Tricyclic Triarylethylene Antiestrogens: Dibenz[*b*,*f*]oxepins, Dibenzo[*b*,*f*]thiepins, Dibenzo[*a*,*e*]cyclooctenes, and Dibenzo[*b*,*f*]thiocins

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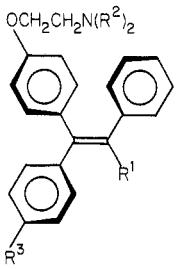
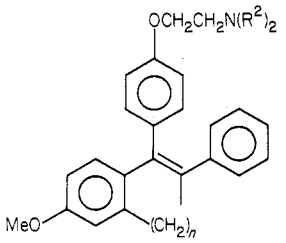
The bridging groups O, S, CH_2CH_2, and SCH_2 were used to produce a series of 26 tricyclic triarylethylenes. Their in vitro binding to rat uterine estrogen receptor was measured in a competitive binding assay. Antifertility and uterotrophic tests in rats showed that antiestrogenic activity was present. The most interesting series had a basic side chain, and the most potent compounds were 3-[2-(dimethylamino)ethoxy]-10-ethyl-11-(4-hydroxyphenyl)dibenzo[*b*,*f*]thiepin (**7b**) and 3-[2-(dimethylamino)ethoxy]-11-ethyl-12-(4-hydroxyphenyl)-5,6-dihydrodibenzo[*a*,*e*]cyclooctene (**7c**), which had good binding (~50% relative to estradiol) and good antiestrogenic activity (ca. one-half of the potency of tamoxifen, III). In this series, the O-bridged compound was the least active, and this is interpreted in terms of the flatness of the dibenzoxepin ring system. Sedative activity was found in some of the compounds.

Triarylethylenes of general structures I and II have



I

III, R^1 = Et; R^2 = Me; R^3 = H
IV, R^1 = Cl; R^2 = Et; R^3 = H
VII, R^1 = Et; R^2 = Me; R^3 = OH

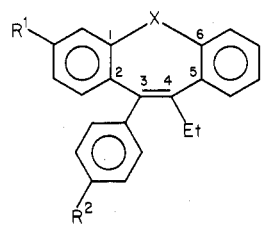


II, n = 1, 2
V, n = 2; R^2 = c-NC_4H_8

antiestrogenic activity.[1] The citrate salt of one of these compounds, tamoxifen ("Nolvadex", a trade mark of Imperial Chemical Industries PLC), III, has been shown to be a useful agent in the treatment of human breast cancer.[2] We were interested in the structure–activity relationships of these compounds and especially in their stereochemical aspects.

An X-ray study of III shows that the aromatic rings are twisted out of the plane of the olefinic double bond with the dihedral angle between the plane of each aromatic ring and that of the double bond being approximately 54°. The upper edge of each aromatic ring in III is shown by a thickened bond. There is a good correlation between the X-ray determinations of III and of the related antiestrogens clomiphene (IV) and nafoxidine (V).[3]

We have investigated the effect on antiestrogenic activity of linking two of the aromatic rings of a triarylethylene with a bridging group, X, to give tricyclic triarylethylenes of general structure VI. By changing the size of the bridging group, the dihedral angle between the planes of the two aromatic rings within the tricycle and that of the double bond can be altered systematically. We chose bridging groups with X = O, S, CH_2CH_2, and SCH_2.



VI, R^1 = $OCH_2CH_2N(CH_3)_2$, $OCH_2CH{=}CH_2$, $OCH_2CH(OH)CH_2OH$; R^2 = H, OH

X	dihedral angle (1, 2, 3, 4 and 6, 5, 4, 3)
O	35°
S	50°
CH_2CH_2	70°
SCH_2	75°

An estimate of these dihedral angles was obtained from Dreiding molecular models. The aromatic rings within the tricycles will of course be inclined toward one another, unlike the situation in III. Compounds with both the usual basic side chain and with nonbasic side chains have been investigated, as the glyceryl side chain is known to confer antiestrogenicity on triarylethylenes.[4]

If the shape of the compound dominates its binding to the estrogen receptor, and problems of compound distribution, pharmacokinetics, or metabolism are of secondary importance, then information about the specificity of the receptor will be obtained from these compounds.

Chemistry. The target compounds were prepared by the general route shown in Scheme I. The deoxybenzoins **2a,b,d** were prepared by reaction of the parent compounds **1a,b,d** with base and ethyl iodide. The CH_2CH_2 compound, **2c**, was prepared from the phenylacetic acid, **12c**, by alkylation prior to cyclization, as shown in Scheme II.

The methyl ethers, **2a–d**, were cleaved with pyridine hydrochloride to the phenols, **3a–d**, which were alkylated with either 2-(dimethylamino)ethyl chloride or allyl bromide to give the ethers **4a–d** and **5a–d**, respectively. These compounds were then treated with phenyllithium and the tetrahydropyranyl (THP) ether of 4-hydroxyphenyllithium to give carbinols, which were readily dehydrated with acid to give the tricyclic triarylethylenes **6a–d**, **7a–d**, **8a,c,d**, and **9a–d**. The allyl side chains reacted with osmium tetroxide, followed by hydrogen sulfide, to give the glyceryl derivatives **10a,c,d** and **11a–d**.

An alternative route to the sulfur-bridged compounds, **8b** and **10b**, was used whereby the triarylethylene, **14b**, was prepared prior to the introduction of the allyl and glyceryl side chains (Scheme III). The close analogue **16b** was

(1) C. B. Lunan and A. Klopper, *Clin. Endocrinol.*, 4, 551 (1975); B. S. Katzenellenbogen, *Prog. Cancer Res. Ther.*, 10, 135 (1978); V. C. Jordan, C. J. Dix, K. E. Naylor, G. Prestwich, and L. Rowsby, *J. Toxicol. Environ. Health*, 4, 363 (1979).
(2) H. Mourisden, T. Palshof, J. Patterson, and L. Battersby, *Cancer Treat. Rev*, 5, 131 (1978); G. Leclercq and J. C. Heuson, *Biochim. Biophys. Acta*, **560**, 427 (1979).
(3) D. Smith, P. J. Taylor, and J. A. J. Jarvis, ICI Pharmaceuticals, unpublished results; N. Camerman, L. Y. Y. Chan, and A. Camerman, *J. Med. Chem.*, **23**, 941 (1980); P. G. Precigoux, G. Courseille, S. Geoffre, and M. Hospital, *Acta Crystallogr., Sect. B*, **35**, 3070 (1979).
(4) D. Lednicer, S. C. Lyster, B. D. Aspergren, and G. D. Duncan, *J. Med. Chem*, 9, 172 (1966); D. Lednicer, D. E. Emmert, G. W. Duncan, and S. C. Lyster, *ibid.*, 10, 1051 (1967); D. Lednicer, D. E. Emmert, S. C. Lyster, and G. W. Duncan, *ibid.*, 12, 881 (1969).

