contrast to the preparations of compounds **9**, 11, and **13**, the N-7 substituted 3-deazaguanine arabinoside **15** presented difficulties. The reduction of its protected precursor **14** proceeded as expected to give the hydrochloride salt of **15** in 89% yield. On conversion to the free nucleoside by passage through DEAE-cellulose, the material (~66% yield) showed a contaminating blue fluorescent impurity (TLC). Several attempts on LC as in case of compound 11 failed to give analytically pure material. Anal. Calcd for $C_{11}H_{14}N_4O_5$: C, 46.81; H, 4.99; N, 19.85. Found: C, 46.79; H, 5.29; N, 17.96. Surprisingly, the NMR spectrum of this material showed acceptable agreement with the structure and did not reveal the presence of any impurity: NMR (Me_2SO-d_6) δ 3.55 (m, 2, 5′-CH_2), 3.93, 4.13, and 4.42 (3 multiplets, 1 each, 4′-, 3′-, and 2′-CH), 4.81 (br, 1, OH), 5.34 (br, 2, NH_2), 5.43 (m, 1, OH), 5.53 (s, 1, –CH=CN), 5.72 (d, 1, OH), 6.18 (d, 1, 1′-CH, $J_{1'-2'}$ = 4 Hz), 8.13 (s, 1, N=CHN imidazole); UV λ_{max} (pH 1) 207 nm (ϵ 19000), 276–277 (9850), 318 (5500); UV λ_{max} (pH 7) 217 (21800), 258 (5600), 317–318 (6700); UV λ_{max} (pH 11) 216–217 (22190), 258–259 (5280), 315–316 (6040). The ^{13}C NMR data for the four 3-deazaguanine arabinosides **9**, 11, **13**, and **15** can be found in Table IV.

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Synthesis and Antiestrogenic Activity of [3,4-Dihydro-2-(4-methoxyphenyl)-1-naphthalenyl][4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]methanone, Methanesulfonic Acid Salt

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Acylation of the sodio anion of β-tetralone with phenyl anisoate, followed by a Grignard reaction of the resultant **4** with 4-methoxyphenylmagnesium bromide, gave rise to two novel dihydronaphthalene isomers **5** and **6**. Regioselective demethylation of either **5** or **6** by NaSEt produced [3,4-dihydro-2-(4-methoxyphenyl)-1-naphthalenyl](4-hydroxyphenyl)methanone (**7**). Etherification of the phenolic group of **7** by *N*-(2-chloroethyl)pyrrolidine and subsequent methanesulfonate salt formation provided [3,4-dihydro-2-(4-methoxyphenyl)-1-naphthalenyl][4-[2-(1-pyrrolidinyl)ethoxy]phenyl]methanone, methane sulfonic acid salt (**3**). Potent antiestrogenic activity of **3** was demonstrated by both oral and subcutaneous administration to rats and mice. In vitro binding studies with rat uterine cytosol estrogen receptors indicate compound **3** has a very high binding affinity which exceeds that of estradiol.

Triarylethylene-derived compounds of general structures **1** and **2** and their ring-oxygenated counterparts have proven for many years an unusually rich source of antiestrogenic agents.[1] More recently, certain of these com-

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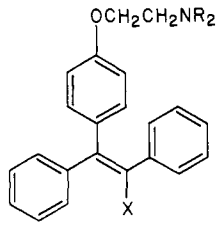
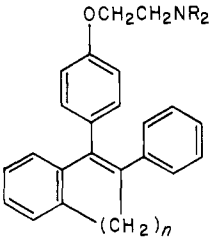


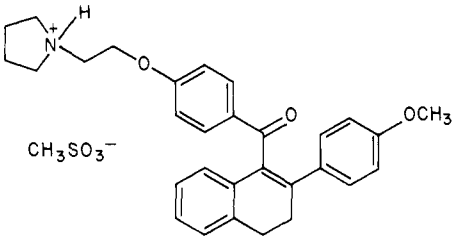
1, R = Me, Et, $-(CH_2)_4-$
X = Cl, NO_2, Et



2, R = Me, Et, $-(CH_2)_4-$
n = 1, 2

pounds have demonstrated clinical effects against human mammary cancer.[2] Other applications in areas such as stimulation of ovulation in nonovulatory females,[3] suppression of lactation,[4] and male infertility[5] have also been documented.

