tamoxifen, 10540-29-1; 2-(3-methoxyphenoxy)benzoic acid, 21905-75-9; 2-(3-methoxyphenoxy)benzyl chloride, 85850-99-3; 2-[(3-methoxyphenyl)thio]benzoic acid, 50900-49-7; 2-[2-(3-methoxyphenyl)ethyl]benzoic acid, 17910-71-3; 2-[[(3-methoxyphenyl)thio]methyl]benzoic acid, 49619-05-8; 2-(dimethylamino)ethyl chloride hydrochloride, 4584-46-7; allyl bromide, 106-95-6; bromobenzene, 108-86-1; 4-bromophenol tetrahydropyranyl ether, 36603-49-3; phenyllithium, 591-51-5.

Ring-Substituted 1,2-Dialkylated 1,2-Bis(hydroxyphenyl)ethanes. 1. Synthesis and Estrogen Receptor Binding Affinity of 2,2′- and 3,3′-Disubstituted Hexestrols

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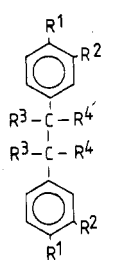
The syntheses of symmetrically 3,3′- and 2,2′-disubstituted meso hexestrol derivatives are described [3,3′-substituents: OH (1), F (2), Cl (3), Br (4), I (5), $CH_2N(CH_3)_2$ (6), CH_3 (7), CH_2OCH_3 (8), $CH_2OC_2H_5$ (9), CH_2OH (10), NO_2 (11), NH_2 (12), $N(CH_3)_2$ (13), $COCH_3$ (14), and C_2H_5 (15); 2,2′-substituents: OH (16), F (17), Cl (18), Br (19), CH_3 (20), and C_2H_5 (21)]. The synthesis of 1–3 was accomplished by reductive coupling of the propiophenones with $TiCl_4/Zn$ and subsequent hydrogenation of the *cis*-3,4-diphenylhex-3-enes. Compounds 4–15 were obtained by substitution of hexestrol, while compounds 16–21 were synthesized by coupling the 1-phenyl-1-propanols with $TiCl_3/LiAlH_4$ and separation of the meso diastereomers. The binding affinity of these compounds to the calf uterine estrogen receptor was measured relative to that of [^{3}H]estradiol by a competitive binding assay. All test compounds showed relative binding affinity (RBA) values between 32 and <0.01% that of estradiol. Only *meso*-3,4-bis(2,4-dihydroxyphenyl)hexane (16) showed an estrogen receptor binding affinity comparable to that of hexestrol (32 and 27%, respectively). Compounds exhibiting RBA values of >5% were evaluated in the mouse uterine weight test. All of them showed uterotrophic activity. Compounds 2, 7, 16, 17, and 20 were strongly active in very small doses (1 μg per animal per day), while 1 and 12 produced full uterotrophic effects only in high doses and inhibited the estrone-stimulated uterine growth strongly in small doses (59 and 78% inhibition, respectively).

In a previous paper we have shown that by displacement of the phenolic hydroxy groups of the synthetic estrogen hexestrol (hex) into the 3,3′-positions, the partial anti-



hex, $R^1 = OH$; $R^2, R^3 = H$; $R^4 = C_2H_5$

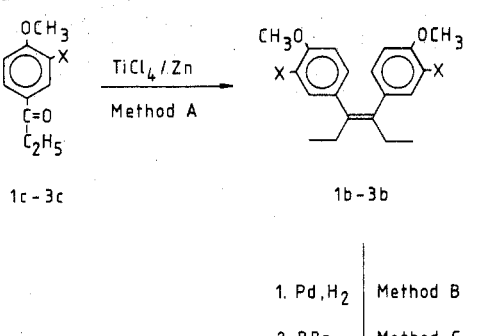
A1, $R^1, R^3 = H$; $R^2 = OH$; $R^4 = C_2H_5$

A2, $R^1 = OH$; $R^2 = H$; $R^3, R^4 = CH_3$

A3, $R^1 = H$; $R^2 = OH$; $R^3, R^4 = CH_3$

estrogen *meso*-3,4-bis(3-hydroxyphenyl)hexane (**A1**) was obtained.[1] Tetramethylation in the 1,2-positions of the diphenylethane skeleton of hexestrol and **A1** led to the corresponding hydroxylated 1,1,2,2-tetramethyl-1,2-diphenylethanes (**A2** and **A3**).[2] Compared to **A1**, the latter compounds showed an increase of antiestrogenic activity[2,3] and, depending on the test system, a further decrease[2] or even a loss[3] of estrogenic activity. Compounds **A1–3** are

Scheme I



of great interest in the treatment of the hormone-dependent human breast cancer, for they show a marked inhibitory activity on the established DMBA-induced mammary carcinoma of the SD rat,[1,2] which is believed to have many similarities with the human breast cancer.[4]

A further increase of the antitumor activity of **A1–3** (i.e., the same antitumor effect obtained by smaller doses) could be realized by synthesizing derivatives with a higher affinity for the estradiol receptor, for antitumor activity of antiestrogens appears to be correlated with their estra-

(1) Hartmann, R. W.; Buchborn, H.; Kranzfelder, G.; Schönenberger, H.; Bogden, A. E. *J. Med. Chem.* **1981**, *24*, 1192.
(2) Hartmann, R. W.; Kranzfelder, G.; von Angerer, E.; Schönenberger, H. *J. Med. Chem.* **1980**, *23*, 841.
(3) Gschwendt, M.; Rincke, G.; Schuster, T. *Mol. Cell. Endocrinol.* **1982**, *26*, 231.
(4) Fiebig, H. H.; Schmähl, D. *Recent Res. Cancer Res.* **1980**, *71*, 80.

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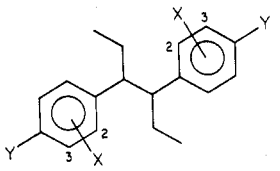
Table I. Substituted *meso*-3,4-Diphenylhexanes