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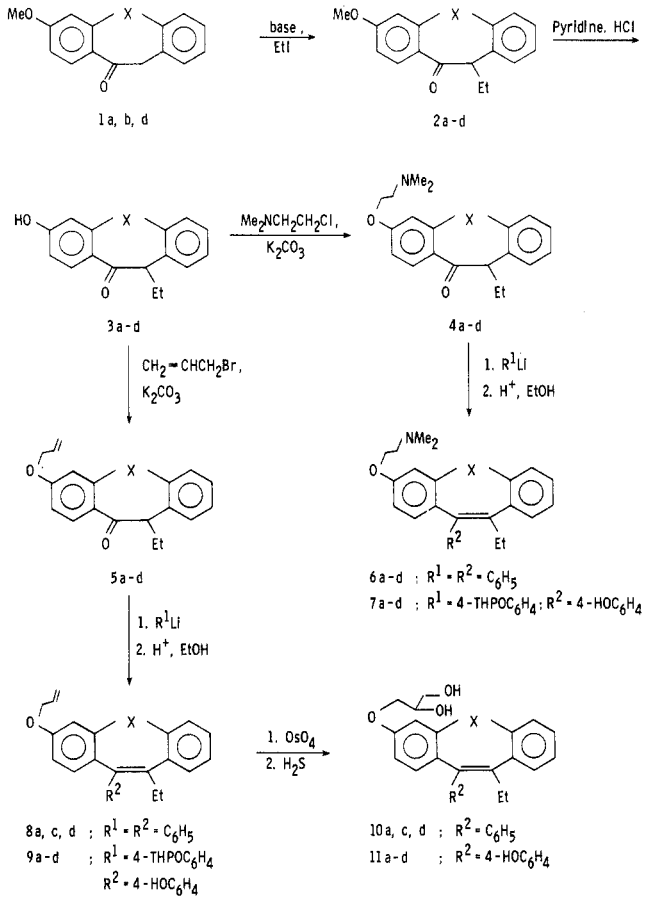
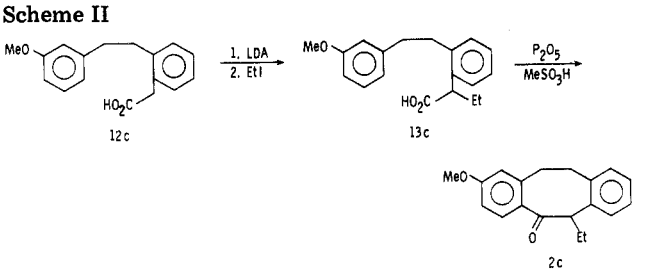
Scheme I[a]

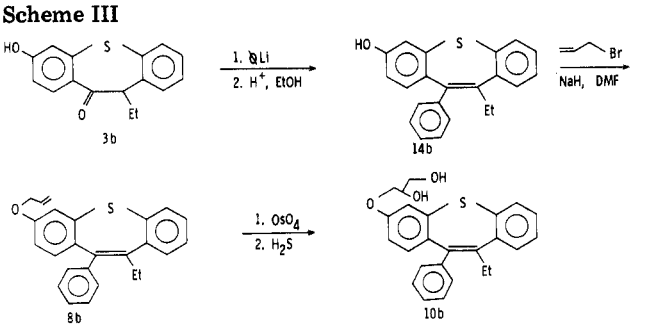


[a] For a, X = O; b, X = S; c, X = CH_2CH_2; d, X = SCH_2.

Scheme II



Scheme III

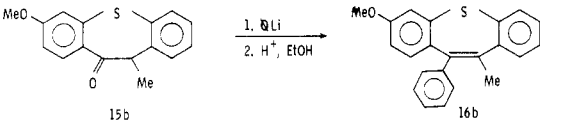


prepared from the deoxybenzoic **15b** (Scheme IV).

Properties of the target compounds are compiled in Table I.

Biological Activity. Antifertility Activity. Most of the compounds reported were initially screened for antifertility activity in a standard test in pregnant rats.[5] The

Scheme IV



minimum dose that prevented implantation was noted, and in some cases the dose that prevented implantation in two out of three rats was also noted. The results are shown in Table II. The most active compounds, **6d**, **7b**, and **7d**, are five times less potent than the triarylethylene drug III. The phenolic analogues are usually slightly more potent than the corresponding phenyl analogues: compare **7b** with **6b**. A comparison of the different side chains shows that the basic side-chain compounds are more potent than either the glyceryl or allyl side-chain compounds: compare **7d** with **11d** and **9d**. In general, the SCH_2-bridged compounds are equipotent with the S-bridged compounds: compare **6d** with **6b**, and compare **11d** and **11b**. In the basic side-chain series **6** and **7**, the O-bridged compounds, which have the smallest dihedral angle of 35°, are the least potent.

In Vitro Binding Studies. Mature rat uterine cytosol was used as a source of estrogen receptor. The binding of the compounds was measured relative to [^{3}H]estradiol (100%) in a competitive binding assay[6] carried out at 3 °C. The results are given in Table II. The antiestrogen, III, has a binding of 5.9% relative to estradiol. All the phenyl-substituted analogues, **6a–d**, **8a–d**, and **10a–d** show lower binding than III. The phenolic compounds bind much better. This was expected, since several literature studies[5,7,8] have shown a dramatic increase in binding when a phenolic group is introduced or unmasked by metabolism of an ether.