We were interested in the antiestrogenic potential of the related 1-acyl-2-aryl-3,4-dihydronaphthalene nucleus embodied in **3**. We now report the synthesis, as well as the potent in vitro estrogen receptor binding activity and in vivo antiestrogenic activity, of Lilly compound LY133314 (**3**).



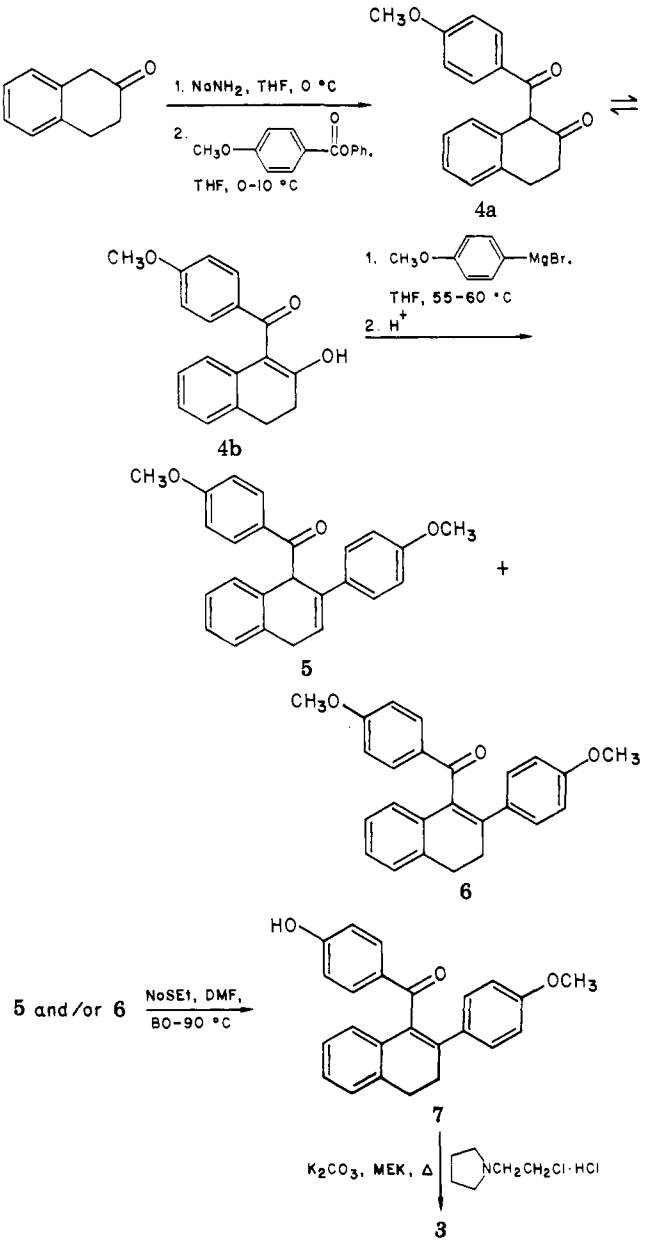
3

Chemistry. The synthetic route used to obtain **3** is delineated in Scheme I. Our approach involves the preparation of a suitable phenolic precursor **7**, followed by attachment of the pyrrolidinylethoxy moiety to provide **3**.

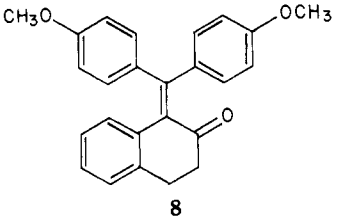
Acylation of the sodio anion of β-tetralone with phenyl anisoate gave a good yield of the acylated tetralone derivative **4**, which was found by NMR spectroscopy to reside virtually exclusively in the enol form **4b**, as evidenced by –O–H proton resonance at 16.33 ppm.