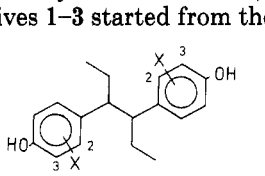
compd	X	Y	synth method[a]	yield,[b] %	mp, °C	recrystn solvent[c]	formula[d]
1a[e]	3-OCH_3	OCH_3	B	94	133	R	$C_{22}H_{30}O_4$
1[e]	3-OH	OH	C[o]	85	237-239	R	$C_{18}H_{22}O_4$
2a[f]	3-F	OCH_3	B	93	165-166	R	$C_{20}H_{24}F_2O_2$
2[f]	3-F	OH	C	85	203-204	R	$C_{18}H_{20}F_2O_2$
3a[f,g]	3-Cl	OCH_3	B[p]	61	158	R	$C_{20}H_{24}Cl_2O_2$
3[f,g]	3-Cl	OH	C	85	147-148	R	$C_{18}H_{20}Cl_2O_2$
4[g,h]	3-Br	OH	D	27	144-145	S	$C_{18}H_{20}Br_2O_2$
5[i]	3-I	OH	E	19	150	S	$C_{18}H_{20}J_2O_2$
6	3-$CH_2N(CH_3)_2$	OH	F	48	156-157	R	$C_{24}H_{36}N_2O_2$
7[k]	3-CH_3	OH	G	73	164	R	$C_{20}H_{26}O_2$
8a	3-CH_2OAc	OAc	H	83	118-119	T	$C_{28}H_{34}O_8$
8	3-CH_2OCH_3	OH	J	79	151-152	R	$C_{22}H_{30}O_4$
9	3-$CH_2OC_2H_5$	OH	J	80	147-148	R	$C_{24}H_{34}O_4$
10	3-CH_2OH	OH	C[q]	99	>240 dec		$C_{20}H_{26}O_4$
11[k-m]	3-NO_2	OH	K	80	239	U	$C_{18}H_{20}N_2O_6$
12[l,m]	3-NH_2	OH	B	98	274-276	U	$C_{18}H_{24}N_2O_2$
13	3-$N(CH_3)_2$	OH	L	77	187-188	T	$C_{22}H_{32}N_2O_2$
14a[f]	3-$COCH_3$	OCH_3	M	78	171-172	U	$C_{24}H_{30}O_4$
14	3-$COCH_3$	OH	C	91	140-141	V	$C_{22}H_{26}O_4$
15a[f]	3-C_2H_5	OCH_3	N	91	109-110	W	$C_{24}H_{34}O_2$
15[f]	3-C_2H_5	OH	C	90	127-128	X	$C_{22}H_{30}O_2$
16a	2-OCH_3	OCH_3	P	36	152-153	S	$C_{22}H_{30}O_4$
16	2-OH	OH	C[o]	68	202.5-203	Y	$C_{18}H_{22}O_4$
17a	2-F	OCH_3	P	21	123	S	$C_{20}H_{24}F_2O_2$
17	2-F	OH	C	87	181-182	Y	$C_{18}H_{20}F_2O_2$
18a	2-Cl	OCH_3	P	18	91.5-92.5	T	$C_{20}H_{24}Cl_2O_2$
18	2-Cl	OH	C	83	190.5-191.5	Y	$C_{18}H_{20}Cl_2O_2$
19a	2-Br	OCH_3	P	12	114-115	T	$C_{20}H_{24}Br_2O_2$
19	2-Br	OH	C	85	201-202	Y	$C_{18}H_{20}Br_2O_2$
20a[n]	2-CH_3	OCH_3	P	39	128-129	S	$C_{22}H_{30}O_2$
20[n]	2-CH_3	OH	C	81	219-220	Y	$C_{20}H_{26}O_2$
21a	2-C_2H_5	OCH_3	P	28	105-106	S	$C_{24}H_{34}O_2$
21	2-C_2H_5	OH	C	79	196-197	Y	$C_{22}H_{30}O_2$

[a] Capital letters refer to synthetic methods B–N and P under Experimental Section. [b] Yield of analytically pure product; no effort was made to optimize yields. [c] R = EtOH/H_2O; S = MeOH; T = EtOH; U = acetone; V = CH_2Cl_2–ligroin; W = MeOH–benzene; X = ligroin; Y = benzene. [d] All compounds were analyzed for C, H, N, Br, and Cl within ±0.4% of the calculated values. [e] See ref 12. [f] See ref 13. [g] See ref 14. [h] See ref 15. [i] See ref 16. [k] See ref 17. [l] See ref 18. [m] See ref 19. [n] See ref 20. [o] Product was not extracted with NaOH solution. [p] See ref 10. [q] After addition of MeOH, the solvent was evaporated. The resulting, pure (TLC, ^1H NMR) solid was not further recrystallized.

diol–receptor association constants.[1]

The paper presented here is the first part of an extensive structure–activity study dealing with the influence of a symmetrical substitution of the two aromatic rings of 1,2-dialkylated 1,2-bis(hydroxyphenyl)ethanes (hex and **A1–3**) on the estradiol receptor binding affinity. While subsequent publications will deal with the effect of ring substituents on compounds **A1**[5] and **A2–3**,[6] respectively, this paper describes the syntheses and the testing for the estradiol receptor affinity of the 3,3′- and 2,2′-disubstituted hexestrol derivatives.[7] The mouse uterine weight test is used to determine and investigate the estrogenicity and antiestrogenicity of these compounds.

Chemistry. The synthesis of the 3,3′-disubstituted hexestrol derivatives **1–3** started from the corresponding



	X		X		X
1	3-OH	8	3-CH_2OCH_3	15	3-C_2H_5
2	3-F	9	3-$CH_2OC_2H_5$	16	2-OH
3	3-Cl	10	3-CH_2OH	17	2-F
4	3-Br	11	3-NO_2	18	2-Cl
5	3-I	12	3-NH_2	19	2-Br
6	3-$CH_2N(CH_3)_2$	13	3-$N(CH_3)_2$	20	2-CH_3
7	3-CH_3	14	3-$COCH_3$	21	2-C_2H_5

4-methoxypropiophenones **1c–3c** (Scheme I). The latter compounds were obtained by Friedel–Crafts acylation of the corresponding 2-substituted anisoles with propionyl chloride and $AlCl_3$. The *cis*-stilbenes **1b–3b** were obtained in good yields by reductive coupling of **1c–3c** with the $TiCl_4$/Zn reaction introduced by Mukaiyama et al.[8] and

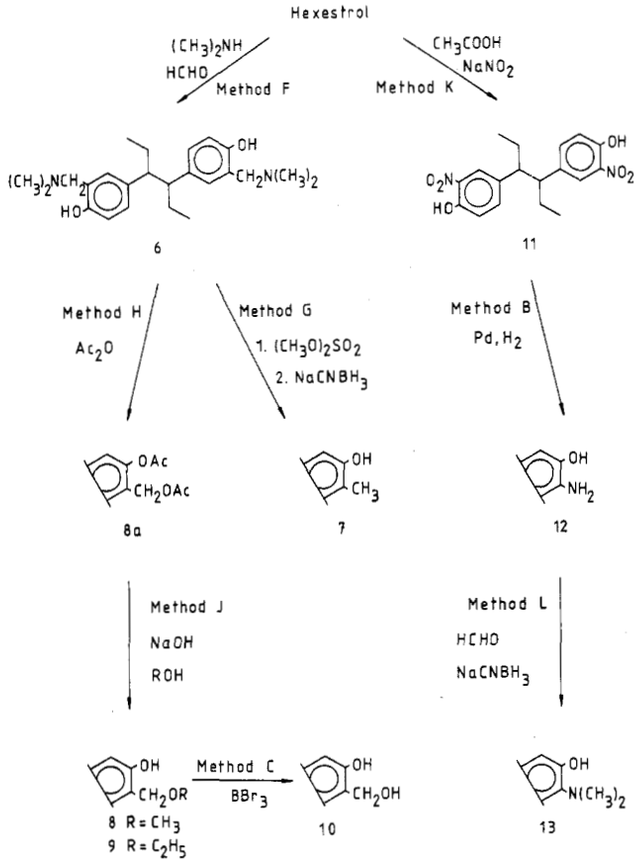
(5) Hartmann, R. W.; Heindl, A.; Schönenberger, H., in preparation.

(6) Hartmann, R. W.; Heindl, A.; Schwarz, W.; Schönenberger, H., in preparation.