Compounds **7b–d** had the highest binding (50–63%, relative to estradiol), but this is less than the binding of the phenolic compound, VII (100% relative to estradiol). The lower binding of the tricyclic compounds implies a detrimental effect due either to the bridging group, X, or to the change in the direction of twist of one of the aromatic rings compared to the situation in III and VII.

A comparison of the different side chains in the phenols indicates that the basic side chain confers better binding than either the allyl or glyceryl side chains: thus, **7a** binds better than **9a** or **11a**, and **7c** binds better than **9c** or **11c**. The result of a comparison of the various bridging groups shows that phenols with an O bridging atom have poorer binding than phenols with the other bridging groups: thus, **7a**, **9a**, and **11a** have the lowest affinities of their groups **7a–c**, **9a–c**, and **11a–c**, respectively. Thus, once again the O-bridged compounds with the smallest dihedral angle are the least potent.

Recent studies[8] have shown that the binding of triarylethylenes to the estrogen receptor is temperature dependent. Compounds with phenolic rings, e.g., VII, show increased binding when the temperature is raised to 25 °C, while compounds lacking phenolic rings, e.g., III, show decreased binding on warming. It is probable that the

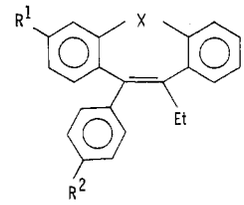
(5) M. J. K. Harper and A. L. Walpole, *J. Reprod. Fertil.*, **13**, 101 (1967); A. E. Wakeling and S. R. Slater, *Cancer Treat. Rep.*, **64**, 741 (1980).

(6) J. S. Major, ICI Pharmaceuticals Division, unpublished methodology based on S. G. Korenman, L. E. Perrin, and T. P. McCallum, *J. Clin. Endocrinol. Metab.*, **29**, 879 (1969).

(7) F. Capony and H. Rochefort, *Mol. Cell. Endocrinol.*, 11, 181 (1978); T. Tatee, K. E. Carlson, J. A. Katzenellenbogen, D. W. Robertson, and B. S. Katzenellenbogen, *J. Med. Chem.*, **22**, 1509 (1979).

(8) A. E. Wakeling and S. R. Slater, "Mechanisms of Steroid Action", G. P. Lewis, Ed., Macmillan Press, London and New York, 1981.

Table I. Tricyclic Triarylethylenes



compd[a]	X	R^1	R^2	mp, °C	recrystn solvent[b]	yield, %	formula	anal.
6a	O	$OCH_2CH_2N(CH_3)_2$	H	87-88	A	45	$C_{26}H_{27}NO_2$	C, H, N
6b	S	$OCH_2CH_2N(CH_3)_2$	H	154	B	80	$C_{26}H_{27}NOS$	C, H, N, S
6c	CH_2CH_2	$OCH_2CH_2N(CH_3)_2$	H	120-121	A	68	$C_{28}H_{31}NO \cdot 0.25H_2O$	C, H, N
6d	SCH_2	$OCH_2CH_2N(CH_3)_2$	H	oil		20	$C_{27}H_{29}NOS$	C, H, N, S
7a	O	$OCH_2CH_2N(CH_3)_2$	OH	213-214	B	38	$C_{26}H_{27}NO_3$	C, H, N
7b	S	$OCH_2CH_2N(CH_3)_2$	OH	110-112	C	43	$C_{26}H_{27}NO_2S \cdot 0.2EtOAc$	C, H, N, S
7c	CH_2CH_2	$OCH_2CH_2N(CH_3)_2$	OH	162-163	B	68	$C_{28}H_{31}NO_2$	C, H, N
7d	SCH_2	$OCH_2CH_2N(CH_3)_2$	OH	174-177	D	18	$C_{27}H_{29}NO_2S \cdot 0.25H_2O$	C, H, N
8a	O	$OCH_2CH=CH_2$	H	119-120	A	70	$C_{25}H_{22}O_2$	C, H
8b	S	$OCH_2CH=CH_2$	H	111-112	B	47	$C_{25}H_{22}OS$	C, H, S
8c	CH_2CH_2	$OCH_2CH=CH_2$	H	85-86	B	75	$C_{27}H_{26}O$	C, H
8d	SCH_2	$OCH_2CH=CH_2$	H	80-81	A	76	$C_{26}H_{24}OS$	C, H, S
9a	O	$OCH_2CH=CH_2$	OH	134-135	E	73	$C_{25}H_{22}O_3$	C, H
9b	S	$OCH_2CH=CH_2$	OH	201-203	E	62	$C_{25}H_{22}O_2S$	C, H, S
9c	CH_2CH_2	$OCH_2CH=CH_2$	OH	131-132	E	72	$C_{27}H_{26}O_2$	C, H
9d	SCH_2	$OCH_2CH=CH_2$	OH	141-143[c]		71	$C_{26}H_{24}O_2S \cdot 0.5H_2O$	C, H, S
10a	O	$OCH_2CH(OH)CH_2OH$	H	111-112	A	82	$C_{25}H_{24}O_4$	C, H
10b	S	$OCH_2CH(OH)CH_2OH$	H	174-177	F	58	$C_{25}H_{24}O_3S \cdot 0.5i\text{-PrOH}$	C, H, S
10c	CH_2CH_2	$OCH_2CH(OH)CH_2OH$	H	137-138	E	85	$C_{27}H_{28}O_3$	C, H
10d	SCH_2	$OCH_2CH(OH)CH_2OH$	H	52-60	(foam)	36	$C_{26}H_{26}O_3S \cdot 0.25H_2O$	C, H, S
11a	O	$OCH_2CH(OH)CH_2OH$	OH	146-148	A/D	83	$C_{25}H_{24}O_5 \cdot 0.25H_2O$	C, H
11b	S	$OCH_2CH(OH)CH_2OH$	OH	231-233	A	89	$C_{25}H_{24}O_4S$	C, H
11c	CH_2CH_2	$OCH_2CH(OH)CH_2OH$	OH	152-153	G	73	$C_{27}H_{28}O_4$	C, H
11d	SCH_2	$OCH_2CH(OH)CH_2OH$	OH	65-80	(foam)	77	$C_{26}H_{26}O_4S \cdot 0.5H_2O$	C, H, S
14b	S	OH	H	93-96	A/B	75	$C_{22}H_{18}OS \cdot 0.75H_2O$	C, H, S
16b[d]	S	OMe	H	129-130	A	75	$C_{22}H_{18}OS$	C, H, S

[a] All compounds gave IR and ^1H NMR spectra consistent with the assigned structures. [b] A = hexane; B = ethanol; C = ethyl acetate; D = ether; E = cyclohexane; F = isopropyl alcohol; G = toluene. [c] A pure oil which crystallized on standing. [d] This compound has a methyl substituent rather than the ethyl of the general formula.

compounds described here which fall into these two classes would behave similarly.

