were performed in vacuo at 30 °C. TLC was performed on glass plates coated with a 0.25-mm layer of silica gel PF-254 (Brinkman) and on polygrams silG UV 254 plates (Brinkman), and descending paper chromatography was carried out on Whatman No. 3MM paper using the following solvent systems: (A) *i*-PrOH–H_2O–concentrated NH_4OH (7:2:1) and (B) EtOH–0.5 M NH_4OAc, pH 7.5 (5:2). Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Where analyses are reported only by the element symbols, results were within ±0.4% of the theoretical values.

5′-(11-Deoxycorticosterone-21-phosphoryl)-1-(β-D-arabinofuranosyl)cytosine (5a). Method A. By Condensation. Ac_3-*ara*-CMP (**3**), prepared by acetylation of 1.62 g (5 mmol) of *ara*-CMP with Ac_2O (30 mL) and pyridine (60 mL) as reported previously,[3,4] was stirred with 3.31 g (10 mmol) of 11-deoxycorticosterone and 4.12 g (20 mmol) of DCC in 250 mL of anhydrous pyridine at room temperature for 2 days. Water (10 mL) was then added and the suspension was stirred at room temperature overnight. After evaporating to dryness, the residue was coevaporated with toluene (10 mL) to remove the residual pyridine and treated with 100 mL of 50% EtOH. The insoluble urea was removed by filtration and the filtrate was evaporated to dryness. The residue was stirred in 200 mL of 2 N NH_3–MeOH at room temperature overnight, followed by evaporating to dryness. The residue was then dissolved in 50 mL of 50% EtOH, and the solution was applied to a DE-52 (acetate) column (300 g, 5.5 × 30 cm) prepacked in 50% EtOH. The column was then eluted by a linear gradient of HOAc in 50% EtOH (0 to 2.0 N, 2 L each). The product was eluted out between 1500 and 2200 mL, and the combined eluate was evaporated to dryness. The residue was then treated with Me_2CO. The resulting white solid was filtered and washed with Me_2CO, yielding 1.153 g (36.3%). The analytical sample (as the NH_4 salt) was prepared by passing the product (100 mg) through a cellulose column (30 g, 2.5 × 23 cm) with solvent A as described previously:[10] mp 215–225 °C (slowly dec); TLC R_f (A) 0.58, R_f (B) 0.80; IR (KBr) 3360 (NH_2) 3200, 2930, 1710 (C=O), 1640, 1610 (C=O, C=C, C=N), 1490, 1220 (P=O), 1055 cm^{-1} (POC). *ara*-CMP was recovered (40%) in the subsequent fractions. Table I lists the conjugates prepared in an analogous manner.

Method B. By Direct Route. To a cooled mixture (−10 °C) of 0.973 g (4 mmol) of dried *ara*-C and 25 mL of redistilled $(MeO)_3PO$ was added 0.7 mL (ca. 7.42 mmol) of $POCl_3$. The mixture was stirred at 0–5 °C for 3 h, and then 2.644 g (8 mmol) of dried 11-deoxycorticosterone was added to the clear reaction mixture. The mixture was stirred at 0–5 °C for 5 days, and the clear solution was poured slowly into ice–water (100 mL) containing $NaHCO_3$ (1 g). The resulting suspension was mixed with 95% EtOH to get a 50% EtOH solution, and the insoluble solid was removed by filtration. The filtrate was then neutralized to pH 7.0 with 1 N NaOH and applied to a DE-52 (acetate) column (300 g, 5.5 × 30 cm) prepacked in 50% EtOH. The product was separated out with a linear gradient of AcOH in 50% EtOH (0 to 2.0 N, 2 L each) as described above, yielding 533 mg (21%). The analytical sample (as the NH_4 salt) was prepared as described previously:[10] mp 215–225 °C (slowly dec); TLC R_f (A) 0.58, R_f (B) 0.80; IR (KBr) 3380 (NH_2), 3200, 2940, 1720 (C=O), 1650, 1610 (C=O, C=C, C=N), 1490, 1210 (P=O), 1070 cm^{-1} (POC). Table I lists the conjugate prepared in an analogous manner.