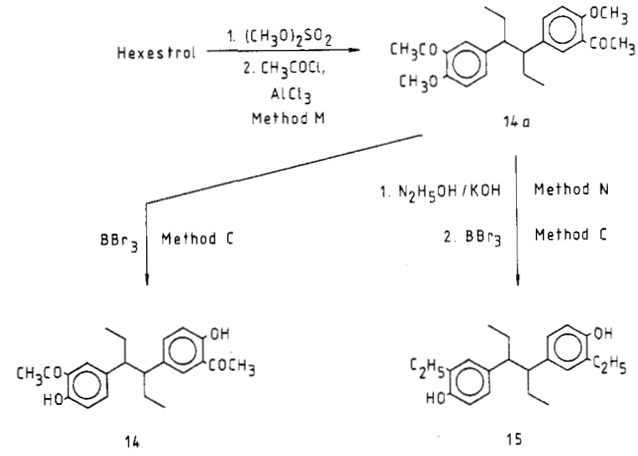
(7) Some of these hexestrol derivatives are already described in the literature (see Table I); in some cases, estrogen receptor affinities are given. In order to get comparable values, we did not take the data out of the literature, for it is known that the binding affinities strongly depend on the experimental conditions used. In some cases, new procedures were used for the synthesis of described compounds.

(8) Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett.* **1973**, 1041.

Scheme II



Scheme III



column chromatography and recrystallization, respectively (method A, Scheme I). Compounds **1b–3b** were free of trans isomers, as was proved by TLC and HPLC. The cis configuration of **1b–3b** was proved by their ^1H NMR spectra: the signals of the CH_3, CH_2, and OCH_3 protons were almost identical with the signals of the previously described *cis*-3,4-bis(methoxyphenyl)hex-3-enes,[9] which were found to be shifted downfield in the case of the CH_3 and CH_2 signals (0.2 and 0.4 ppm) and shifted upfield in the case of the OCH_3 signal (0.3 ppm) in comparison with the trans isomers.[9,10] Catalytic hydrogenation of the *cis*-alkenes **1b–3b** with palladium on carbon (method B, Scheme I) gave the isomerically pure (TLC and HPLC) *meso*-3,4-diphenylhexane derivatives **1a–3a** (Table I).[11] The ether cleavage of **1a–3a** to **1–3** was accomplished with BBr_3 (method C, Scheme I, Table I).

The bromo and iodo derivatives **4** and **5** were synthesized by direct halogenation of hexestrol according to the procedure of Heiman and co-workers[15] (method D) and Katzenellenbogen and Hsiung[16] (method E), respectively. Mono-, tri-, and tetrasubstituted side products were separated by column chromatography.[21]

The dimethylaminomethyl compound **6** was obtained by reaction of hexestrol with dimethylamine and formaldehyde (method F, Scheme II, Table I). The separation of mono-, tri-, and tetrasubstituted side products was accomplished by repeated fractional crystallization.

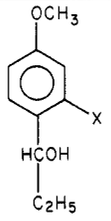
The methyl derivative **7** was synthesized in a "one-pot" reaction converting the dimethylaminomethyl compound **6** to the quaternary ammonium salt with dimethyl sulfate and reducing the latter compound with $NaCNBH_3$ in hexamethylphosphoramide according to the procedure of Yamada et al.[22] (method G, Scheme II, Table I).

In order to synthesize the hydroxymethyl compound **10**, the dimethylaminomethyl derivative **6** was converted to the acetoxy compound **8a** by reaction with Ac_2O by the method of Stempet and Buzzi[23] (method H, Scheme II, Table I). Experiments of directly converting the acetic acid ester **8a** to compound **10** were not successful. The benzyl methyl ether (compound **8**) and the benzyl ethyl ether (compound **9**) were obtained by alkaline saponification of **8a** with NaOH in 80% methanol and ethanol, respectively (method J, Scheme II, Table I). The cleavage of the ethers of compound **8** and **9** was accomplished with BBr_3 (method C, Scheme II). In both cases, the hydroxymethyl derivative **10** was obtained, which was found to be relatively unstable (see Table I).

The nitro compound **11** was obtained by reaction of hexestrol with $NaNO_2$ in glacial acetic acid (method K, Scheme II, Table I). Catalytic hydrogenation of **11** by using palladium on carbon gave compound **12** (Method B, Scheme II, Table I). The latter compound was converted with formaldehyde and $NaCNBH_3$ to the dimethylamino

(9) Kranzfelder, G.; Hartmann, R. W.; von Angerer, E.; Schönenberger, H.; Bogden, A. E. *J. Cancer Res. Clin. Oncol.* **1982**, *103*, 165.
(10) Schneider, M.; von Angerer, E.; Kranzfelder, G.; Schönenberger, H. *Arch. Pharm. (Weinheim, Ger.)* **1980**, *313*, 919.
(11) In the case of **3a**, dehalogenated side products (3-chlorohexestrol and hexestrol) were separated by column chromatography.
(12) Wessely, F.; Kotlan, J.; Sinwel, F. *Monatsh. Chem.* **1952**, *83*, 902.
(13) Sisido, K.; Udo, Y.; Nozaki, H.; Jensen, E. V. *J. Org. Chem.* **1961**, *26*, 1227.
(14) Hamacher, H.; Sand, J. M. *Arch. Pharm. (Weinheim, Ger.)* **1981**, *314*, 631.
(15) Heiman, D. F.; Senderoff, S. G.; Katzenellenbogen, J. A.; Neeley, R. J. *J. Med. Chem.* **1980**, *23*, 994.
(16) Katzenellenbogen, J. A.; Hsiung, H. M. *Biochemistry* **1975**, *14*, 1736.
(17) Marson, L. M. *Boll. Chim. Farm.* **1963**, *102*, 317.
(18) Buu-Hoi, N. P.; Lavit, D.; Xuong, N. D. *J. Chem. Soc.* **1953**, 2612.
(19) Hamacher, H. *Arch. Pharm. (Weinheim, Ger.)* **1978**, *311*, 184.
(20) Shishido, K.; Nozaki, H.; Kayama, H. *J. Org. Chem.* **1949**, *14*, 1124.
(21) Compound **4** was also synthesized starting from 3-bromo-4-methoxypropiophenone according to the procedure described above. However, dehalogenation in the step of catalytic hydrogenation made this procedure inferior to method D regarding overall yield.
(22) Yamada, K.; Itoh, N.; Iwakuma, T. *J. Chem. Soc., Chem. Commun.* **1978**, 1089.
(23) Stempet, A.; Buzzi, E. C. *J. Am. Chem. Soc.* **1949**, *71*, 2969.

Table II. 1-(2-Substituted-4-methoxyphenyl)-1-propanols



compd	X	synth method[a]	yield,[b] %	mp, °C	formula
16b	OCH_3	c	78	30-31	$C_{11}H_{16}O_3$
17b	F	O	75	oil	$C_{10}H_{13}FO_2$
18b	Cl	O	86	oil	$C_{10}H_{13}ClO_2$
19b	Br	O	84	oil	$C_{10}H_{13}BrO_2$
20b	CH_3	O	81	29	$C_{11}H_{16}O_2$
21b	C_2H_5	O	89	oil	$C_{12}H_{18}O_2$

[a] O refers to synthetic method O under Experimental Section. [b] Yield of analytically pure (TLC) product; no effort was made to optimize yields. [c] Obtained by Grignard reaction of 2,4-dimethoxybenzaldehyde with EtMgI according to the standard procedure.

derivative **13** according to the method of Borch and Hassid[24] (method L, Scheme II, Table I).

The acetyl compound **14** was obtained by Friedel–Crafts acylation of hexestrol dimethyl ether with acetyl chloride and $AlCl_3$ by the procedure of Sisido et al.[13] (method M, Scheme III, Table I) and subsequent cleavage of the methyl ethers of **14a** with BBr_3 (method C, Scheme III, Table I).