Uterotrophic and Antiuterotrophic Activity. These activities were determined in immature 21-day-old rats by measuring the uterine response to the compounds.[5,8] Antiestrogenic activity was shown by a significant antagonism of the effect of estradiol benzoate. Partial estrogenicity was shown by the effect of the compound dosed alone.

The compounds with basic side chains, **6a–d** and **7a–d**, and those with glyceryl side chains, **10a–d** and **11a–d**, all showed antiestrogenic activity with partial estrogenicity (Table II). Their biological profile in this test is like that of the triarylethylene drug III. The most potent compounds are the S-bridged compound **7b** and the CH_2CH_2-bridged compound **7c** (ca. one-half of the potency of III).

The basic side chain confers greater potency than the glyceryl side chain: compare **6a–d** with **10a–d**, and compare **7a–d** with **11a–d**. The allyl side chain did not confer antiestrogenicity on the compounds, more agonism being seen, especially in the phenols **9a–d**. A comparison of the phenol- and phenyl-substituted compounds shows a clear difference in potency: compare **7a–d** with **6a–d**, and compare **11a–d** with **10a–d**, where, with the exception of **10b** and **11b**, the more potent compounds are always phenolic. The two must potent compounds, **7b** and **7c**, are also phenolic.

A comparison of the various bridging groups give different results, depending on the side chain and aryl substituent. In the series of phenolic compounds with a basic side chain, **7a–d**, the S-, CH_2CH_2-, and SCH_2-bridged compounds, **7b–d**, are slightly more potent than the O-bridged compound **7a**. In the series of phenolic compounds with a glyceryl side chain, **11a–d**, all the bridging groups confer similar potencies. This is also true for the basic side-chain compounds with a phenyl substituent, **6a–d**. Thus, the uterotrophic test shows a smaller change in potency as the bridging group is changed than does the antifertility test.

Sedative Activity. Many tricyclic compounds with basic side chains are known to have antidepressant activity or sedative activity. The position of the basic side chain in the tricyclic antidepressants is very different from the position in compounds **6a–d** and **7a–d**. However, selected compounds were tested for sedative activity. The results are shown in Table II. The basic side-chain containing compounds, **6b** and **7a**, **7b**, and **7d**, were found to be quite potent sedatives, showing activity at 5–10 mg/kg, compared to chloropromazine, which is active at 1 mg/kg. Compounds **8b**, **10b**, **11a**, and **11d**, with nonbasic side chains, were then tested and also found to be active at 5 mg/kg. The parent phenolic tricycle, **14b**, without any side chain, was also active, indicating that the sedative activity resided in the tricyclic nucleus irrespective of the side chain.

Conclusion

A series of novel triarylethylene antiestrogens has been discovered in this study. A major aim of the study was the investigation of the effect on biological activity of the changing shape of the tricycle as the bridging group was

Table II. Biological Activities of Tricyclic Triarylethylenes

compd	antifertility act.: MFED,[a] mg/kg		estrogen receptor binding[c]	uterotrophic and antiuterotrophic act.[d] dose, mg/kg	% Ag:% antag	sedative act. dose,[e] mg/kg	% reduction in movement
6a	25	~10[b]	0.02	1	20:20		
				5	23:51		
				10	33:66		
6b	5	~1	0.12	0.5	17:26	1	49
				5	34:60	10	46
6c			0.22	10	36:57		
6d	0.5		1.1	1	23:25		
				5	27:50		
7a	10		6.1	1	22:38	5	70
				5	30:61		
				10	32:63		
7b	0.5		63	0.1	21:31	10	45
				0.5	18:55		
				1	25:58		
7c			50	0.1	27:37		
				0.5	32:59		
				1	38:58		
7d	0.5		52	0.5	10:20	5	61
				1	38:59		
8a	>25		0.1	25	53:34		
8b	>25		0.54	10	29:46	1	48
						5	76
8c			0.36	10	40:43		
8d	5		0.12	5	49:35		
9a	>25		0.21	25	58:40		
9b	5		5.2	10	72:19		
9c			15	10	43:20		
9d	25	~10	9.2	5	68:24		
10a	10		0.07	10	36:54		
10b		~25	0.65	10	29:61	1	33
				3.6	26:43	5	84
10c			0.12	10	23:31		
10d		5	0.02	5	21:35		
				10	24:27		
11a	25	10	0.92	10	34:53	5	61
11b	5		11	5	36:45		
11c			9.1	10	33:44		
11d	5		5.0	5	33:43	5	62
				10	34:53		
14b	>5		14			1	34
						5	60
						10	72
16b			0.005	25	67:17		
III	0.1		5.9	0.05	33:35		
				0.1	35:46		
				1	42:52		
chlorpromazine						1	73

[a] MFED = the minimum fully effective dose that prevented implantation of eggs in three out of three rats. [b] These doses prevented implantation in two out of three rats. [c] Various concentrations of test compound (10^{-3} to 10 μg/mL) were incubated with 10^{-9} M [^{3}H]estradiol and rat uterine cytosol for 16 h at 3 °C. Free ligands were removed by a brief treatment with dextran-coated charcoal. The affinity of the test compound relative to that of estradiol (100) was determined by comparison of the displacement of [^{3}H]estradiol by the compound relative to that observed with unlabeled estradiol. Relative affinities are reproducible within 20% between assays. [d] Compounds were dissolved in Tween 80 and dosed orally. % ag = $100 \times (T - C)/(E - C)$ where T = the average uterine weight obtained from the test compound; C = the average uterine weight of the control animals, = 56 ± 4 mg/100 g of body weight; E = the average uterine weight of animals dosed with estradiol benzoate (0.5 μg/rat daily subcutaneously for 3 days), = 255 ± 12 mg/100 g of body weight. % antag = $100 \times [E - (ET)]/[E - C]$ where ET = the average uterine weight of the animals dosed concomitantly with the test compound and estradiol benzoate (0.5 μg/rat daily). [e] Compounds dissolved in Tween 80 and dosed intraperitoneally.

