was suspended in 50 mL of toluene, heated to reflux for 1 h, treated with 3 mL of concentrated HCl, and refluxed for an additional hour. It was cooled and filtered. Recrystallization from EtOH–Et_2O gave 1.6 g (63%) of white needles, mp 235–237 °C dec.

1,2,3,4-Tetrahydro-5,8-dimethyl-2-naphthalenamine Hydrochloride (17). A solution of 4.0 g (24.3 mmol) of 2,5-dimethylphenylacetic acid and 3.6 g (30 mmol) of $SOCl_2$ was stirred at 25 °C for 16 h. Excess $SOCl_2$ was removed, and the residue was dissolved in 30 mL of CH_2Cl_2. This was added to a suspension of 33 g (25 mmol) of $AlCl_3$ in 60 mL of CH_2Cl_2 in a dry-ice bath. Ethylene was bubbled through the mixture vigorously for 7 min, and the reaction was allowed to warm to 25 °C and stirred for 30 min. The reaction was quenched with H_2O, and the layers were separated, washed with 3 N HCl and 5% $NaHCO_3$, dried, and evaporated. The residue was quickly chromatographed over silica gel eluting with 70:30 cyclohexane–Et_2O to give 2.0 g (47%) of tan oil. This was dissolved in 50 mL of dry MeOH containing 8.0 g of NH_4OAc. Sodium cyanoborohydride (3.3 g, 55 mmol) was added, and the mixture was stirred for 16 h. The reaction was treated carefully with 15 mL of concentrated HCl and stirred for 1 h. The MeOH was removed, and the residue was partitioned between Et_2O and H_2O. The aqueous layer was separated, made basic, and extracted again with Et_2O. The basic extracts were dried and treated with HCl/Et_2O. The resulting precipitate was removed by filtration and crystallized from MeOH–EtOAc to give 0.40 g (22%) of white solid, mp 243–245 °C.

1,2,3,4-Tetrahydro-8-chloro-*N*-ethyl-5-methoxy-2-naphthalenamine Hydrochloride (27). The primary amine **15** was acylated with acetyl chloride and reduced with diborane to give **27** as white crystals, mp 255–257 °C dec.

Preparation of Aminotetralins 20, 25, 26, 28, 29 and 31. Compound **20** was obtained by acetylation and diborane reduction of 6,7-dimethoxy-2-aminotetralin.[24] Compounds **25** and **26** were prepared by acylation of **22** with acetyl or propionyl chloride, followed by diborane reduction. Compounds **28**, **29**, and **31** were synthesized by diborane reduction of the corresponding acetamides **6**, **9**, and **11**.

1,2,3,4-Tetrahydro-8-methoxy-5-(methylthio)-2-naphthalenamine Hydrochloride (30). A solution of 1.0 g (3.8 mmol) of **11** in 100 mL of toluene containing 0.474 g (6 mmol) of pyridine was heated to 65 °C. Phosphorus pentachloride (1.25 g, 6 mmol) was added and heating continued for 2 h. The toluene was removed under reduced pressure, 200 mL of MeOH was added, and the solution was stirred overnight at 25 °C. The MeOH was evaporated and 100 mL of 1:1 THF–H_2O was added. After 30 min the THF was removed and the aqueous layer was extracted with Et_2O. It was made alkaline with NH_4OH and extracted with 3 portions of CH_2Cl_2. The combined extracts were dried and evaporated to yield free base as an oil. This was dissolved in Et_2O and treated with excess ethereal HCl. The resulting precipitate was removed by filtration and recrystallized from MeOH–EtOAc–Et_2O to give 0.45 g (45%) of a white solid, mp 290 °C dec.

7,8-Dimethoxy-2-aminotetralin (21). The compound was prepared by the method of Barfknecht et al.,[24] starting with 2,3-dimethoxybenzyl chloride. It was recrystallized from 2-propanol–ether as colorless rosettes, mp 212–213 °C.