Biochemical Studies. Growth-Inhibiting Assays in Cultured Cells. Compounds shown in Table II were screened for in vitro growth-inhibiting activity against L1210 lymphoid leukemia in culture using the methodology described previously.[3,4,6] In some instances, the conjugate was preincubated in the medium at 37 °C for various lengths of time, and the assays were performed as described previously.

Antitumor Activity in Vivo. Compounds shown in Table III were screened for in vivo antitumor activity against the ascites cell form of L1210 lymphoid leukemia grown in $C_3D_2F_1$/J female mice (C_3H/HEJ female × DBA/2J male mice, supplied by Jackson Labs) using the methodology described previously.[3,4,7] The mice in groups of six to eight (average weight 25 g) were inoculated ip with 1 × 10^6 cells of L1210 from donor mice (DBA/2Ha, supplied by Roswell Park Memorial Institute) bearing 3–5 day old tumor cells. Compounds were dissolved first in 0.154 N NaOH and then the solutions were neutralized with 0.154 N HCl (final 0.9% NaCl solution). The dose (0.5 mL) was administered ip daily for 5 consecutive days beginning 24 h after tumor implantation. Antitumor activity was evaluated by the comparison of the median survival time of the treated animals (T) to that of the control animals (C), i.e., the percentage increase in life span (ILS), (T/C − 1) × 100 (%).

Enzymatic Hydrolysis. Enzymatic cleavage of the phosphodiester bond of the conjugates was studied by incubating the compounds (5 μmol) with phosphodiesterase I (EC 3.1.4.1), 5′-nucleotidase (EC 3.1.3.5), acid phosphatase (EC 3.1.3.2), alkaline phosphatase (EC 3.1.3.1), and mouse and human plasmas in appropriate buffer (final volume 1.0 mL) as described previously.[4] Aliquots (0.1 mL) of the incubation mixtures at various lengths of time were streaked on Whatman No. 3 MM paper (23 × 57 cm) or on TLC plates (0.05 × 10 × 20 cm) with authentic markers, followed by developing in solvent A. Each band was eluted with 50% EtOH and quantitated by UV.

Acknowledgment. This investigation was supported, in part, by American Cancer Society Grant RD-76, National Institute of Health Institutional Biomedical Research Support Grant RR-05648-13, and contributions from the Alison Zach Memorial Fund. The technical assistance of Ms. M. T. Hope and J. Huang and Mr. P. Kim, participants of the Summer Research Program for students, is also acknowledged.

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N,N′-Dialkylbis(dichlorophenyl)ethylenediamines and -imidazolidines: Relationship between Structure and Estradiol Receptor Affinity

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Received May 23, 1980

Diastereomeric *N,N′*-dialkylbis(dichlorophenyl)ethylenediamines (**2**) and the corresponding imidazolidines (**3**) with chlorine in the 2,4, 2,6, 3,4, and 3,5 positions were synthesized. Only the stereoisomers of the 2,6-dichloro-substituted compounds exhibit for N-CH_3 (**2e**, **3e**), N-C_2H_5 (**2f**, **3f**), and N-C_3H_7 (**2g**, **3g**) an affinity to the estradiol receptor (K_a values ranging from 9.1 × 10^4 to 9.1 × 10^6), because the nitrogen atoms are shielded by the ortho-located chlorine atoms; therefore, a binding interaction with hydrophobic receptor areas is possible. These substances show weak uterotrophic activity and no significant effect on the growth of the DMBA-induced hormone-dependent mammary adenocarcinoma of the rat.