changed. The in vitro binding data and antifertility tests showed that the oxygen-bridged series, the flatest of the tricycles investigated with a dihedral angle of approximately 35° between the plane of the double bond and that of the aromatic rings in the tricycle, had the lowest binding and poorest activity. The results of the uterotrophic tests, however, were less clear cut. Only in the basic side-chain series with phenolic substituents were the SCH_2-, CH_2CH_2-, and S-bridged compounds more potent than the O-bridged compound. For the glyceryl side-chain series with phenyl substituents and for the basic side-chain series with phenyl substituents, activity was similar for all the bridging groups. The most interesting compounds were in the basic side-chain series with phenolic substituents, where the most potent compounds, **7b** and **7c**, had good binding (~50% relative to estradiol) and good antiestrogenic activity (ca. one-half that of III).

As antiestrogens, the compounds disclosed here have the synthetic advantage of avoiding the geometric isomers which arise in the synthesis of acyclic triarylethylenes, but they have the disadvantage that they also possess sedative activity.

Experimental Section

Chemical Methods. General. Melting points were recorded on a Buchi melting point apparatus and were not corrected. NMR spectra were obtained in $CDCl_3$ with tetramethysilane as internal standard on a Varian EM 390 and a Bruker HX90E.

7-Methoxydibenz[*b*,*f*]oxepin-10(11*H*)-one (1a). Method A. A solution of 2-(3-methoxyphenoxy)benzoic acid[9] (73.2 g, 0.3 mol) in a mixture of ether (500 mL) and THF (100 mL) was slowly added to a stirred suspension of lithium aluminium hydride (22.8 g, 0.6 mol) in ether (400 mL) under an atmosphere of argon at room temperature. The mixture was stirred and heated to reflux for 4 h. After the mixture had cooled to room temperature, water was added dropwise to destroy residual reducing agent. The mixture was acidified with 5 N HCl, and an ether extract was taken, washed with water, dried ($MgSO_4$), and concentrated to give a light brown oil (67 g, 97%), identified as 2-(3-methoxyphenoxy)benzyl alcohol (**17a**). Anal. ($C_{14}H_{14}O_3$) C, H.

A solution of the alcohol (66 g, 0.29 mol) in toluene (300 mL) was warmed to 80 °C, and thionyl chloride (42.8 g, 0.36 mol) was added over 20 min. The mixture was stirred at 80 °C for 1 h. The solvent and excess of thionyl chloride were removed to leave the crude product, 2-(3-methoxyphenoxy)benzyl chloride, as a brown oil (71 g). The chloride was dissolved in EtOH (400 mL), and a solution of potassium cyanide (28 g, 0.43 mol) in water (100 mL) was added. The mixture was heated to reflux with stirring for 12 h. The bulk of the EtOH was evaporated, and the residue was extracted with ether (1 L). The ether solution was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure to leave a brown oil (64 g, 93%), identified as 2-(3-methoxyphenoxy)phenylacetonitrile (**18a**). Anal. ($C_{15}H_{13}NO_2$) C, H, N.

The nitrile was dissolved in EtOH (300 mL), and a solution of potassium hydroxide (36 g, 0.64 mol) in water (100 mL) was added. The mixture was heated to reflux with stirring for 3 h. Most of the EtOH was removed under reduced pressure, and the residue was washed with ether. The aqueous solution was acidified with 5 N HCl, and the oily product was taken into ether and dried ($MgSO_4$). Removal of the solvent left an oil, which crystallized from hexane. The solid was recrystallized from cyclohexane to give 2-(3-methoxyphenoxy)phenylacetic acid (**19a**; 51 g, 76%), mp 85–86 °C. Anal. ($C_{15}H_{14}O_4$) C, H.

Polyphosphoric acid was prepared by heating a stirred mixture of phosphorus pentoxide (70 g) and phosphoric acid (50 mL) at 150 °C for 1 h. The temperature was lowered to 100 °C, and a solution of the acid (44 g, 0.17 mol) in toluene (100 mL) was added. The mixture was heated to reflux with strong stirring for 4 h and then poured onto ice, and an ether extract was taken. The extract was washed with potassium carbonate solution, dried ($MgSO_4$), and concentrated under reduced pressure to leave a red oil, which crystallized from EtOH. The solid was recrystallized from EtOH to give **1a** (34 g, 83%), mp 102–103 °C. Anal. ($C_{15}H_{12}O_3$) C, H.

7-Methoxydibenzo[*b*,*f*]thiepin-10(11*H*)-one (**1b**) was prepared from 2-[(3-methoxyphenyl)thio]benzoic acid in 35% yield by method A as a crystalline solid, mp 129–132 °C (lit.[10] mp 131–132 °C).

2-[2-(3-Methoxyphenyl)ethyl]phenylacetic acid (**12c**) was prepared by method A from 2-[2-(3-methoxyphenyl)ethyl]benzoic acid[11] in 51% yield, mp 67–68 °C. Anal. ($C_{17}H_{18}O_3$) C, H.