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Mammary Tumor Inhibiting Effect of 3,3′-Diacetoxy-α,β-dialkylstilbenes and of Related Stilbene Oxides

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3,3′-Diacetoxy-α,β-dialkylstilbenes (alkyl = CH_3 to C_4H_9, **1–4**), 3,3′-dihydroxy-α,β-diethylstilbene (**5**), and their corresponding stilbene oxides (**6–10**) were synthesized. Compounds **1–10** competitively antagonized in vitro the interaction of [^{3}H]estradiol with its receptor. 3,3′-Diacetoxy-α,β-diethylstilbene (**2**), 3,3′-diacetoxy-α,β-diethylstilbene oxide (**7**), and their phenolic analogues (**5** and **10**) were most effective. Shortening or lengthening the alkyl side chains led to a decrease in receptor affinity. Among the stilbenes and epoxides, those with C_2H_5 and C_3H_7 groups (**2**, **3**, **5** and **7**, **8**, **10**) caused the strongest inhibition of the growth of a hormone-dependent postmenopausal human mammary carcinoma serially implanted in nude mice. The strong antitumor activity of **5** and **10** was confirmed by experiments on the 9,10-dimethyl-1,2-benzanthracene-induced, hormone-dependent mammary carcinoma of the Sprague–Dawley rat.

The displacement of the phenolic hydroxy groups of the synthetic estrogens 4,4′-dihydroxy-α,β-dialkylstilbenes into the 3,3′ positions led to compounds with antiestrogenic and mammary tumor inhibiting properties.[1,2] Since the transformation of 4,4′-dihydroxy-α,β-diethylstilbene into its oxide did not cause a reduction of the affinity to the estradiol receptor and since this oxide exhibits a strong mammary tumor inhibiting effect,[3] these 3,3′-dihydroxy-α,β-dialkylstilbenes were connected with the potentially alkylating epoxide group. Thus, it might be possible to get compounds with antiestrogenic and cytotoxic properties that might have a more selective effect on the hormone-dependent mammary carcinoma because of their affinity to the estradiol receptor than common cytostatic drugs.

Chemistry. 3,3′-Diacetoxy-α,β-dialkylstilbenes **1–4** were prepared from the corresponding 3,3′-dihydroxy com-

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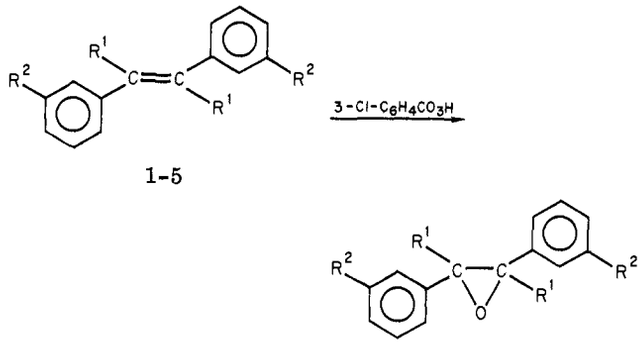
Scheme I



		R^1	R^2
1	6	CH_3	$OCOCH_3$
2	7	C_2H_5	$OCOCH_3$
3	8	C_3H_7	$OCOCH_3$
4	9	C_4H_9	$OCOCH_3$
5	10	C_2H_5	OH

Table I. Chemical Data and Relative Binding Affinity (RBA) of Compounds 1-10

no.	R^1	R^2	mp, °C	formula[a]	RBA,[b] %
1	CH_3	$OCOCH_3$	132	$C_{20}H_{20}O_4$	0.4
2	C_2H_5	$OCOCH_3$	83	$C_{22}H_{24}O_4$	2.2
3	C_3H_7	$OCOCH_3$	46	$C_{24}H_{28}O_4$	1.3
4	C_4H_9	$OCOCH_3$	45	$C_{26}H_{32}O_4$	0.6
5	C_2H_5	OH	176	$C_{18}H_{20}O_4$	3.2
6	CH_3	$OCOCH_3$	96	$C_{20}H_{20}O_5$	0.8
7	C_2H_5	$OCOCH_3$	94	$C_{22}H_{24}O_5$	4.2
8	C_3H_7	$OCOCH_3$	57	$C_{24}H_{28}O_5$	1.7
9	C_4H_9	$OCOCH_3$	59	$C_{26}H_{32}O_5$	0.8
10	C_2H_5	OH	169	$C_{18}H_{20}O_3$	5.4

[a] All compounds were analyzed for C and H within ±0.4% of the calculated values. [b] RBA = [E2]/[I] × 100; [E2] and [I] are the molar concnetrations of unradioactive E2 and inhibitor required to halve the bound radioactivity; E2 = 17β-estradiol.

pounds[1] in the usual manner with acetic anhydride and pyridine (Table I, Scheme I). From these diacetates were synthesized the corresponding stilbene oxides **6–9** using 3-chloroperbenzoic acid as the epoxidizing agent (Table I, Scheme I). The compound **5** with free aromatic hydroxy groups[1] was epoxidized to give **10**.