Despite the presence of an apparently acidic proton in **4b**, we found that 4-methoxyphenylmagnesium bromide added in moderate yield, thereby providing a mixture of products from which the two dihydronaphthalene isomers **5** and **6** could be isolated following dehydration. We have not determined whether the attack of the Grignard reagent proceeds via addition to the magnesium enolate anion of **4**, by normal 1,2 addition to the keto tautomer **4a**, or perhaps even by some other mechanism. Although the relative and total yields of **5** and **6** in this Grignard reaction were rather capricious, the isomers were separable by fractional crystallization and chromatography. The structures of **5** and **6** were assigned primarily on the basis of their NMR spectra. Taken at 360 MHz, the spectrum of **5** exhibited two benzylic protons at δ 3.64 and 3.90, a one proton vinyl signal at δ 6.41, and a signal for the benzylic proton α to C=O at δ 5.70, each resonance with appropriate coupling constants. The spectral pattern is consistent with those of representative 1,4-dihydronaphthalenes described in a recent review by Rabideau.[6] The 100-MHz spectrum of compound **6**, however, showed a much simpler pattern, the most salient feature being the signal for the $-CH_2CH_2-$ moiety which appeared at δ 2.5–3.3. Both **5** and **6** exhibited large peaks in their mass spectra attributable to the ion p-CH_3O-C_6H_4-$C{\equiv}O^+$ (m/e 135). These observations, taken with the conversion of

Scheme I



both **5** and **6** into a common product (**7**) which follows, indicate **5** and **6** to be simple double-bond positional isomers rather than one being the alternate structure **8**.



8

Either dihydronaphthalene isomer **5** or **6** or a mixture of the two compounds underwent regioselective demethylation with sodium thioethoxide in DMF to provide a good yield of the phenolic dihydronaphthalene **7**. The position of the double bond in **7** follows from the presence of a signal in the 60-MHz NMR spectrum for a $-CH_2CH_2-$ moiety closely analogous to that of compound **6**. Demethylation of the methoxy group para to C=O was apparent from the mass spectral fragmentation of **7** which showed a very large peak for the ion p-HO-C_6H_4-$C{\equiv}O^+$ (m/e 121) with only a small peak at m/e 135 which would

Table I. Influence of 3 on the Uterotropic Response of the Immature Cox Mouse

total dose[a] of 3, μg	route	estrone total dose (sc),[a,b] μg	mean diff from control group, mg[c]	mean diff from estrone treat. alone, mg[c]	SE	% inhibn
			(a) concomitant with estrone			
300	sc[b]	0.3		-22.0	2.6	44.1
100	sc	0.3		-26.7	1.6	53.5
30	sc	0.3		-12.9	3.4	25.9
10	sc	0.3		-11.4	2.4	22.8
3	sc	0.3		-5.1	3.5	12.7
1	sc	0.3		+2.6	3.3	0.0
300	or[d]	0.3		-21.7	1.4	52.3
100	or	0.3		-20.4	1.5	49.2
30	or	0.3		-12.9	2.7	31.1
			(b) compound 3 alone			
300	sc		+19.1		1.0	
100	sc		+24.2		2.2	
30	sc		+21.2		1.5	
10	sc		+34.0		3.0	
3	sc		+28.8		2.2	
1	sc		+8.6		1.6	

[a] Administered subcutaneously in 0.1 mL of corn oil vehicle (ten animals per group). [b] sc, subcutaneous. [c] Uterine wet weight. [d] or, oral.

Table II. Antiuterotropic Effects of 3 in Ovariectomized Rats

treatment[e]	no. of animals	av uterine wt[a] (±SE)
E2[b] alone	8	268.7 ± 10.3
E2 + 3[c] (3 μg)	7	231.7 ± 15.5[d]
E2 + 3 (5 μg)	7	222.3 ± 14.4[d]
E2 + 3 (10 μg)	7	200.9 ± 17.2[d]

[a] Milligrams per rat. [b] E2 refers to 0.3 μg of 17β-estradiol per day subcutaneously administered in corn oil containing 5% beeswax. [c] Compound 3 was administered orally in 0.1 mL of corn oil. [d] Groups significantly below control group (95% confidence level by Dunnett's procedure). [e] Daily for 7 days.