Structural modification of the synthetic estrogen hexestrol (**1**) by variation of the hydroxy position[1,2] and the length (C_4–C_{10})[3] and ramification of the alkyl chain[4] yields antiestrogens, which show a marked inhibition on the

0022-2623/80/1823-1347$01.00/0

Table I. *N,N'*-Dialkyl-1,2-bis(dichlorophenyl)ethylenediamines Dihydrochlorides (2·2HCl)

compd	position of Cl_2	R	mp, °C (recrystn solvent)[a] meso	mp, °C (recrystn solvent)[a] *d,l*	formula[b]	K_a[c,d] meso	K_a[c,d] *d,l*
2a	2,4	CH_3	185-186 (A)	250-254 (A)	$C_{16}H_{16}Cl_4N_2 \cdot 2HCl$	*e*	*e*
2b	2,4	C_2H_5	150-155 (A)	193-195 (A)	$C_{18}H_{20}Cl_4N_2 \cdot 2HCl$	*e*	*e*
2c	2,4	C_3H_7	170-175 (A)	128-132 (B)	$C_{20}H_{24}Cl_4N_2 \cdot 2HCl$	*e*	*e*
2d	2,4	C_4H_9	144-156 (B)	115-132 (B)	$C_{22}H_{28}Cl_4N_2 \cdot 2HCl$	*e*	*e*
2e	2,6	CH_3	215-220 (A)	260-263 (A)	$C_{16}H_{16}Cl_4N_2 \cdot 2HCl$	9.1×10^4	1.4×10^5
2f	2,6	C_2H_5	195-200 (B)	230-232 (B)	$C_{18}H_{20}Cl_4N_2 \cdot 2HCl$	6.7×10^5	1.3×10^5
2g	2,6	C_3H_7	172-180 (A)	215-221 (B)	$C_{20}H_{24}Cl_4N_2 \cdot 2HCl$	2.3×10^6	8.3×10^5
2h	2,6	C_4H_9	168-174 (A)	210-218 (C)	$C_{22}H_{28}Cl_4N_2 \cdot 2HCl$	*e*	*e*
2i	3,4	C_2H_5	235-237 (D)	170-175 (D)	$C_{18}H_{20}Cl_4N_2 \cdot 2HCl$	*e*	*e*
2k	3,4	C_4H_9	212-220 (A)	185-197 (A)	$C_{22}H_{28}Cl_4N_2 \cdot 2HCl$	*e*	*e*
21	3,5	C_2H_5	246-248 (D)	200-205 (D)	$C_{18}H_{20}Cl_4N_2 \cdot 2HCl$	*e*	*e*

[a] A = MeOH, B = MeOH/Et_2O, C = $CHCl_3$, D = EtOH, E = *i*-PrOH, F = MeCN. [b] All compounds, except *cis*-**3b**, were analyzed for C and H within ±0.40% of the calculated values. [c] Association constant of inhibitor receptor complex, determined by Lineweaver-Burk plot. [d] K_a of hexestrol, 8.3×10^8. [e] Inhibition less than 10% at a ratio of [^{3}H]estradiol/substance of 10^{-4}.

Table II. 1,3-Dialkyl-4,5-bis(dichlorophenyl)imidazolidines (3)

compd	position of Cl_2	R	mp, °C (recrystn solvent)[a] cis	mp, °C (recrystn solvent)[a] trans	formula[b]	K_a[c] cis	K_a[c] trans
3b	2,4	C_2H_5	oil	97-99 (E)	$C_{19}H_{20}Cl_4N_2$	*e*	*e*
3e	2,6	CH_3	121-123 (E)	133-134 (A)	$C_{17}H_{16}Cl_4N_2$	1.8×10^5	4.8×10^5
3f	2,6	C_2H_5	65-67 (A)	98-101 (A)	$C_{19}H_{20}Cl_4N_2$	2.0×10^5	9.1×10^6
3g	2,6	C_3H_7	oil	92-95 (D)	$C_{21}H_{24}Cl_4N_2$	3.2×10^5	1.6×10^6
3h	2,6	C_4H_9	74-75 (A)	55-57 (A)	$C_{22}H_{28}Cl_4N_2$	*e*	*e*
3i	3,4	C_2H_5	oil	oil	$C_{19}H_{20}Cl_4N_2$	*e*	*e*
3l	3,5	C_2H_5	97-99 (F)	85-86 (F)	$C_{19}H_{20}Cl_4N_2$	*e*	*e*

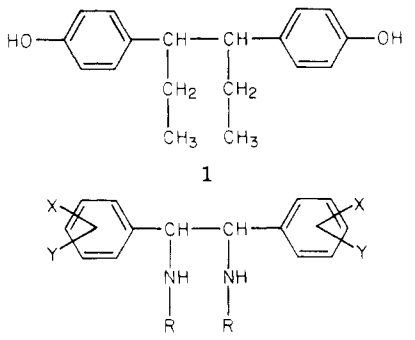
[a-e] See corresponding footnotes in Table I.