Biological Properties. In vitro, compounds **1–10** competitively inhibited the interaction of [^{3}H]estradiol with its receptor. The stilbenes and stilbene oxides with ethyl groups in the α,β positions (**2**, **7**, **5**, and **10**) showed the highest receptor affinity (Table I). Shortening or lengthening the alkyl side chains in **2** and **7** led to a decrease of this effect. Acetylation of the phenolic hydroxy groups in **5** and **10** diminished the receptor affinity only slightly. The transformation of the stilbenes to their oxides did not reduce the affinity; on the contrary, a slight increase was obtained.

In the mouse uterine weight test in vivo the uterotrophic properties of the epoxides **6–10** were only weak (Table II). Whereas potent estrogens, such as diethylstilbestrol or estrone, cause a maximum stimulation of uterine growth at a dose of about 0.4 μg per mouse,[2,3] **7** and its phenolic analogue **10** reached this maximum effect only at very high doses. The effect of **8** and **9** did not equal that of estrone, even at high doses. Compound **6** did not show any significant uterotrophic activity. The comparison between the stilbene **2** and its oxide **7** indicated that both compounds have similar estrogenic properties (Table II).

Table II. Uterotrophic Activity of 2 and 6-10 in the Mouse Uterine Weight Test

compd	dose,[a] μg	effect[b]
solvent		13.1 ± 2.3
estrone	0.4	40.7 ± 4.2
2	1	15.9 ± 2.3
	10	24.3 ± 2.5
	50	27.4 ± 2.8
	100	32.7 ± 1.7
	500	42.0 ± 4.8
7	1	22.2 ± 2.9
	10	30.3 ± 1.7
	50	33.4 ± 3.0
	100	36.2 ± 3.4
	500	38.6 ± 1.7
solvent		16.8 ± 2.6
estrone	0.4	41.0 ± 6.2
6	10	17.0 ± 4.4
	100	15.0 ± 2.8
	500	20.6 ± 4.6
8	5	21.8 ± 4.0
	50	22.1 ± 5.3
	100	31.1 ± 5.9
	500	33.3 ± 7.7
solvent		10.9 ± 2.3
estrone	0.4	45.6 ± 4.6
9	10	19.8 ± 3.2
	100	34.3 ± 3.5
	1000	35.5 ± 3.9
solvent		14.6 ± 2.8
estrone	0.4	46.3 ± 5.1
10	8	29.4 ± 4.9
	80	33.0 ± 2.5
	800	43.6 ± 4.9

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

Among the epoxides, compounds **6**, **7**, **9** and **10** significantly inhibited the estrone-stimulated uterine growth of the immature mouse. However, high doses of **7–10**, but not of **6**, led to a nearly complete loss of the estrone-antagonizing effect. The epoxide **10** exhibited nearly the same antiuterotrophic effect as its corresponding stilbene (**5**). The antiuterotrophic properties of the phenolic analogues of **1**, **3**, and **4**, which are already published,[2] are similar to those of **6**, **8**, and **9**. It is noteworthy that inhibitory effects were obtained at doses at which these compounds had only weak or even no uterotrophic activity (Table III).

In order to determine the potential alkylating properties of the epoxides **6–10** the 4-(*p*-nitrobenzyl)pyridine test (NBP test)[4] was carried out. In this test, an alkylating compound reacts with the nucleophilic center of NBP. The resulting product is converted with KOH to a colored compound whose extinction at 600 nm is measured. However, none of the stilbene oxides exhibited any considerable effect.

In another test to detect prophage-inducing activities[5] (a further hint at alkylating properties), only **6** showed a slight effect [n = 1.5 (10^{-4} M)].