Table III. Uterotropic Effect of 3 in Rats

3 treatment (mg per animal per day) × 7	route[a]	uterine wt increase[b]
1.0	sc	66.8
0.1	or	35.0
0.5	or	54.9
1.0	or	58.7

[a] Compound 3 was prepared for administration in 0.1 mL of corn oil; or = oral, sc = subcutaneous. [b] The value given is the average uterine weight in milligrams of the treated group (five animals per group) minus the average weight of the control group (eight animals).

be dominant if a CH_3O-C_6H_4-C=O moiety were present in **7**.

The synthesis was completed by attachment of the pyrrolidinylethoxy moiety to **7** and subsequent formation of the methanesulfonic acid salt to provide **3** as a stable, crystalline material.

Determination and Discussion of Biological Activity. In Vivo Studies. The influence of **3** on the uterotropic responses of the immature (11–13 g) Cox standard mouse was examined. Mice in groups of ten were treated daily for 3 days with compound **3** alone or concomitantly with 0.1 μg of estrone and sacrificed on the fourth day when uterine wet weights were determined. Table I shows the results of these studies. Compound **3** administered subcutaneously inhibited the uterotropic response to estrone in a dose-related fashion over a broad range of doses. Significant inhibition was observed with as little as 1 μg of **3** per animal per day. Compound **3** was also highly antiuterotropic when administered orally. Nevertheless, compound **3** appears limited in its intrinsic ability to produce uterotropic effects in the immature mouse. The moderate uterotropic response to subcutaneously administered **3** observed at the 1 μg per animal per day dose did not increase significantly as the dose was increased.

Antiuterotropic activity in ovariectomized adult rats was tested by administering compound **3** orally together with 0.3 μg of estradiol given subcutaneously for 7 days. Table II shows that as little as 3 μg per animal per day produced a significant reduction in uterine weight.

The ability of compound **3** to increase uterine weight was also tested in ovariectomized adult rats. Table III shows the small but statistically significant ($p < 0.05$ by student's t test) increases in uterine weight produced by doses many times greater than those used to demonstrate antiuterotropic activity.

Postcoital antifertility potency in female rats was determined by 11 daily treatments of **3** beginning with the first evidence of breeding. The animals were killed and examined for the presence of viable or resorbing fetuses on day 12. When given orally or subcutaneously, 5 μg per animal per day of **3** was totally effective (0/4 and 0/5 animals pregnant, respectively). Reduction of daily dose administration to 1.0 μg per animal by either route reduced the fertility rate to 3/5, while 0.5 μg per animal had no effect. The animals treated with **3** that were pregnant at sacrifice showed normal implantation and no fetal resorption. In similar assays, the intermediates **5** and **6** were devoid of postcoital antifertility activity at a dose of 1 mg per animal per day.

In Vitro Binding Studies. The in vitro competition for estrogen binding sites by **3** was determined in immature rat uterine cytosol using the dextran-coated charcoal-adsorption technique.[7] Log concentrations of **3** from 1 to 1000 nM were incubated at 4 °C with 10 nM [2,4,6,7-^{3}H]estradiol in aliquots of uterine cytosol drawn from a pool. Additional samples contained 1 to 1000 nM unlabeled estradiol. The difference between total binding of [^{3}H]estradiol alone and that in the presence of 1000 nM unlabeled estradiol was used to determine specific binding. The IC_{50} concentration was used for the calculation of relative binding affinity. At 4 °C, where binding is presumed to be irreversible, **3** competed effectively for estrogen binding sites. In seven separate assays, a mean relative binding affinity of 1.7 ± 0.3 for compound **3** relative to estradiol was obtained under these conditions.

Summary. The evidence presented describes a structurally novel highly potent antiestrogen which is

equally potent by an oral or subcutaneous route. Antiestrogenic activity was demonstrated in rats and in mice. Antifertility activity was demonstrated in rats with as little as 1 μg per animal per day. In vitro binding studies with rat uterine cytosol estrogen receptors indicate a very high binding affinity (averaging 1.7 × estradiol). These data indicate that **3** is an excellent candidate for the treatment of estrogen-dependent mammary tumors and in other applications where antagonism of estrogen action would be desirable.