2-[2-[2-(3-Methoxyphenyl)ethyl]phenyl]butyric acid (**13c**) was prepared by alkylation of **12c** by using a literature method.[12] A solution of butyllithium (0.564 mol) in hexane was added to a stirred solution of diisopropylamine (57 g, 0.564 mol) in THF (400 mL) at −70 °C under an atmosphere of argon. The mixture was allowed to warm to room temperature and stir for 15 min before cooling again to −70 °C. A solution of **12c** (38 g, 0.14 mol) in THF (100 mL) was slowly added, and the yellow solution was stirred at −70 °C for 1.5 h. A solution of ethyl iodide (44 g, 0.28 mol) in THF (100 mL) was then added, and the mixture was stirred and allowed to warm to room temperature. The solution was poured onto ice and acidified with 5 N HCl. An ether extract was taken, washed with water, dried ($MgSO_4$), and concentrated to leave an oil (40 g), which crystallized from hexane solution to give 36.4 g (87%) of **13c**, mp 72–73 °C. Anal. ($C_{19}H_{22}O_3$) C, H.

6-Ethyl-11,12-dihydro-2-methoxydibenzo[*a*,*e*]cycloocten-5-(6*H*)-one (**2c**) was prepared from **13c**. Phosphorus pentoxide (50 g) was added to methanesulfonic acid (500 mL), and the mixture was stirred at 50 °C for 1 h. The dehydrating reagent[13] was cooled to room temperature, and **13c** (32.8 g, 0.11 mol) was added portionwise. The reaction mixture was stirred at room temperature for 1 h and then poured into water (2 L), and an ether extract was taken, washed with a saturated solution of sodium bicarbonate, dried ($MgSO_4$), and concentrated to leave a brown oil (27 g). This was purified by chromatography on silica eluting with petrol (40–60 °C)/ether, 10:3, to give a solid, which was recrystallized from hexane to give **2c** (16.8 g, 55%), mp 76–77 °C. Anal. ($C_{19}H_{20}O_2$) C, H.

5-Hydro-8-methoxydibenzo[*b*,*f*]thiocin-11(12*H*)-one (**1d**) was prepared from 2-[[(3-methoxyphenyl)thio]methyl]benzoic acid[14] in 28% yield by method A, mp 109–110 °C (recrystallized from cyclohexane). Anal. ($C_{16}H_{14}O_2S$) C, H, S.

11-Ethyl-7-methoxydibenz[*b*,*f*]oxepin-10(11*H*)-one (2a). Method B. A solution of tetrabutylammonium hydrogen sulfate (45.8 g, 0.135 mol) and NaOH (10.8 g, 0.27 mol) in water (100 mL) was added to a solution of **1a** (32.4 g, 0.135 mol) and ethyl iodide (42.1 g, 0.27 mol) in methylene chloride (200 mL), and the mixture was stirred strongly for 0.5 h. The organic phase was washed with water, dried ($MgSO_4$), and concentrated to leave a brown oil from which tetrabutylammonium iodide (46 g) crystallized under ether. The filtrate was concentrated to leave an oil, which crystallized from hexane solution. The solid was recrystallized from ethanol to give 34 g (95%) of **2a**: mp 81–82 °C. Anal. ($C_{17}H_{16}O_3$) C, H.

11-Ethyl-7-methoxydibenzo[*b*,*f*]thiepin-10(11*H*)-one (2b). Method C. Sodium (1.1 g, 0.047 mol) was added to dry liquid ammonia (200 mL). A crystal of ferric nitrate was added to form a gray color of sodamide. The mixture was cooled to −70 °C, and a solution of **1b** (12 g, 0.047 mol) in THF (150 mL) was added. Ethyl iodide (7.3 g, 0.047 mol) was added, and the mixture was stirred at −30 °C for 1 h. Ammonium chloride (25 g) was slowly added, followed by water (200 mL). An ether extract was taken, washed with water, dried ($MgSO_4$), and evaporated to leave an oil (13 g), which was purified by chromatography on silica eluting with petrol (40–60 °C)/ether, 10:1. This gave an oil, which crystallized from hexane solution at −20 °C to give 7.5 g (57%) of **2b**, mp 76–78 °C. Anal. ($C_{17}H_{16}O_2S$) C, H, S.

7-Methoxy-11-methyldibenzo[*b*,*f*]thiepin-10(11*H*)-one (**15b**) was prepared from **1b** and methyl iodide in 62% yield by method B: mp 96–97 °C (recrystallized from hexane). Anal. ($C_{16}H_{14}O_2S$) C, H, S.

12-Ethyl-5-hydro-8-methoxydibenzo[*b*,*f*]thiocin-11(12*H*)-one (**2d**) was prepared from **1d** in 45% yield by method C: mp 123–126 °C. Anal. ($C_{18}H_{18}O_2S$) C, H, S.

11-Ethyl-7-hydroxydibenz[*b*,*f*]oxepin-10(11*H*)-one (3a). Method D. Concentrated HCl (89 mL, 1 mol) was added to stirred pyridine (79 g, 1 mol), and the mixture was gradually heated to distill off the water, leaving molten pyridine hydrochloride. This was cooled to 150 °C and **2a** (32.2 g, 0.12 mol) was added. The mixture was heated to reflux (210 °C) for 0.5 h. After cooling, the reaction mixture was partitioned between ether and water, and the organic solution was washed with water, dried ($MgSO_4$), and evaporated to leave an oil, which crystallized from toluene solution. Recrystallization from toluene gave 19.5 g (58%) of **3a**, mp 100–101 °C. Anal. ($C_{16}H_{14}O_3$) C, H.

11-Ethyl-7-hydroxydibenzo[*b*,*f*]thiepin-10(11*H*)-one (**3b**) was prepared in 82% yield from **2b** by method D, mp 199–200 °C (recrystallized from toluene). Anal. ($C_{16}H_{14}O_2S$) C, H, S.

6-Ethyl-11,12-dihydro-2-hydroxydibenzo[*a*,*e*]cycloocten-5-(6*H*)-one (**3c**) was prepared in 90% yield from **2c** by using method D, mp 155–156 °C (recrystallized from toluene). Anal. ($C_{19}H_{18}O_2$) C, H.

12-Ethyl-5-hydro-8-hydroxydibenzo[*b*,*f*]thiocin-11-one (**3d**) was prepared in 79% yield from **2d** by method D, mp 171–172 °C

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(recrystallized from cyclohexane/ethyl acetate). Anal. ($C_{17}H_{16}O_2S$) C, H, S.