For testing the tumor-inhibiting properties we used an estrogen receptor and progesterone receptor positive postmenopausal human mammary carcinoma serially implanted in nude mice. The strongest inhibiting effect was shown by 3,3′-dihydroxy-α,β-diethylstilbene (**5**) and its oxide (**10**), i.e., the compounds with the highest receptor affinity, at a dose of 4 mg/kg (Figure 1). These two compounds were also tested at doses of 1 and 2 mg/kg

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Table III. Antiuterotrophic Activity of 5-10 in the Mouse Uterine Weight Test

compd	dose,[a] μg	effect[b]	inhibn,[c,d] %
solvent		10.0 ± 0.9	
estrone	0.1	44.8 ± 6.8	
5	2.5	38.3 ± 0.6	18.7[e]
	5	28.1 ± 5.5	48.0[e]
	25	29.9 ± 4.1	42.8[e]
	50	29.1 ± 3.9	45.1[e]
solvent		10.3 ± 4.5	
estrone	0.1	43.7 ± 6.8	
6	5	37.9 ± 5.1	17.4
	25	36.1 ± 2.6	23.0[e]
	100	32.6 ± 3.9	33.4[e]
	250	33.1 ± 3.9	31.7[e]
solvent		13.8 ± 1.4	
estrone	0.1	43.0 ± 3.7	
7	5	33.2 ± 4.8	33.5[e]
	50	36.4 ± 4.7	22.6[e]
	100	43.7 ± 4.1	0
10	5	27.6 ± 2.9	52.5[e]
	50	33.0 ± 4.4	34.3[e]
	100	42.2 ± 4.0	2.7
solvent		12.9 ± 3.4	
estrone	0.1	38.0 ± 7.1	
8	5	34.1 ± 5.0	15.6
	25	36.3 ± 5.6	7.8
	100	39.4 ± 4.7	0
solvent		16.4 ± 1.9	
estrone	0.1	42.5 ± 3.4	
9	5	32.4 ± 5.8	38.8[e]
	50	42.0 ± 5.4	2.2
	100	42.4 ± 5.0	0.4

[a] Dose per animal and 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 ($\alpha < 0.01$).

Table IV. Effect of 1-10 on the Growth of an Estrogen Receptor and Progesterone Receptor Positive Hormone-Dependent Postmenopausal Human Mammary Carcinoma Implanted in Nude Mice

dose,[a] (mg/kg)/day	compd	tumor size[b]	compd	tumor size[b]
	control	3.43	control	3.43
2.4	1	3.42[d]	6	2.72[d]
2.6	2	2.30[c]	7	2.38[c]
2.8	3	2.32[c]	8	1.85[c]
3.0	4	4.10[d]	9	3.37[d]
1.0	5	2.78[d]	10	2.90[d]
2.0	5	1.76[c]	10	1.85[c]

[a] Compounds were administered 6 times a week sc. [b] Average after 5 weeks of therapy; for definition of tumor size, see Experimental Section. [c] Significant ($\alpha < 0.05$). [d] Not significant ($\alpha > 0.05$).

(Table IV). A dose-dependent effect was observed.

5 and **10** also strongly inhibited the growth of the DMBA-induced, hormone-dependent mammary carcinoma of the SD rat (Table V, Figure 2). At a dose of 1 mg/kg of **10**, 76% of the tumors showed a complete remission. At the same dose, **5** was less active (Table V).

The remaining compounds were administered in the xenograft tumor experiment at a dose that is equimolar to the dose of 2 mg/kg of **5**. Whereas **1** and **4**, as well as **6** and **9**, caused no significant inhibition of tumor growth, **2**, **3**, **7**, and **8** showed a significant effect ($\alpha \leq 0.05$) (Table V).

Comparison of the antitumor activity to the RBA values shows a correlation between these two effects. This was also confirmed by Hartmann et al.,[6] who administered several compounds of the type of 1,2-dialkyl-1,2-bis(3'-hydroxyphenyl)ethanes in doses proportional to their in-