Experimental Section

General. Melting points were recorded on a Thomas-Hoover capillary melting point apparatus and were uncorrected. NMR spectra were obtained in $CDCl_3$ with Me_4Si as internal standard (except as otherwise noted) on a Varian A-60A, a Varian HA-100, or a Bruker WH360 spectrometer. IR spectra were recorded on a Beckman IR4250 or a Perkin-Elmer 457A spectrometer. UV spectra were run in EtOH on a Cary 15 spectrometer. Mass spectra were obtained with a Varian MAT 731 spectrometer. Although only selective spectral data are presented herein, all new compounds exhibited IR, UV, and NMR spectra consistent with the structures given. Unless otherwise indicated, all new compounds were subjected to elemental analysis, and analytical results were within ±0.4% of the theoretical values for those elements shown.

3,4-Dihydro-1-(4-methoxybenzoyl)-2(1*H*)-naphthalenone (4). Fifty grams (0.342 mol) of β-tetralone (Aldrich) was added dropwise to a suspension of 15.2 g (0.38 mol) of $NaNH_2$ in 250 mL of THF at 0 °C. After stirring the mixture for 20 min, 78.0 g (0.342 mol) of phenyl anisoate,[8] dissolved in a minimum amount of THF, was added while maintaining the temperature below 10 °C. The reaction was kept at room temperature overnight, and then most of the THF was evaporated, water was added, and the product was extracted with EtOAc after adjusting to pH 8.0. The organic layer was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated to a dark oil. The oil was purified on a 50 × 150 mm SiO_2 column using toluene for elution. The fractions containing the desired product appeared at TLC R_f 0.6 (SiO_2; toluene–EtOAc, 9:1). They were combined and concentrated, and the residue was crystallized from MeOH. The crude (mp 88–91 °C) product was recrystallized from hexane to give **4**: mp 91–92 °C; IR ($CHCl_3$) 1600 cm^{-1} (enolized β-dicarbonyl); UV λ_{max} (ε) 210 nm (sh) (ε 26 000), 263 (14 500), 365 (9000); NMR (60 MHz) δ 2.3–3.2 (4, m, $-CH_2CH_2-$), 3.78 (3, s, OCH_3), 6.6–7.3 (4, m, aromatic), 6.76 (2, d, J = 9.0 Hz, aromatic ortho to OCH_3), 7.50 (2, d, J = 9.0 Hz, aromatic ortho to C=O), 16.33 (1, s, enolic –OH). Anal. ($C_{18}H_{16}O_3$) C, H, O.

[1,4-Dihydro-2-(4-methoxyphenyl)-1-naphthalenyl](4-methoxyphenyl)methanone (5) and [3,4-Dihydro-2-(4-methoxyphenyl)-1-naphthalenyl](4-methoxyphenyl)-methanone (6). To a suspension of 28.8 g (1.2 mol) of Mg in 50 mL of dry THF under N_2 was added 0.6 mL of 1,2-dibromomethane. As soon as the Grignard reaction began, as indicated by evolution of ethylene, 162 g (0.9 mol) of 4-bromoanisole in 100 mL of dry THF was added at a rate that kept the reaction temperature between 55 and 60 °C and with ice-bath cooling. After the addition, stirring was continued at room temperature for 1 h. Then, 84.0 g (0.3 mol) of **4** in 200 mL of dry THF was added rapidly with ice-bath cooling so as to keep the reaction mixture at below 60 °C. After stirring the mixture overnight, the supernatant was decanted into ice–water, with excess Mg left behind. While cooling (ice bath), the mixture was adjusted to pH 1–2 with 5 N HCl and extracted with EtOAc. The EtOAc layer was washed with water and saturated aqueous NaCl. After drying (anhydrous Na_2SO_4) and evaporating the solvents, a brownish oil was obtained, which was dissolved in 100 mL of benzene containing 0.7 g of *p*-toluenesulfonic acid and stirred overnight at room temperature. In most instances, a precipitate of crude **5** was obtained. The precipitate was washed with cold MeOH and recrystallized from EtOAc to provide 18.4 g of **5** (16%): mp 170–172 °C; IR ($CHCl_3$) 1670 cm^{-1} (C=O); UV λ_{max} 268 nm (ε 22 009); NMR (360 MHz) δ 3.64 (1, m, H_4, $J_{4,4}$ = 22, $J_{3,4}$ = 4.9, and $J_{1,4}$ = 3.5 Hz), 3.78 (3, s, OCH_3), 3.84 (3, s, OCH_3), 3.90 (1, m, H_4, $J_{3,4}$ = 2.5 and $J_{1,4}$ = 3.4 Hz), 5.70 (1, dd, H_1, $J_{1,3}$ = 0 Hz), 6.41 (1, dd, H_3), 6.75–7.29 (10, m, aromatic), 7.95 (2, d, aromatic ortho to C=O, J = 9 Hz). Anal. ($C_{25}H_{22}O_3$) C, H, O.