The synthesis of the ethyl derivative **15** started from compound **14a** (Scheme III). The reduction of the acetyl groups was carried out with KOH and hydrazine hydrate according to the Wolff–Kishner method as modified by Huang-Minlon[25] (method N, Scheme III, Table I). The ether cleavage of the methoxy ethyl derivative (**15a**) to **15** was accomplished with BBr_3 (method C, Scheme III, Table I).

The synthesis of the 2,2′-disubstituted hexestrol derivatives **16–21** (Scheme IV, Table I) started from the corresponding 1-(2-substituted-4-methoxyphenyl)-1-propanols **16b–21b**.[26] The secondary alcohols **17b–21b** were obtained by reduction of the corresponding propiophenones using $LiAlH_4$ (method O, Table II). Compound **16b** was prepared by Grignard reaction of 2,4-dimethoxybenzaldehyde with EtMgI according to the standard procedure (Table II). Reductive coupling of the secondary alcohols **16b–21b** with $TiCl_3/LiAlH_4$ according to the method of McMurry and Silvestri[27] (method P, Scheme IV, Table I) gave a mixture of the corresponding *meso*- and *dl*-dibenzyl derivatives, as was proved by TLC, HPLC, and ^1H NMR. The meso diastereomers **16a–21a** were separated by fractional crystallization from methanol or ethanol (Table I).[28] The ether cleavage of **16a–21a** to **16–21** was accomplished with BBr_3 (method C, Scheme IV, Table I).

Scheme IV

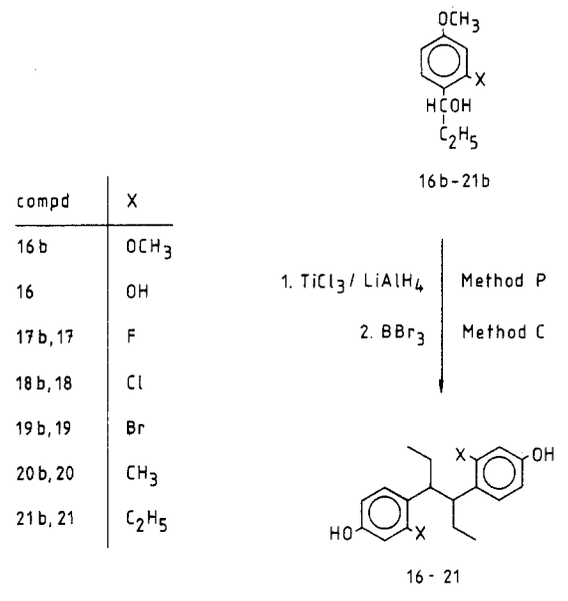


Table III. Relative Binding Affinity (RBA) of Hexestrol and Compounds **1–21** for Calf Uterine Estrogen Receptor

compd	RBA value[a]	compd	RBA value[a]
hex	27	11	0.14
1	20	12	5.6
2	16	13	<0.01
3	1.6	14	<0.01
4	0.25	15	1.2
5	0.17	16	32
6	0.04	17	6.5
7	8.1	18	2.2
8	0.55	19	1.8
9	0.18	20	8.5
10	0.71	21	3.7

[a] Relative binding affinity for the calf uterine estrogen receptor = ratio of molar concentrations of 17β-estradiol (E_2) and inhibitor required to decrease the amount of bound [^3H]E_2 by 50% × 100.

Biological Properties. The affinities of the hexestrol derivatives **1–21** for the estrogen receptor were determined by a competitive binding assay with 17β-[^3H]estradiol and the dextran-coated charcoal method.[2] All test compounds exhibited a binding affinity with RBA values between 32 and <0.01% that of estradiol (Table III). In the semilogarithmic plot of receptor-bound [^3H]estradiol vs. con-

(24) Borch, R. F.; Hassid, A. J. *J. Org. Chem.* **1972**, *37*, 1673.
(25) Huang-Minlon *J. Am. Chem. Soc.* **1946**, *68*, 2487.
(26) This procedure was used for the synthesis of the 2,2′-disubstituted hexestrol derivatives **16–21**; the reductive coupling according to ref 8, starting from the propiophenones and yielding the *cis*-stilbenes, failed with compounds **16c** and **18c–21c**. Compound **17c** was successfully coupled (data not given).
(27) McMurry, J. E.; Silvestri, M. *J. Org. Chem.* **1975**, *40*, 2687.
(28) The NMR assignments of **16a–21a** were made by comparing their NMR spectra with those of described *meso*- and *dl*-3,4-bis(methoxyphenyl)hexanes (see ref 1 and 9). In the meso compounds, the signals of the CH_3, CH_2, and CH protons are shifted upfield, whereas the singlet of the OCH_3 protons is shifted downfield compared to the *dl* diastereomer.

Table IV. Estrogenic Activity of Compounds 1, 2, 7, 12, 16, 17, and 20 in the Mouse Uterine Weight Test

	uterotrophic test	
compd	dose,[a] μg	effect,[b] mean ± SD
1	0	15.4 ± 2.1
	2	24.6 ± 6.3
	10	34.7 ± 3.8
	50	39.1 ± 4.8
	250	50.1 ± 7.2
	500	49.8 ± 3.0
estrone	0.4	54.3 ± 6.5
2	0	10.0 ± 1.3
	1	50.7 ± 5.7
	10	43.4 ± 2.9
	100	40.4 ± 4.8
	1000	38.8 ± 3.4
estrone	0.4	44.9 ± 4.9
7	0	10.0 ± 1.3
	1	48.7 ± 5.4
	10	40.0 ± 4.6
	100	33.8 ± 3.9
	1000	34.0 ± 3.5
estrone	0.4	44.9 ± 4.9
12	0	16.9 ± 2.9
	1	23.3 ± 3.9
	10	24.3 ± 2.9
	100	44.7 ± 4.9
	1000	45.6 ± 5.2
estrone	0.4	50.4 ± 5.2
16	0	16.4 ± 1.3
	1	53.6 ± 2.0
	10	41.6 ± 3.7
estrone	0.4	51.4 ± 5.3
17	0	16.9 ± 2.8
	1	47.6 ± 6.4
	10	39.0 ± 4.3
	100	34.3 ± 3.8
	1000	30.5 ± 2.5
estrone	0.4	43.9 ± 4.2
20	0	16.9 ± 2.8
	1	46.3 ± 6.0
	10	36.6 ± 4.3
	100	38.4 ± 3.5
	1000	32.6 ± 3.6
estrone	0.4	43.9 ± 4.2

[a] Dose per animal per day. [b] Uterus dry weight (milligrams)/body weight (grams) × 100.

centration of inhibitor, the curves of all hexestrol derivatives were parallel to the binding curve of estradiol. Therefore, it can be assumed that these compounds exhibited a competitive inhibition of the interaction of estradiol with its receptor.

All 3,3'-disubstituted hexestrol derivatives (1–15) showed a decreased binding affinity compared to hexestrol (Table III). It is striking that an increase of the van der Waals radius (the length of chain) of the substituents (H < F < Cl < Br < I; H < CH_3 < C_2H_5; CH_2OH < CH_2OCH_3 < $CH_2OC_2H_5$) led to a decrease of binding affinity for the receptor (RBA of hex > **2** > **3** > **4** > **5**; hex > **7** > **15**; **10** > **8** > **9**), but not only steric effects seem to have an influence on estrogen receptor interaction. Though the acetyl and ethyl substituents have approximately the same volume (25.4 and 23.9 $cm^3 \cdot mol^{-1}$, respectively[29]), the binding affinity of the acetyl compound **14** is markedly decreased compared to that of **15**. This is probably due

(29) Bondi, A. "Physical Properties of Molecular Crystals, Liquids and Glasses"; Wiley: New York, 1968; p 453–468.