7-[2-(Dimethylamino)ethoxy]-11-ethyldibenz[*b*,*f*]oxepin-10(11*H*)-one (4a). Method E. A mixture of **3a** (2.54 g, 0.01 mol), 2-(dimethylamino)ethyl chloride hydrochloride (2.88 g, 0.02 mol), and potassium carbonate (5.52 g, 0.04 mol) in acetone/DMF (1:1, 150 mL) was heated to reflux with stirring under argon for 18 h. The mixture was filtered, and the acetone was evaporated under reduced pressure from the filtrate. A 5 N HCl extract was taken and washed. The aqueous solution was basified with 10% NaOH, and an ether extract was taken, washed with water, dried ($MgSO_4$), and evaporated to leave 2.5 g of crude **4a**. The amine in acetone solution was converted to its oxalate salt, mp 149–151 °C. Anal. ($C_{20}H_{23}NO_3 \cdot C_2H_2O_4 \cdot 0.25H_2O$) C, H, N. The salt was reconverted with base to 2 g (60%) of pure **4a**.

7-[2-(Dimethylamino)ethoxy]-11-ethyldibenzo[*b*,*f*]thiepin-10-(11*H*)-one (**4b**) was prepared in 62% yield from **3b** by method E, oxalate salt mp 160–163 °C. Anal. ($C_{20}H_{23}NO_2S \cdot C_2H_2O_4$) C, H, N, S.

2-[2-(Dimethylamino)ethoxy]-6-ethyl-11,12-dihydrodibenzo-[*a*,*e*]cycloocten-5(6*H*)-one (**4c**) was prepared in 68% yield from **3c** by method E, mp 52–54 °C (recrystallized from hexane). Anal. ($C_{22}H_{27}NO_2$) C, H, N.

8-[2-(Dimethylamino)ethoxy]-12-ethyl-5-hydrodibenzo[*b*,*f*]-thiocin-11(12*H*)-one (**4d**) was prepared in 88% yield from **3d** by method E, oxalate salt mp 121–126 °C. Anal. ($C_{21}H_{25}NO_2S \cdot C_2H_2O_4 \cdot 0.75H_2O$) C, H, N, S.

7-(Allyloxy)-11-ethyldibenz[*b*,*f*]oxepin-10(11*H*)-one (5a). Method F. A mixture of **3a** (4.1 g 0.016 mol), potassium carbonate (3.3 g, 0.024 mol), and allyl bromide (2.42 g, 0.02 mol) in acetone (40 mL) was stirred and heated to reflux for 3 h. The mixture was filtered, and the solvent was evaporated from the filtrate to leave an oil, which crystallized from hexane to give 4.2 g (90%) of **5a**, mp 70–71 °C. Anal. ($C_{19}H_{18}O_3$) C, H.

7-(Allyloxy)-11-ethyldibenzo[*b*,*f*]thiepin-10(11*H*)-one (5b). Method G. Compound **3b** (3.6 g, 0.013 mol) was dissolved in DMF (40 mL), and NaH (0.6 g of a 65% dispersion in oil, 0.017 mol) was added. After 15 min when the evolution of hydrogen had ceased, allyl bromide (2.1 g, 0.017 mol) was added, and the solution was stirred under argon for 30 min. Water was added, and an ether extract was taken, washed with water, dried ($MgSO_4$), and evaporated to leave an oil, which was purified by chromatography on silica, eluting with petrol (40–60 °C)/ether, 10:2, to give from hexane solution 3.0 g (73%) of **5b** as a crystalline solid: mp 72–74 °C. Anal. ($C_{19}H_{18}O_2S$) C, H, S.

2-(Allyloxy)-6-ethyl-11,12-dihydrodibenzo[*a*,*e*]cycloocten-5-(6*H*)-one (**5c**) was prepared in 93% yield from **3c** by method F, mp 76–77 °C (recrystallized from hexane). Anal. ($C_{21}H_{22}O_2$) C, H.

8-(Allyloxy)-12-ethyl-5-hydrodibenzo[*b*,*f*]thiocin-11(12*H*)-one (**5d**) was prepared in 83% yield from **3d** by method G, mp 60–63 °C (recrystallized from hexane). Anal. ($C_{20}H_{20}O_2S$) C, H, S.

3-[2-(Dimethylamino)ethoxy]-10-ethyl-11-phenyldibenz-[*b*,*f*]oxepin (6a). Method H. Butyllithium (1.9 mL of 1.6 M, 3 mmol) was added to a stirred solution of bromobenzene (0.47 g, 3 mmol) in THF (10 mL) at −70 °C under argon. After 1 h, a solution of **4a** (0.81 g, 2.5 mmol) in THF (5 mL) was added, and the mixture was allowed to warm to room temperature and stirred for 18 h. Water was added, and an ether extract was taken, washed with water, dried ($MgSO_4$), and concentrated to leave the carbinol as a yellow oil (0.68 g, 67%). This was dissolved in EtOH (25 mL), concentrated HCl (1 mL) was added, and the solution was heated to reflux for 1 h. The bulk of the solvent was removed under reduced pressure, and the residue was basified with dilute ammonium hydroxide solution. An ether extract was taken, washed with water, dried ($MgSO_4$), and evaporated to leave a yellow oil, which crystallized from hexane solution to give 0.44 g (68%) of **6a**, mp 87–88 °C. Anal. ($C_{26}H_{27}NO_2$) C, H, N. The properties of **6b–d**, prepared by this method, are given in Table I.

3-Methoxy-10-methyl-11-phenyldibenzo[*b*,*f*]thiepin (**16b**) was prepared in 75% yield from **15b** by method H. Its properties are included in Table I.

3-[2-(Dimethylamino)ethoxy]-10-ethyl-11-(4-hydroxyphenyl)-dibenz[*b*,*f*]oxepin (**7a**) was prepared in 38% yield from **4a** and the THP ether of 4-bromophenol by method H. Its properties and those of **7b–d**, also prepared by this method, are included in Table I.

3-(Allyloxy)-10-ethyl-11-phenyldibenz[*b*,*f*]oxepin (**8a**) was prepared in 70% yield from **5a** by method H. Its properties and those of **8c** and **8d**, also prepared by this method, are included in Table I.