The benzene filtrate from the tosic acid treatment was washed with water, dried (Na_2SO_4), and concentrated to a dark oily residue. The oil was dissolved in toluene and passed through a column (65-mm diameter) of 100 g of neutral Woelm Al_2O_3, which served to remove the starting material **4** and other polar impurities.

The toluene eluents were concentrated and the resulting oil was chromatographed through a 40-mm diameter column of 200 g of silica gel, using 5% EtOAc in toluene as eluent. The elution was stopped as soon as TLC (SiO_2; toluene–EtOAc, 9:1) indicated that all of the desired product (**6**, R_f 0.6) was out of the column. The appropriate fractions were concentrated, and the resulting oil was crystallized by suspensing it in 150 mL of MeOH and stirring vigorously at room temperature. A light yellow solid gradually crystallized, which was usually crude compound **6**, although in several instances a mixture of **5** and **6** precipitated. Recrystallization from MeOH provided 27.6 g (25%) of pure **6**: mp 102.5–103.5 °C; IR ($CHCl_3$) 1643 cm^{-1} (C=C); UV λ_{max} 222 nm (ε 23 000), 290 (28 000); NMR (60 MHz) δ 2.5–3.3 (4, m, $-CH_2CH_2-$), 3.67 (3, s, OCH_3), 3.73 (3, s, OCH_3), 6.50–7.30 (10, m, aromatic), 7.83 (2, d, J = 9.0 Hz, aromatic ortho to C=O). Anal. ($C_{25}H_{22}O_3$) C, H, O.

[3,4-Dihydro-2-(4-methoxyphenyl)-1-naphthalenyl](4-hydroxyphenyl)methanone (7). A solution of NaSEt in DMF was prepared as follows: 135 g of 57% NaH/mineral oil suspension was washed three times with hexane prior to using. The washed hydride was slurried with 2.5 L of *dry* DMF in a 5-L three-neck flask equipped with mechanical stirrer, addition funnel with N_2 inlet, and $CaCl_2$ drying tube. The flask and contents were cooled to 0 °C. Two-hundred grams of HSEt was added at such a rate as to keep the temperature between 10 and 20 °C and the foaming minimal. The reaction was allowed to stir at room temperature overnight. The reaction mixture was then poured into a calibrated flask and diluted with *dry* DMF to yield a 0.5 M solution. To 200 mL (0.10 mol) of the above NaSEt solution was added 21.0 g (0.0567 mol) of **5**. (Compound **6** or a mixture of **5** + **6** can also be used.) The mixture was heated in a 80–90 °C oil bath, and the course of the reaction was followed by TLC (SiO_2; 10% EtOAc in toluene). After 2.5 h, the desired product spot at R_f 0.3 was predominant. The DMF was removed in vacuo, and the residual oil was acidified by shaking with 1 N HCl and EtOAc. The EtOAc layer was separated, washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated to yield a syrupy oil. Addition of hexane, followed by vigorous mechanical stirring, produced 13.6 g (67%) of crystalline **7**, mp 153–155 °C. Final purification was accomplished by column chromatography over SiO_2 (Woelm activity I; elution with 5% EtOAc in toluene), followed by recrystallization of the product from EtOAc–isooctane: mp 167.5–168.0 °C; IR ($CHCl_3$) 3575 (–OH), 1650 cm^{-1} (C=O); UV λ_{max} 221 nm (ε 24 250), 293 (33 000); NMR (60 MHz) δ 2.5–3.3 (4, m, $-CH_2CH_2-$), 3.67 (3, s, $-OCH_3$), 6.55–7.35 (10, m, aromatic), 7.75 (2, d, J = 8.5 Hz, aromatic ortho to C=O), 9.50 (1, s, –OH). Anal. ($C_{24}H_{20}O_3$) C, H, O.