Table V. Antiestrogenic Activity of Compounds 1 and 12 in Mouse Uterine Weight Test

	antiuterotrophic test		
compd	dose,[a] μg	effect,[b] mean ± SD	% inhibn[c,d]
1	0	10.3 ± 4.6	
	5	24.1 ± 5.1	59[e]
	25	37.0 ± 4.5	20
	100	39.2 ± 6.4	13
	250	43.6 ± 5.0	0
estrone	0.1	43.8 ± 6.8	
12	0	16.2 ± 1.8	
	5	19.4 ± 2.0	78[e]
	25	34.6 ± 2.3	0
estrone	0.1	30.6 ± 1.6	

[a] Dose per animal per day. [b] Uterus dry weight (milligrams)/body weight (grams) × 100. [c] Percent inhibition = $100 - (E_{S,T} - E_V)/(E_S - E_V) \times 100$; E_S = effect of estrone standard; $E_{S,T}$ = effect of standard under simultaneous application of test substance; E_V = effect of vehicle. [d] The U test according to Wilcoxon, Mann, and Whitney was used. [e] Significant ($\alpha = 0.01$).

to an intramolecular hydrogen bond between the oxygen of the carbonyl group and the hydrogen of the phenolic OH group, thus reducing the hydrogen-bond interaction with the receptor area. This phenomenon may also explain the small binding affinity of the NO_2 compound **11**.

In case of the 2,2'-disubstituted hexestrol derivatives, the hydroxy compound **16** exhibited a RBA value comparable to that of hexestrol (Table III). Compound **16** is the first hexestrol derivative described in the literature showing a similar binding affinity for the estradiol receptor than the parent compound hexestrol. The other 2,2'-disubstituted hexestrols (compounds 17–21) showed decreased RBA values compared to the nonsubstituted compound. The increase of the van der Waals radius of the substituents (H < F < Cl < Br; H < CH_3 < C_2H_5) also led to a decrease of the RBA values (hex > **17** > **18** > **19**; hex > **20** > **21**).

With the exception of the fluoro compounds **2** and **17**, the binding affinity is reduced more by substituents ortho to the OH group than meta.

The most active inhibitors of the estradiol receptor interaction (RBA > 5), compounds **1**, **2**, **7**, **12**, **16**, **17**, and **20**, were tested for their uterotrophic activity in the immature mouse as a measure of estrogenicity.

With the exception of the catechol derivative **1** and the amino compound **12**, all other compounds stimulated the uterine growth strongly like true estrogens do, reaching their maximum effect at very small doses (Table IV). Because of these strong estrogenic properties, these compounds were not further tested for their antiuterotrophic activities.

Compounds **1**[30] and **12** showed a pattern of action different from that of the other compounds, exhibiting only low uterotrophic activity in small doses (Table IV). In high doses, however, the maximum effect of estrone was almost reached. Compounds **1** and **12** reduced the estrone-stimulated uterine growth strongly in small doses (Table V). However, inhibitory effects were diminished by increasing the dose and finally disappeared completely.

Discussion

In our studies we were able to show that, with the exception of the hydroxy substituents in the 2,2'-positions, all other substituents in the 2,2'-positions and especially

(30) Detailed endocrinological studies and mammary tumor inhibiting activity of **1** have been described recently (see ref 9).

in the 3,3′-positions decreased the affinity of hexestrol for the estrogen receptor.

In the case of the 3,3′-disubstituted compounds, this is probably due to a steric hindrance of the interaction of the phenolic hydroxy groups with the receptor site. The bulkier the substituents are, the larger is the decrease of the receptor affinity of the corresponding compound.

In the case of the 2,2′-disubstituted derivatives, we had expected that substituents that increase the lipophilicity in the center of the molecule increase the affinity of the parent compound for the estrogen receptor as well, for it is known that the introduction of chlorine atoms in the 2,6-positions of the aromatic rings of *N,N′*-dialkyl-1,2-bis(4-hydroxyphenyl)ethylenediamines leads to a substantial increase of the estrogen receptor affinity of these N-isosteric hexestrol derivatives.[31] Even without phenolic hydroxy groups, the chlorinated ethylenediamines exhibit considerable receptor affinities.[32]

Our finding that increased lipophilicity leads to decreased estrogen receptor affinity can be explained by an increasing steric hindrance of the formation of the estrogen receptor complex, for the increase of lipophilicity correlates with an increase of the van der Waals radius of the corresponding substituents.

Our finding that the 2,2′-dihydroxylated compound 16 shows at least the same—maybe a slightly increased—affinity for the estrogen receptor compared to hexestrol and the fact that *meso*-3,4-bis(2-hydroxyphenyl)hexane also exhibits affinity for the estrogen receptor (RBA = 0.06)[33,34] might be indications of an additional binding area for the OH groups on the receptor.

What is the explanation of our result that the 3,3′-dihydroxylated compound 1 shows a slightly decreased binding affinity compared to hexestrol in spite of the relatively high binding affinity of *meso*-3,4-bis(3-hydroxyphenyl)hexane (**A1**; RBA = 10)?[1] The hydroxy groups of hexestrol and **A1** probably interact with the same binding site at the receptor molecule. In the case of the catechol compound 1, the hydroxy groups standing in the 3,3′-positions impair the maximum interaction with the receptor area of the hydroxy groups standing in the 4,4′-positions probably by intramolecular hydrogen bonds.

Since the discovery that the replacement of the 1,2-diethyl groups by isopropyl groups in the compound **A1** destroys the antiestrogenic activity and generates a true estrogen[35] and the finding that tetramethylation in the 1,2-positions of the diphenylethane skeleton of hexestrol produces a strong antiestrogen (**A2**),[2] it is known that also the center of the diphenylethane molecules strongly influences agonistic and antagonistic properties of the corresponding compounds. Since the highly estrogenic compound *trans*-2-(4-hydroxyphenyl)-3-(2-methyl-4-hydroxyphenyl)pent-2-ene showed the same affinity for the estrogen receptor as diethylstilbestrol,[36] one could have imagined that the introduction of CH_3 substituents in the 2,2′-positions of hexestrol would change the mode of action of the parent compound, mimicing isopropyl groups at the benzylic C atoms. However, the result of the mouse uterine weight test clearly demonstrated that, with the exception of the catechol compound 1 and the N-isosteric catechol derivative **12**, the substituents in the 2,2′-positions or 3,3′-positions did not change the agonistic property of hexestrol.