3-(Allyloxy)-10-ethyl-11-phenyldibenzo[*b*,*f*]thiepin (**8b**) was prepared in 47% yield from **3b** by a slight variation of method H, taking 2.5 equiv of phenyllithium, to furnish **14b**, followed by alkylation by method G. The properties of **8b** and **14b** are included in Table I.

3-(Allyloxy)-10-ethyl-11-(4-hydroxyphenyl)dibenzo[*b*,*f*]oxepin (**9a**) was prepared in 73% yield from **5a** and the THP ether of 4-bromophenol by method H. Its properties and those of **9b–d** also prepared by this method are included in Table I.

3-(2,3-Dihydroxypropoxy)-10-ethyl-11-phenyldibenz[*b*,*f*]oxepin (10a). Method I. A solution of **8a** (0.4 g, 1.1 mmol) in THF (5 mL) was added to a stirred solution of osmium tetroxide (0.3 g, 1.2 mmol) in THF (10 mL) under argon. The mixture was stirred at room temperature for 18 h. Hydrogen sulfide gas was passed into the mixture to cleave the osmate ester, and the resulting mixture was filtered. The filtrate was evaporated to leave a foam, which was dissolved in ether and treated with hexane to deposit 0.36 g (82%) of crystalline **10a**. Its properties and those of **10b–d** also prepared by this method are included in Table I. Similarly, treatment of **9a–d** by this method gave **11a–d**.

Biological Methods. Antifertility Activity. The compounds were screened in a standard test in pregnant rats.[5] A single dose of each compound was given orally on day 4 of pregnancy to three rats, and on the morning of day 5, the uteri were examined for the presence of any implanted eggs. The minimum dose that prevented implantation was noted.

Binding Studies. Mature rat uterine cytosol was used as a source of estrogen receptor. In a competitive binding assay,[6] various concentrations of the test compound (10^{-3} to 10 μg/mL) were incubated with 10^{-9} M [^{3}H]estradiol and rat uterine cytosol for 16 h at 3 °C. Free ligands were removed by a brief treatment with dextran-coated charcoal. The affinity of the test compound relative to that of estradiol (100) was determined by comparison of the displacement of [^{3}H]estradiol by the compound relative to that observed with unlabelled estradiol. Relative affinities are reproducible with 20% between assays.

Uterotrophic and Antiuterotrophic Activity. The uterine response in 21-day-old immature rats to the compounds was used to measure these activities.[5,8] Compounds were dissolved in Tween 80, and each compound was dosed orally to the animals (five per group) daily for 3 days with and without the concomitant dosing of estradiol benzoate (0.5 μg/rat daily subcutaneously). The effect on uterine weight was measured on the 4th day. Antiestrogenic activity and partial estrogenicity were calculated as described in footnote *d* of Table II.

Sedative Activity. The test compound was dissolved in Tween 80 and dosed intraperitoneally to female mice (four groups with five mice per group), and their horizontal movement around an "animex" type activity cage was monitored once every 10 min for 1.5 h. This was compared with the activity of the control animals (four groups with five mice per group).

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Registry No. **1a**, 85850-97-1; **1b**, 51723-75-2; **1d**, 85851-05-4; **2a**, 85851-06-5; **2b**, 85851-07-6; **2c**, 85851-04-3; **2d**, 85851-08-7; **3a**, 85851-09-8; **3b**, 85851-10-1; **3c**, 85851-11-2; **3d**, 85851-12-3; **4a**, 85851-13-4; **4a** oxalate, 85851-14-5; **4b**, 85851-22-5; **4b** oxalate, 85864-56-8; **4c**, 85851-15-6; **4d**, 85851-16-7; **4d** oxalate, 85851-17-8; **5a**, 85851-18-9; **5b**, 85851-19-0; **5c**, 85851-20-3; **5d**, 85851-21-4; **6a**, 85850-76-6; **6b**, 85850-77-7; **6c**, 85850-78-8; **6d**, 85850-79-9; **7a**, 85850-80-2; **7b**, 85850-74-4; **7c**, 85850-75-5; **7d**, 85850-81-3; **8a**, 83807-07-2; **8b**, 85850-82-4; **8c**, 85850-83-5; **8d**, 85850-84-6; **9a**, 85850-85-7; **9b**, 85850-86-8; **9c**, 85850-87-9; **9d**, 85850-88-0; **10a**, 85850-89-1; **10b**, 85850-90-4; **10c**, 85850-91-5; **10d**, 85850-92-6; **11a**, 85850-93-7; **11b**, 85850-94-8; **11c**, 85850-95-9; **11d**, 85864-54-6; **12c**, 85851-02-1; **13c**, 85851-03-2; **14b**, 85850-96-0; **15b**, 85864-55-7; **16b**, 83807-06-1; **17a**, 85850-98-2; **18a**, 85851-00-9; **19a**, 85851-01-0;

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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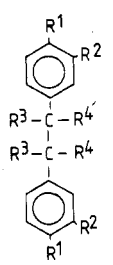
The syntheses of symmetrically 3,3′- and 2,2′-disubstituted meso hexestrol derivatives are described [3,3′-substituents: OH (1), F (2), Cl (3), Br (4), I (5), $CH_2N(CH_3)_2$ (6), CH_3 (7), CH_2OCH_3 (8), $CH_2OC_2H_5$ (9), CH_2OH (10), NO_2 (11), NH_2 (12), $N(CH_3)_2$ (13), $COCH_3$ (14), and C_2H_5 (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, $R^1 = OH$; $R^2, R^3 = H$; $R^4 = C_2H_5$

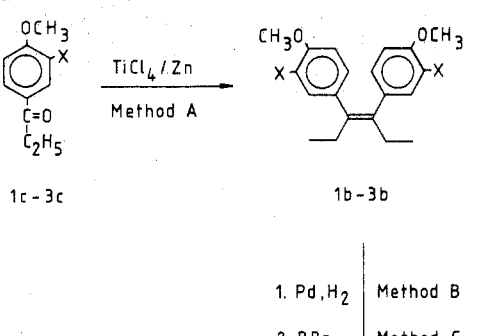
A1, $R^1, R^3 = H$; $R^2 = OH$; $R^4 = C_2H_5$

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-

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