DMBA-induced hormone-dependent mammary adenocarcinoma of the Sprague–Dawley rat. Similar pharmacological results were obtained by analogous variations of the silbestrol structure.[5]

Substitution of the methylene groups of 1 by isosteric imine groups leads to inactive 1,2-bis(4-hydroxyphenyl)-*N,N'*-dimethylethylenediamines (**2**, R = CH_3; X = 4-OH; Y = H), from which antagonists of the [^{3}H]estradiol ([^{3}H]E2) receptor interaction (in vitro) are developed by elongation of the *N*-alkyl chains (Scheme I).[6] Not only these ethylenediamines but also ethylenediamines with other or without substituents on the phenyl ring exhibit a moderate inhibition on the DMBA-induced hormone-dependent mammary adenocarcinoma of the SD rat.[1]

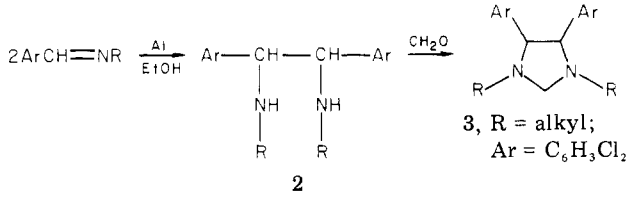
Our preliminary studies of hexestrol and stilbestrol derivatives[5] have shown a good correlation between E2-receptor affinity in vitro and antitumor effect in vivo; so we tried to increase the receptor affinity by a rise of the lipophilic character of the 1,2-diphenylethylenediamines by ring halogenation (enhancement of the hydrophobic interaction between substance and the E2 receptor). In the case of the *N,N'*-dialkyl-1,2-bis(hydroxyphenyl)-ethylenediamines (**2**, X = OH; Y = H), the introduction of one chlorine atom into each ring led to a noticeable improvement of their affinity to the E2 receptor.[6] This

Scheme I



2, R = alkyl; X = H, Cl, OH; Y = H, Cl

Scheme II



3, R = alkyl; Ar = $C_6H_3Cl_2$

effect could be increased considerably by two more chlorine atoms. A similar trend was observed at the unsubstituted *N,N'*-dialkyl-1,2-diphenylethylenediamines.

Chemistry. The isomeric *N,N'*-dialkyl-1,2-bis(dichlorophenyl)ethylenediamines (**2**; Table I) were synthesized by reductive dimerization of the dichloro-substituted benzaldehyde alkylimines with activated aluminum.[7] The resulting mixtures of *meso*- and *d,l*-1,2-bis(dichlorophenyl)ethylenediamines and dichlorobenzyl-

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amines were separated by fractionated crystallization of the hydrochlorides.

We related the meso structure to the diastereomers with the larger paramagnetic shift of the α-hydrogen atoms in the ^{1}H NMR spectrum by converting these structures with formaldehyde to the imidazolidines, **3**, (Scheme II) and studying the NMR of the latter.[8] The cis-configurated imidazolidines, obtained from the *meso*-ethylenediamines, show a doublet for each for the two protons at C-2 with a coupling constant of 3.5 Hz; the imidazolidines with trans-located aryl groups exhibit one singlet for the CH_2 group.