[3,4-Dihydro-2-(4-methoxyphenyl)-1-naphthalenyl][4-[2-(1-pyrrolidinyl)ethoxy]phenyl]methanone, Methanesulfonic Acid Salt (3). To a solution of 20.0 g (0.056 mol) of **7** and 8.25 g (0.062 mol) of *N*-2-(chloroethyl)pyrrolidine in 200 mL of methyl ethyl ketone was added 14.8 g (0.112 mol) of finely powdered anhydrous K_2CO_3, and the resulting mixture was refluxed for 16 h. The reaction mixture was cooled and poured over iced aqueous NaCl. The organic phase was separated and the aqueous phase was washed with EtOAc. The combined organic layers were washed with 100 mL of saturated aqueous NaCl, dried (anhydrous K_2CO_3), and evaporated to give a brown oil. This was purified by chromatography on an 80 × 270 mm column of 550 g of SiO_2 (Woelm activity I) made up in EtOAc–CH_3CN–Et_3N (50:30:5, v/v). Elution with the same solvent mixture provided the free base of **2** as a yellow oil: yield 20.0 g; TLC (SiO_2; EtOAc–CH_3CN–Et_3N, 50:30:5) R_f 0.6 as a single spot material.

The above free base (19.8 g, 0.0437 mol) was dissolved in 50 mL of acetone, cooled to 10 °C, and CH_3SO_3H (4.20 g, 0.0437 mol) in 10 mL of acetone was added rapidly. The solution was diluted to a total volume of 225 mL and the flask cooled slowly to 0 °C. White crystals were collected and washed with portions of cold

(−40 °C) acetone (3 × 25 mL). After drying in vacuo at 140 °C, the product (3) weighed 19.7 g (64% based on 6): mp 171.5–172.5 °C; IR ($CHCl_3$) 2400–2600 (NH^+), 1650 cm^{-1} (C=O); UV λ_{max} 220 nm (ε 24 500), 285 (31 750); NMR (100 MHz) δ 2.08 [4, m, N-(CH_2CH_2)$_2$], 2.72 (3, s, CH_3SO_3), 2.92 (6, m, $ArCH_2CH_2$ + N-CH_2CH_2O–), 3.67 [4, m, N-(CH_2CH_2)$_2$], 3.69 (3, s, OCH_3), 4.40 (2, t, J = 4.5 Hz, OCH_2-C), 6.68 (2, d, J = 9 Hz, aromatic ortho to –OCH_3), 6.83 (2, d, J = 9 Hz, aromatic ortho to –OCH_2), 6.9–7.3 (4, m, aromatic), 7.20 (s, d, J = 9 Hz, aromatic meta to –OCH_3), 7.83 (2, d, J = 9 Hz, aromatic ortho to C=O), 11.23 (1, br s, NH). Anal. ($C_{31}H_{35}NO_6S$) C, H, N, O, S.

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Synthesis of 11β,13β- and 13β,16β-Propano Steroids: Probes of Hormonal Activity

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Syntheses of 11β,13β- and 13β,16β-propano derivatives of 17α-ethynyl-17β-hydroxygon-4-en-3-one are described. The 13β,16β bridge was constructed by intramolecular alkylation of the C-16 enolate anion from 3-methoxy-13β-[3′-(tosyloxy)propyl]gona-3,5-dien-17-one, the latter being obtained via Birch reduction of both aryl groups of 17β-hydroxy-3-methoxy-13β-(3′-phenoxypropyl)gona-1,3,5(10),8-tetraene (1). The 11β,13β bridge was constructed by Prins cyclization of 17β-acetoxy-3-methoxy-13β-(3′-oxopropyl)gona-1,3,5(10),9(11)-tetraene, itself obtained via Birch reduction of only the side-chain aryl group of 1. Binding affinities of certain of these compounds and substituted 13β-propyl derivatives of 17α-ethynyl-17β-hydroxygon-4-en-3-one for the uterine cytosol receptor of progesterone are reported, and the origin of the high progestational activity of norgestrel and 11β-substituted progestins is discussed.