It has recently been described that synthetic catechol estrogens show different endocrinological properties compared to true estrogens.[9,37] Depending on the conditions used, they even show antiestrogenic activity. It has been suggested that endogenous catechol estrogens may play the antiestrogen role in endocrine regulation.[38-40] Our finding that the 3,3′-disubstituted amino derivative of hexestrol (compound **12**) and the catechol estrogen 1 show identical properties in the mouse uterine weight test is not surprising, since Terenius had found that the replacement of one or two hydroxy groups in hexestrol by amino groups lessened the binding affinities of the corresponding compounds but did not change their uterotrophic action.[41,42]

As a conclusion it can be stated that it is possible to enhance slightly the binding affinity of hexestrol for the estrogen receptor by ring substitution without changing the estrogenic nature of the parent compound. Subsequent publications will show to what extent the findings of this study are transferable to the antiestrogens **A1–3**.[5,6]

Experimental Section

General Procedures. TLC of each compound was performed on Merck F 254 silica gel plates. Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. Elemental analyses were performed by the Mikroanalytisches Laboratorium, Universität Regensburg. The structures of all compounds were confirmed by their IR (Beckman AccuLab 3) and ^1H NMR spectra (Varian EM 360 A, 60 MHz). HPLC was accomplished with an Altex 110A pump and a Kontron Uvikon 720 LC spectrometer. A LiChrosorb Si 60 5-μM (Merck) column and a RP 18 10-μM (Altex) column were used [solvent systems: CH_2Cl_2–hexane (1:1) and MeOH–H_2O (3:1), respectively].

Method A. *cis*-3,4-Bis(3-fluoro-4-methoxyphenyl)hex-3-ene (2b). Zinc powder (1.96 g, 0.03 mol) was added slowly under N_2 into a mixture of 3-fluoro-4-methoxypropiophenone (**2c**; 1.82 g, 0.01 mol) and $TiCl_4$ (2.85 g, 0.015 mol) in 20 mL of dry dioxane at 15 °C. The yellow solution changed to purple and turned dark brown when heated to reflux. After 4 h at 101 °C, the reaction mixture was cooled, and alkaline hydrolysis was performed with 10% K_2CO_3 solution. After extraction with ether and removal of the ether, the crude product was purified by chromatography [silica gel column eluted with CH_2Cl_2–hexane (1:1)] to give 1.00 g (60%) of **2b** as an oil: ^1H NMR ($CDCl_3$) δ 0.95 (t, J = 7 Hz, 6 H, CH_3), 2.52 (q, J = 7 Hz, 4 H, CH_2), 3.77 (s, 6 H, OCH_3), 6.60–6.88 (m, 6 H, ArH).

***cis*-3,4-Bis(3,4-dimethoxyphenyl)hex-3-ene (1b).** The crude product was recrystallized from EtOH/H_2O to give 1.30 g (73%) of **1b**: mp 100 °C; ^1H NMR ($CDCl_3$) δ 0.98 (t, J = 7 Hz, 6 H, CH_3), 2.55 (q, J = 7 Hz, 4 H, CH_2), 3.60 and 3.78 (2 s, 6 H each, OCH_3), 6.43–6.63 (m, 6 H, ArH). Anal. Calcd for $C_{22}H_{28}O_4$ (M_r 356.5): C, 74.13; H, 7.92. Found: C, 74.20; H, 8.01.

***cis*-3,4-Bis(3-chloro-4-methoxyphenyl)hex-3-ene (3b)**: yield 57%; oil; ^1H NMR ($CDCl_3$) δ 0.95 (t, J = 7 Hz, 6 H, CH_3), 2.52 (q, J = 7 Hz, 4 H, CH_2), 3.80 (s, 6 H, OCH_3), 6.57–7.27 (m, 6 H, ArH).

(31) von Angerer, E. *J. Med. Chem.* **1982**, *25*, 1374.
(32) von Angerer, E. Kranzfelder, G.; Taneja, A. K.; Schönenberger, H. *J. Med. Chem.* **1980**, *23*, 1347.
(33) Kranzfelder, G. Ph.D. Thesis, University of Munich, 1977.
(34) Just like hexestrol and in contrast to 3,4-bis(3-hydroxyphenyl)hexane (**A1**), this compound is a true estrogen. It shows a steep dose–response curve in the uterotrophic test going parallel to that of estrone (see ref 33).
(35) Schmitt-Wallenborn, H. Ph.D. Thesis, University of Munich, 1978.
(36) Geynet, C.; Millet, C.; Truong, H.; Baulieu, E. E. *Gynecol. Invest.* **1972**, *3*, 2.
(37) Schneider, M. R.; Schönenberger, H.; Michel, R. T.; Fortmeyer, H. P. *J. Cancer Res. Clin. Oncol.* **1982**, *104*, 219–227.
(38) Gethmann, U.; Ball, P.; Knuppen, R. *Acta Endocrinol. (Copenhagen), Suppl.* **1978**, *215*, 102.
(39) Martucci, C. P.; Fishman, J. *Endocrinology* **1979**, *105*, 1288.
(40) Paul, S. M.; Axelrod, J. Satellite Symposium of the 7th International Congress of Pharmacology: Pharmacological Modulation of Steroid Action, Turin, 1978, abstracts book, p 2.
(41) Terenius, L. *Acta Pharmacol. Toxicol.* **1972**, *31*, 441.
(42) Terenius, L. *Acta Pharmacol. Toxicol.* **1972**, *31*, 449.

The following compounds are representatives of synthetic methods B–P reported in Tables I and II.

Method B. *meso*-3,4-Bis(3-fluoro-4-methoxyphenyl)hexane (2a). Palladium on charcoal (10%, 0.1 g) was added to a solution of **2b** (3.32 g, 0.01 mol) in 100 mL of EtOH. The suspension was shaken under a hydrogen atmosphere until no more H_2 was accepted. The reaction mixture was filtered. The alcohol was removed, and the crude product was recrystallized from EtOH/H_2O to give 3.11 g of **2a**.

Method C. *meso*-3,4-Bis(3-fluoro-4-hydroxyphenyl)hexane (2). A solution of **2a** (3.34 g, 0.01 mol) in 250 mL of dry CH_2Cl_2 was cooled to −60 °C. BBr_3 (7.52 g, 0.03 mol) was added under nitrogen with stirring. After 0.5 h, the freezing mixture was removed, and the reaction mixture was kept at room temperature for 4 h. Fifty milliliters of MeOH was added, and the mixture was shaken with 2 N NaOH. After neutralization of the aqueous layer with 3 N H_2SO_4, the solution was extracted with ether. After removal of the ether, the crude product was recrystallized from EtOH/H_2O to give 2.61 g of **2**.

Method D. *meso*-3,4-Bis(3-bromo-4-hydroxyphenyl)hexane (4). A solution of anhydrous potassium acetate (5.00 g, 0.05 mol) in 75 mL of glacial acetic acid was added to a solution of hexestrol (2.70 g, 0.01 mol) in 25 mL of THF. The mixture was cooled in an ice bath, and 25 mL of a freshly prepared solution of bromine (4.00 g, 0.025 mol) in acetic acid was added dropwise. After 5 min the products were isolated by partitioning between EtOAc and H_2O. After washing with H_2O, the EtOAc layer was removed, and the mixture of mono-, di-, tri-, and tetrabromo compounds was separated by chromatography (silica gel column eluted with CH_2Cl_2) to yield 1.16 g of **4**.

Method E. *meso*-3,4-Bis(4-hydroxy-3-iodophenyl)hexane (5). A solution of iodine (5.08 g, 0.02 mol) in 25 mL of THF was added dropwise to a solution of hexestrol (2.70 g, 0.01 mol) in a mixture of 75 mL of MeOH and 25 mL of concentrated NH_4OH with stirring. After 0.5 h, glacial acetic acid was added to neutralize NH_3. Water was then added, and reaction products were extracted with EtOAc. After removal of the solvent, **5** (0.99 g) was separated by silica gel chromatography with $CHCl_3$ as eluent.