Biological Properties. Of all the tested dichlorophenyl-substituted ethylenediamines (**2**) and imidazolidines (**3**), only the 2,6-dichlorophenyl compounds up to a *N*-alkyl chain length of three carbons (**2e–g** and **3e–g**) were able to inhibit the interaction of [^{3}H]E2 with the receptor in vitro competitively, as the interpretation of the Lineweaver–Burk plot shows. In comparison to other synthetic estrogens, the results of our studies appear interesting in two respects: (1) Generally, a high affinity to the E2 receptor is associated with an oxygen function at the aromatic ring.[9] We achieved a lower but pronounced receptor affinity of compounds without aromatic hydroxy groups by introduction of chlorine in appropriate positions. (2) No appreciable differences of the association constants (K_a) were found with the corresponding diastereomeric ethylenediamines, as observed in the cases of stereoisomeric hexestroles and 1,2-bis(4-hydroxyphenyl)ethylenediamines, probably due to the lower affinity.[6] In the test for the reversibility of the inhibitor receptor bonding of **2g** ("hot chase experiment" with [^{3}H]E2), however, a slight preference of the meso compound is noticed (rise of the percentage of [^{3}H]E2 receptor complex after treatment of calf uteri cytosol, preincubated with **2g** (2×10^{-5} M) and [^{3}H]E2 (10^{-9} M) at 0 °C, with [^{3}H]E2 (10^{-9} M) at 25 °C: *d,l*-**2g**, 66 to 100%; *meso*-**2g**, 21 to 38%; control, 100%).

The imidazolidines **3e–g** show only a small preference for the trans form. If the *meso*-ethylenediamines are converted to the corresponding *cis*-4,5-diarylimidazolidines, a small decrease of receptor affinity is recognized (especially **2g** to **3g**); in contrast, the receptor affinity increases slightly on changing from *d,l*-ethylenediamines to *trans*-4,5-diarylimidazolidines (especially **2f** to **3f**). The small differences in the affinities of the stereoisomers are probably due to the lack of the two hydroxy groups, which seem to have an important share of the substance receptor bonding. Some influence of the *N*-alkyl chain length is noticed. Steric reasons can be assumed for the loss of receptor affinity in the case of the dibutyl compounds **2h** and **3h**.

Obviously the configurative effects play a less important role than the hydrophobic interaction with lipophilic receptor areas. Since the nitrogen atoms can act as a hydrogen-bridge acceptor for water, their shielding by ortho chlorine atoms (**2e–g**, **3e–g**) favors the affinity for the receptor. Any shifting of a chlorine atom away from the center of the molecule in the meta or para position (**2a–d**, **2i–l**, **3b**, **3i**, **3l**) inhibits a binding interaction with the receptor totally, because the shielding of the nitrogen atoms is reduced and hydrophilic areas of the drug are free for interaction with water. The diphenylethane skeleton seems to be essential, since 2,6-dichlorobenzylalkylamines do not show any E2-receptor affinity.

Table III. Uterotrophic Effect of **2f**, **2g**, **3f**, and **3g** in the Immature Mouse

compd	dose,[a] μg	effect[b]	compd	dose,[a] μg	effect[b]
meso-**2f**	0	12.8 ± 1.5	*cis*-**3f**	0	12.8 ± 1.5
	100	22.7 ± 5.3		100	17.1 ± 6.1
	500	23.5 ± 3.6		500	19.7 ± 2.6
	1000	27.4 ± 5.9			
	2500	35.6 ± 1.6		2500	22.3 ± 5.6
estrone	0.4	41.2 ± 5.5	estrone	0.4	41.2 ± 5.5
d,l-**2f**[c]			*trans*-**3f**	0	14.9 ± 2.0
				24	22.8 ± 2.3
				80	24.2 ± 1.8
				400	38.1 ± 11.9
				2400	46.2 ± 2.0
			estrone	0.4	45.8 ± 2.3
meso-**2g**	0	12.9 ± 2.2	*cis*-**3g**	0	12.8 ± 1.5
	20	14.8 ± 2.3		100	17.7 ± 2.3
	100	17.5 ± 4.4		500	16.2 ± 2.7
	500	22.6 ± 7.3		2500	19.7 ± 3.3
	2500	31.3 ±10.6		5000	24.5 ± 2.8
estrone	0.4	43.4 ± 5.6	estrone	0.4	41.2 ± 5.5
d,l-**2g**	0	12.9 ± 2.2	*trans*-**3g**	0	12.9 ± 2.2
	20	15.5 ± 4.1		20	19.6 ± 5.4
	100	19.6 ± 6.8		100	21.4 ± 5.0
	500	27.1 ± 7.6		500	28.0 ± 4.6
				2500	43.0 ± 4.5
estrone	0.4	43.4 ± 5.6	estrone	0.4	43.4 ± 5.6

[a] Dose per animal and day. [b] Uterus dry weight (mg)/body weight (g) × 100. [c] Not tested.