Introduction of alkyl substituents above the β face of rings C and D of the steroid skeleton can lead to significant enhancement of hormonal activity.[1-3] For example, methylation of C-11β[1] or C-18[2] of 17α-ethynyl-17β-hydroxyestr-4-en-3-one (norethindrone) produces a marked increase in progestational activity, while 11β-methylestradiol is a more potent estrogen than the natural hormone.[2] A priori, these observations might be attributed to enhanced metabolic stability or to an enhanced affinity for the receptor protein. The latter could arise directly from favorable hydrophobic interaction of the alkyl substituent and a cavity in the receptor or indirectly from ring-conformation changes induced by buttressing effects. A recent structure–activity study[3] of a variety of 11β-substituted derivatives of 17α-ethynylestr-4-en-17β-ol (lynestrol) suggested that buttressing effects are dominant. We have sought to identify the origin of the increased potency by synthesis of 11β,13β- and 13β,16β-propano bridged steroids. The conformation of the C-13 substituent in these steroids is rigidly defined and skeletal distortions due to nonbonded interactions of the C-13β substituent with the C-11β and C-16β substituents are eliminated. The starting point for both of these bridge systems was 17β-hydroxy-3-methoxy-13β-(3′-phenoxypropyl)gona-1,3,5(10),8-tetraene (1), obtained by our recently reported procedure.[4]

Chemistry. The synthesis of the 13β,16β-propano bridge system is shown in Scheme I. Birch reduction of 1 with lithium in ammonia and *tert*-butyl alcohol followed by Oppenauer oxidation gave the bisenol ether 2. Acid hydrolysis provided the 3,17-dione 3 (64%), which was converted to the tosylate 4 along with a minor amount of chloride 5 by treatment with tosyl chloride and pyridine.

Attempts to convert 4 to the 13β,16β-propano bridged compound by intramolecular C alkylation, using potassium *tert*-butoxide (1–2 mol-equiv) in either benzene or benzene/*tert*-butyl alcohol or sodium hydride/Me_2SO to generate the C-17 enolate anion, were totally unsuccessful. It was felt that the presence of the more acidic Δ^4-3-one functionality of 4 might be interfering with the formation of the enolate anion of the C-17 ketone. The tosylate 4 was therefore converted to the enol ether 6 by treatment with trimethyl orthoformate and *p*-toluenesulfonic acid in dioxane. Initial attempts to cyclize 6 by intramolecular C alkylation using potassium *tert*-butoxide in benzene or benzene/*tert*-butyl alcohol were no more successful than with 4. However, it was then determined that treatment of 6 with potassium *tert*-butoxide in refluxing *tert*-butyl alcohol for 18 h gave the desired pentacyclic gonane 7 in 80% yield. The IR and ^1H NMR spectra of 7 were in complete agreement with the assigned structure. Since the stereochemistry of the C-13 substitutent in 1 has been rigorously established[4] as β, the configuration of the propano bridge at C-16 must also be β in 7. Inspection of Dreiding models indicates that it is impossible to construct a 13β,16α-propano bridged system.

Ethynylation of 7 with freshly prepared lithium acetylide[5] afforded 8 which, upon hydrolysis, gave the desired propanogonane 9 in 21% overall yield from 2.

The 11β,13β-Propano Bridge. The synthesis of this bridge system is shown in Scheme II. It was previously determined that the first step, treatment of 1 with Li/NH_3/THF, effected reduction of the 8,9 double bond and the side-chain phenoxy group without reduction of the A ring. However, the yield of the product 10 was only 12%. Selective reduction of the side-chain aryloxy group is probably promoted by intramolecular protonation of the intermediate radical anion by the 17-hydroxy group. Windholz et al.[6] have reported a similar selectivity for the Birch reduction of 3-methoxy-13β-phenylgona-1,3,5(10)-trien-17β-ol.

In an effort to improve the yield of 10, this reduction was examined using different conditions. Treatment of

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