Method F. *meso*-3,4-Bis[3-[(dimethylamino)methyl]-4-hydroxyphenyl]hexane (6). Hexestrol (2.70 g, 0.01 mol) was dissolved in 100 mL of EtOH. Solutions of dimethylamine (2.25 mL of a 40% aqueous solution, 0.02 mol) and formaldehyde (1.60 mL of a 37% aqueous solution, 0.02 mol) were added dropwise with stirring. The reaction mixture was then refluxed for 8 h. After the solvent had been removed, the crude product was fractionally crystallized from EtOH/H_2O. The yield of **6** was 1.85 g.

Method G. *meso*-3,4-Bis(4-hydroxy-3-methylphenyl)hexane (7). A solution of Me_2SO_4 (25.2 g, 0.2 mol) in 50 mL of ether was added dropwise at room temperature to a solution of **6** (3.85 g, 0.01 mol) in 800 mL of ether. After the solution was stirred for 1 h, the ether was removed. A solution of $NaCNBH_3$ (2.50 g, 0.04 mol) in 200 mL of hexamethylphosphoramide was added to the quaternary ammonium salt. The reaction mixture was kept at 120 °C for 16 h. After the mixture was cooled and H_2O was added, the reaction mixture was extracted with ether. The ether was removed, and the crude product was recrystallized from EtOH/H_2O to yield 2.18 g of **7**.

Method H. *meso*-3,4-Bis[4-acetoxy-3-(acetoxymethyl)-phenyl]hexane (8a). A solution of **6** (3.85 g, 0.01 mol) in 30 mL of Ac_2O was heated to refux for 1.5 h. The solvent was removed, and the residual oil was dissolved in $CHCl_3$. This solution was washed ($NaHCO_3$ and H_2O) and dried ($MgSO_4$). The solvent was removed, and the crude product was recrystallized from EtOH to give 4.14 g of **8a**.

Method J. *meso*-3,4-Bis[4-hydroxy-3-(methoxymethyl)-phenyl]hexane (8). A solution of **8a** (4.99 g, 0.01 mol) and NaOH (8.00 g, 0.2 mol) in 200 mL of MeOH (80%) was heated to reflux for 4 h. After cooling, the solution was neutralized with glacial acetic acid and extracted with ether. The ether was removed, and the crude product was recrystallized from EtOH/H_2O to yield 2.83 g of **8**.

Method K. *meso*-3,4-Bis(4-hydroxy-3-nitrophenyl)hexane (11). Hexestrol (2.70 g, 0.01 mol) was dissolved in 200 mL of hot acetic acid. After the mixture was cooled, $NaNO_2$ (6.20 g, 0.09 mol) was added in small portions to the stirred solution. After stirring for 5 h at room temperature, the reaction mixture was poured into 400 mL of H_2O. The resulting precipitate was separated and recrystallized from acetone to yield 2.88 g of **11**.

Method L. *meso*-3,4-Bis[3-(dimethylamino)-4-hydroxyphenyl]hexane (13). To a stirred solution of compound **12** (3.00 g, 0.01 mol) and 20 mL of aqueous 37% formaldehyde (0.25 mol) in 150 mL of acetonitrile was added $NaCNBH_3$ (5.00 g, 0.08 mol) in small portions. The reaction mixture was stirred for 15 min, and then glacial acetic acid was added dropwise until the solution tested neutral. Stirring was continued for an additional 45 min, glacial acetic acid being added to maintain the pH near neutrality. The solvent was removed, and H_2O was added to the residue. The resulting mixture was extracted with ether. The solvent was removed, and the crude product was recrystallized from EtOH to give 2.75 g of **13**.

Method M. *meso*-3,4-Bis(3-acetyl-4-methoxyphenyl)hexane (14a). A solution of hexestrol dimethyl ether (2.98 g, 0.01 mol) and acetyl chloride (3.92 g, 0.05 mol) in 40 mL of nitrobenzene was cooled in an ice bath. Finely powdered $AlCl_3$ (6.66 g, 0.05 mol) was added in small portions with stirring. After stirring for 4 h at room temperature, the reaction mixture was poured onto ice and acidified with HCl. The nitrobenzene was removed by steam distillation. The crude product was extracted with $CHCl_3$. After the extract was washed with 1 N NaOH and H_2O, the solvent was removed, and the remaining solid was recrystallized from acetone to give 2.98 g of **14a**.

Method N. *meso*-3,4-Bis(3-ethyl-4-methoxyphenyl)hexane (15a). A mixture of compound **14a** (3.83 g, 0.01 mol), KOH (9.00 g, 0.16 mol), 9 mL of 85% hydrazine hydrate, and 100 mL of diethylene glycol was heated under reflux for 1.5 h. After the water that formed was removed, the mixture was heated at 195 °C for an additional 4 h. The solution was diluted with cold H_2O, poured into HCl, and extracted with ether. The solvent was removed, and the crude product was recrystallized from MeOH/benzene to yield 3.23 g of **15a**.

Method O. 1-(2-Chloro-4-methoxyphenyl)-1-propanol (18b). A solution of 2-chloro-4-methoxypropiophenone (**18c**; 1.99 g, 0.01 mol) in 10 mL of ether was added dropwise to a stirred suspension of $LiAlH_4$ (0.10 g, 2.8 mmol) in 20 mL of ether. After stirring for 3 h at room temperature, the mixture was heated to reflux for 1 h. The mixture was cooled and decomposed by dropwise addition of ice–water, followed by 10% H_2SO_4, to give two clear phases. The ethereal layer was separated, washed (H_2O), and dried ($MgSO_4$). The solvent was removed, and 1.73 g of **18b** was obtained.

Method P. *meso*-3,4-Bis(2-chloro-4-methoxyphenyl)hexane (18a). $TiCl_3$ (4.60 g, 0.03 mol) was placed under N_2 in a flask with 150 mL of dry glyme. $LiAlH_4$ (0.38 g, 0.01 mol) was quickly added to the stirred $TiCl_3$ slurry. The resulting black suspension was stirred for 10 min. Compound **18b** (2.01 g, 0.01 mol) was dissolved in 10 mL of dry glyme and added dropwise with stirring. The mixture was heated to reflux and kept there for 16 h. After cooling, the reaction mixture was quenched by the addition of 2 N HCl, diluted with water, and extracted with ether. The ether extract was washed ($NaHCO_3$ and H_2O) and dried ($MgSO_4$). The solvent was removed, and the resulting crude product was fractionally crystallized from EtOH to give 0.33 g of **18a**.

Biological Methods. Estradiol Receptor Binding Assay. The relative binding affinity (RBA) of the test compounds was determined by the displacement of [^{3}H]estradiol. A previously described procedure[2] was used with modifications. Test compounds were incubated with cytosol from calf uteri and [^{3}H]estradiol at 4 °C for 16 h. Incubation was stopped by adding dextran-coated charcoal. After centrifugation, the radioactivity of a 100-μL supernatant aliquot was counted. The percentage bound radioligand was plotted vs. the concentration of unlabeled test compounds. Six concentrations of the competitors were tested. They were chosen to provide a linear portion on a semilog plot crossing the point of 50% competition. From this plot, the molar concentrations of unlabeled estradiol and of test compounds reducing radioligand binding by 50% were determined.