Surprisingly *meso*- and *d,l*-*N,N'*-dialkyl-1,2-bis(2,6-dichlorophenyl)ethylenediamines and their imidazolidines have estrogenic properties in spite of the lack of hydroxy groups, as the examples *meso*-**2f**, **2g**, **3f**, and **3g** show (Table III); they produce a stimulation of the uterine growth of immature mice according to their receptor affinity. The dose–effect plot corresponds to an "impeded estrogen"; the rather small association constants require a high dosage. In the antiuterotrophic test (100–2500 μg/day per animal), these compounds do not lead to an inhibition but to a further increase of the estrone-induced uterine growth.

Within the scope of biological tests, the effect of *meso*-**2g** on the established DMBA-induced hormone-dependent mammary adenocarcinoma of the SD rat was studied in a therapy experiment. No significant change of tumor growth was noticed even at high dosage (3×60 mg/kg ip per week, duration of therapy 4 weeks; change of tumor area +225%, control +340%). *meso*-**2e–g** and *d,l*-**2e–g** in a concentration of 10^{-4} M do not inhibit the incorporation of [^{3}H]thymidine, [^{3}H]uridine, and [^{3}H]leucine into DNA, RNA, and protein of Walker-256 carcinosarcoma cells in vitro.[2]

As a conclusion, it can be stated that it is possible to achieve a rather high receptor affinity of compounds which lack a hydroxy group solely by introduction of chlorine atoms into the appropriate positions, as it has been shown in a series of N-isosteric hexestrol derivatives. Because of the lower binding activity than the parent compound, these substances exhibit only small biological effects. These results could lead to an increase of the binding affinity of synthetic estrogens and antiestrogens simply by additional chlorine substitution.

Experimental Section

Melting points were determined on a Kofler hot stage or a Büchi melting point apparatus and are uncorrected. Elemental analyses were performed by the Mikroanalytisches Laboratorium at the University of Regensburg. ^{1}H NMR spectra were recorded with

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a Varian EM 360A spectrometer.

General Procedure for the Synthesis of Dichlorobenzaldehyde Alkylimines. While stirring and cooling in a water bath, the alkylamine (0.33 mol) was added slowly to a solution of the dichlorobenzaldehyde (0.30 mol) in a small volume of $CHCl_3$. After the solution stirred for 1 h at room temperature, the organic layer was separated and dried over $MgSO_4$. The solvent was removed and the residue was destilled in vacuo. The yields ranged from 65 to 95%.

General Procedure for the Synthesis of *N,N'*-Dialkyl-1,2-bis(dichlorophenyl)ethylenediamines (2). Spectral pure aluminum foil (21 g, 0.75 g-atom), cut in small pieces, was added to a solution of $HgCl_2$ (2.0 g) in EtOH (15 mL) and heated. When the gas evolution had started, a solution of dichlorobenzaldehyde alkylimine (0.25 mol) in toluene (250 mL) was added slowly under mechanical stirring. Finally, the mixture was kept for 4 h at 100 °C. HCl (6 N, 100 mL) was added; 30 min later, the solution was made alkaline by the addition of 6 N NaOH. The organic layer was separated and the aqueous solution was extracted several times with $CHCl_3$. After drying ($MgSO_4$), the solvent was removed under reduced pressure and the residue was dissolved in a small volume of MeOH. After filtration, the hydrochlorides were precipitated in fractions by addition of etheral HCl. Further separation and purification were achieved by factionated crystallization of the hydrochlorides from EtOH. The yields were 25–45% for the *d,l*-ethylenediamines, 15–30% for the *meso*-ethylenediamines, and 15–40% for the benzylamines. Melting points and recrystallization solvents of **2** are reported in Table I.

General Procedure for the Synthesis of *N,N'*-Dialkyl-4,5-bis(dichlorophenyl)imidazolidines (3). A solution of **2** (0.010 mol) and paraformaldehyde (0.015 mol) in benzene (25 mL) was refluxed for 7 h. The cold solution was filtered or decanted from a precipitate. After evaporation of the solvent, the residue was crystallized from EtOH. Compounds which resisted crystallization (*cis*-**3b**, *cis*-**3g**, and *cis*- and *trans*-**3i**) were chromatographed on alumina (activity I) with eluation by CH_2Cl_2/ligroin (1:1). The yields varied from 55 to 85%. For further data, see Table II.

Biological Methods. The applied methods (E2-receptor binding assay, Dorfman uterine weight test, and mammary tumor inhibition test) have been described in detail in a previous paper.[4] All diarylethylenediamines (**2**) and -imidazolidines (**3**) were tested for their affinity to the E2 receptor in concentrations ranging from 10^{-4} to 10^{-8} M. The association constants (K_a) for the inhibitor–receptor complexes were determined only for compounds which showed a strong affinity to the E2 receptor in preliminary tests (inhibition of the [^{3}H]E2 receptor interaction greater than 10% at a 10^4-fold excess of inhibitor; [^{3}H]E2 concentration 5×10^{-9} M). The reversibility test method has been described earlier.[5] *meso*-**2f** and the diastereomeric pairs of **2g**, **3f**, and **3g** (dissolved in arachis oil, application sc) were screened for their estrogenic[5,10] and antiestrogenic[5,11] properties by the Dorfman uterine weight test (Table III). *meso*-**2g** was tested as the hydrochloride in isotonic NaCl solution (application ip) for its effect on the DMBA-induced hormone-dependent mammary adenocarcinoma of the female Sprague–Dawley rat (Zentralinstitut für Versuchstierzucht, Hannover, Germany) according to published methods.[5]

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 R. Ringshandl and Ch. Steinberger is gratefully acknowledged.

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Synthesis, Biological Evaluation, and Preliminary Structure–Activity Considerations of a Series of Alkylphenols as Intravenous Anesthetic Agents

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Received October 3, 1979

Following our discovery of the intravenous (iv) anesthetic activity of 2,6-diethylphenol in mice, a series of alkylphenols was examined in this species and the most active analogues were further evaluated in rabbits. The synthesis of compounds which were not commercially available was accomplished by adaptations of standard ortho-alkylation procedures for phenols. Structure–activity relationships were found to be complex, but, in general, potency and kinetics appeared to be a function of both the lipophilic character and the degree of steric hindrance exerted by ortho substituents. The most interesting compounds were found in the 2,6-dialkyl series, and the greatest potency was associated with 2,6-di-*sec*-alkyl substitution. In particular, 2,6-diisopropylphenol (ICI 35868) emerged as a candidate for further development and has subsequently been shown to be an effective iv anesthetic agent in man.

The concept of total intravenous (iv) anesthesia has in recent years prompted attempts to improve on existing drugs, but alternative agents have not proved to be entirely satisfactory.[1] The use of the surfactant Cremophor EL for the formulation of compounds otherwise poorly soluble in water alone has enabled an examination of the anesthetic potential of numerous structural types with high lipophilic character which could not previously have been administered by the intravenous route. This paper describes the synthesis and biological evaluation of a series of alkyl-substituted phenols which resulted from the discovery of anesthetic activity in 2,6-diethylphenol (**8**) in mice, during the search for an agent which would demonstrate advantages over existing iv anesthetics.

Chemistry. Many of the phenols listed in Tables II–V were available either from commercial or ICI interdivisional sources and only required purification prior to biological evaluation. The remaining examples were synthesized by the introduction of alkyl groups into the ortho position of an appropriate phenol by the following methods (Schemes I–III).

Direct ortho alkylation of phenols by alkenes in the presence of the corresponding aluminum phenolate[2]

(1) B. Davies, *Adv. Drug. Res.*, **10**, 1 (1975).
(2) A. J. Kolka, J. P. Napolitano, A. H. Filbey, and G. G. Ecke, *J. Org. Chem.*, **22**, 642 (1957).

0022-2623/80/1823-1350$01.00/0