Estrogen and Antiestrogen Assays. Estrogenic and antiestrogenic activities were determined by stimulation of the uterine growth and the inhibition of the uterine growth stimulated by estrone, respectively, with immature NMRI mice as described previously.[2] Twenty-day-old female mice (weight 14.5 ± 1.2 g,

mean ± SD) were randomly distributed into groups of 10 animals. They were subcutaneously injected daily for 3 days with 0.1 mL of olive oil solutions containing the test compound. The uteri were removed 24 h after the last injection, fixed with Bouin's solution, washed, dried, and weighed.

Acknowledgment. Thanks are due to the Deutsche Forschungsgemeinschaft and to the Verband der Chemischen Industrie, Fonds der Chemischen Industrie, who supported this work by grants. The technical assistance of Fritz Birk is gratefully acknowledged.

Registry No. 1, 79199-51-2; **1a**, 85720-33-8; **1b**, 85720-34-9; **1c**, 1835-04-7; **2**, 74536-61-1; **2a**, 74536-60-0; **2b**, 85720-35-0; **2c**, 586-22-1; **3**, 79140-57-1; **3a**, 79140-65-1; **3b**, 85720-36-1; **3c**, 4394-54-1; **4**, 74536-64-4; **5**, 55508-15-1; **6**, 85720-37-2; **7**, 10465-10-8; **8**, 85720-38-3; **8a**, 85720-39-4; **9**, 85720-40-7; **10**, 85720-41-8; **11**, 66877-40-5; **12**, 66877-41-6; **13**, 85720-42-9; **14**, 85720-43-0; **14a**, 85720-44-1; **15**, 85720-45-2; **15a**, 85720-46-3; **16**, 85720-47-4; **16a**, 85720-48-5; **16b**, 830-99-9; **17**, 85720-49-6; **17a**, 85720-50-9; **17b**, 85720-51-0; **18**, 85720-52-1; **18a**, 85720-53-2; **18b**, 85720-54-3; **18c**, 13329-61-8; **19**, 85720-55-4; **19a**, 85720-56-5; **19b**, 23600-60-4; **20**, 85720-57-6; **20a**, 85735-20-2; **20b**, 53773-75-4; **21**, 85720-58-7; **21a**, 85720-59-8; **21b**, 85720-60-1; hexestrol, 84-16-2; hexestrol dimethyl ether, 28231-25-6.

Supplementary Material Available: ^{1}H NMR data (Tables VI–VIII) of the 2,2′- and 3,3′-disubstituted hexestrol derivatives (**1–21** and **1a–21a**) and the 1-(2-substituted-4-methoxyphenyl)-1-propanols (**16b–21b**) (8 pages). Ordering information is given on any current masthead page.

Pyridazinones. 3. Synthesis, Antisecretory, and Antiulcer Activities of 2-Cyanoguanidine Derivatives

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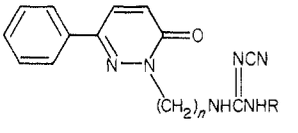
3(2*H*)-Pyridazinone derivatives having a 2-cyanoguanidine moiety, as well as a sulfur or an oxygen atom in the alkylene side chain, were synthesized and evaluated for gastric antisecretory and antiulcer activities. The key intermediates, free amines having a thioether linkage, were synthesized by the reaction of 2-(ω-chloroalkyl) derivatives with cysteamine, while other intermediates having an ether linkage were synthesized from 2-(ω-chloroalkyl)oxymethyl derivatives. These free amines were converted via the 3-cyano-2-methyl-1-isothiourea derivatives into the desired 2-cyano-3-substituted-1-guanidine derivatives. All compounds synthesized were evaluated for gastric antisecretory activity in the pylorus-ligated rat by the method of Shay, and selected compounds were evaluated in the stress-induced ulcer test in rat. Structure–activity relationships are discussed. The molecular features for the best activities are a phenyl group in the C-6 position of the 3(2*H*)-pyridazinone ring, a four-atom chain length between the 3(2*H*)-pyridazinone ring and the 2-cyanoguanidine moiety, and a thioether rather than an ether linkage. Among them, compound **14**, 2-[[[2-(2-cyano-3-methyl-1-guanidino)ethyl]thio]methyl]-6-phenyl-3(2*H*)-pyridazinone, had the most potent antisecretory and antiulcer activities. These compounds are neither histamine H_2 receptor inhibitors nor anticholinergic agents.

A variety of derivatives that incorporate an aminoalkylthio unit [$NH(CH_2)_nS$] have been synthesized, and their pharmacological activities, such as cardiovascular,[1] cholinesterase inhibitor,[2] active transport,[3] antibacterial,[4] and antidepressant,[5] have been reported. Since the discovery of metiamide by Black et al.[6] as a histamine H_2 receptor antagonist, several histamine H_2 receptor antagonists, e.g., cimetidine,[7] ranitidine (AH 19065),[8] tiotidine (ICI 125211),[9] oxmetidine (SKF 92994),[10] and etintidine (BL-5641),[11] have been reported. All these compounds bear an aminoethylthio unit as a common structural feature; hence, the unit may be thought to be general for the antagonistic activity.

For the development of new types of antiulcer agents without anticholinergic activity, a series of novel 3(2*H*)-pyridazinone derivatives were synthesized, and the structural requirements for activity were defined by molecular modification. We recently reported the synthesis of a series of 3(2*H*)-pyridazinone derivatives (1) having a



1
MUN-114, n = 4; R = CH_3
MUN-118, n = 5; R = C_2H_5

thiourea or a 2-cyanoguanidine moiety, which were shown

(1) Wise, L. D.; Morrison, G. C.; Egan, K.; Commarato, M. A.; Kopia, G.; Lattime, E. C. *J. Med. Chem.* **1974**, *17*, 1232.
(2) Kutty, K. M.; Jacob, J. C.; Hutton, P. J.; Peterson, S. C. *Clin. Biochem.* **1975**, *8*, 379.
(3) Schuldrin, S.; Kerwar, G.; Kaback, H.; Weil, R. *J. Biol. Chem.* **1975**, *250*, 1361.
(4) Neu, H. C.; Labthavikul, P. *Int. Conf. Antimicrob. Agents Chemother., 20th* **1980**, 260.
(5) Ong, H. H.; Profitt, J. A.; Anderson, V. B.; Spaulding, T. C.; Wilker, J. C.; Geyer III, H. M.; Kruse, H. *J. Med. Chem.* **1980**, *23*, 494.
(6) Black, J. W.; Duncan, W. A. M.; Emmett, J. C.; Ganellin, C. R.; Hesselbo, T.; Parsons, M. E.; and Wyllie, J. H. *Agents Actions* **1973**, *3*, 133.
(7) Brimblecombe, R. W.; Duncan, W. A. M.; Durant, G. J.; Emmett, J. C.; Ganellin, C. R.; Parsons, M. E. *J. Int. Med. Res.* **1975**, *3*, 86.
(8) Bradshaw, J.; Brittain, R. T.; Clitherow, J. W.; Daly, M. J.; Jack, D.; Price, B. J.; Stables, R. *Br. J. Pharmacol.* **1979**, *66*, 464p.
(9) Yellin, T. O.; Buck, S. H.; Gilman, D. J.; Jones, D. F.; Waldleworth, J. M. *Life Sci.* **1979**, *25*, 2001.
(10) Blakemore, R. C.; Brown, T. H.; Durant, G. J.; Emmett, J. C.; Ganellin, C. R.; Parsons, M. E.; Rasmussen, A. C. *Br. J. Pharmacol.* **1980**, *70*, 105p.
(11) Cavanagh, R. L.; Usakewicz, J. J.; Buyniski, J. P. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1980**, *39*, 768.

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