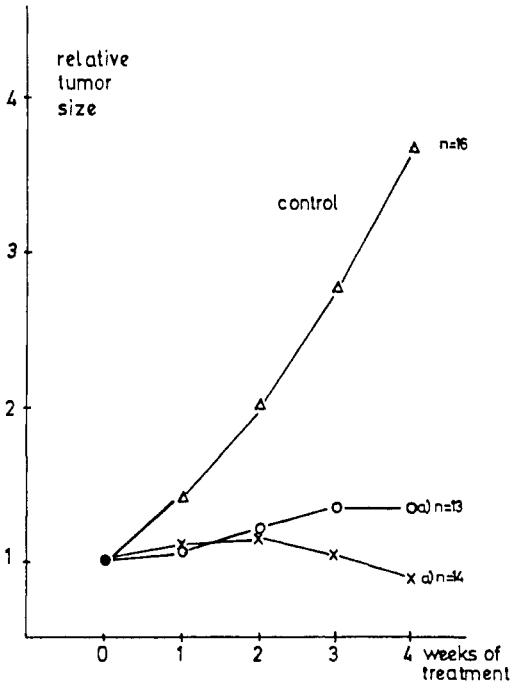

Figure 1. Effect of **5** and **10** on the growth of an estrogen receptor and progesterone receptor positive, hormone-dependent postmenopausal human mammary carcinoma implanted in nude mice: 6 × 4.0 (mg/kg)/week sc; duration of treatment, 4 weeks; a), significant ($\alpha \leq 0.05$); n = number of tumors per group. The change of body weight of the treated animals was in the ±10% range in comparison with the controls.

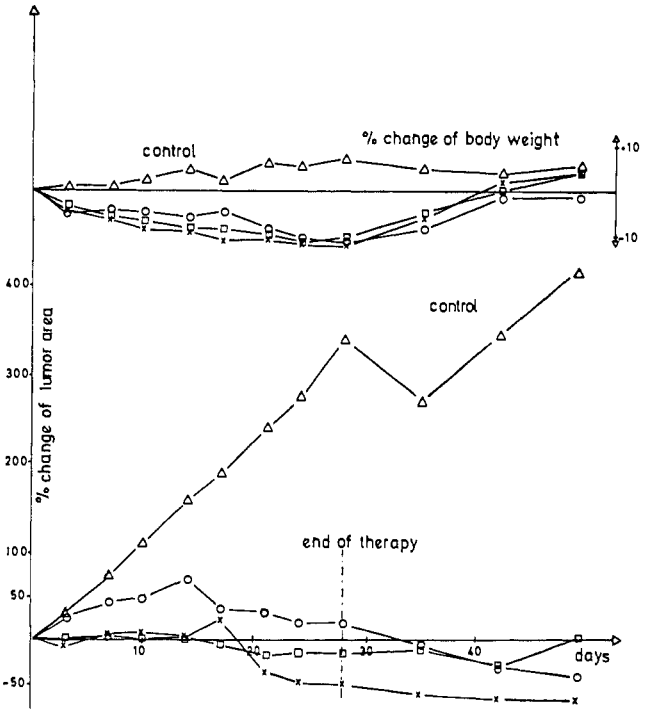

Figure 2. Effect of **10**, at 6 × 0.5 (O–O), 1.0 (x–x), and 4.0 (□–□) (mg/kg)/week sc, on the growth of the DMBA-induced, hormone-dependent mammary carcinoma of the SD rat; duration of treatment, 28 days.

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Table V. Effect of 5 and 10 on the Growth of the DMBA-Induced Hormone-Dependent Mammary Carcinoma of the SD Rat[a]

compd	dose,[b] (mg/kg)/day	no. of tumors B	no. of tumors NT	% of tumors with CR	PR	NC	P	% change of tumor area[c]
control		39	32	6	14	44	37	247
5	1.0	32	34	15	23	38	24	40
5	2.0	32	21	25	26	32	17	2[d]
5	4.0	37	17	27	22	32	19	−26[d]
control		25	38	2	3	33	62	430
10	0.5	27	18	69	13	5	13	18[d]
10	1.0	31	10	76	13	0	10	−52[d]
10	4.0	29	4	61	12	12	15	−16[d]

[a] B = at test beginning; NT = occurring during the test; CR = complete remission, tumor not palpable; PR = partial remission, tumor size ≤ 50% of initial size; NC = no change, tumor size 51–150% of initial tumor size; P = progression = tumor size > 150% of initial size. [b] Compounds were administered 6 times a week sc. [c] Average on the 28th day of therapy. [d] Significant ($\alpha < 0.01$).

dividual receptor affinity to animals bearing DMBA-induced carcinomas. In these different doses they showed nearly the same antitumor activity. Compared with their corresponding stilbenes, no significantly better antitumor effect of the stilbene oxides was detected in the xenograft tumor model.

Compounds **5** and **10** were also tested on a premenopausal human mammary carcinoma implanted in nude mice. At a dosage of 6 × 4 (mg/kg)/week, no effect on the tumor growth was detected. A therapy with tamoxifen did not cause any growth inhibition either.[7] This is not surprising, since mammary tumors that are estrogen receptor positive and progesterone receptor negative, like the tumor mentioned above, are only weakly influenced by endocrine therapy.[8]

Discussion

The estradiol receptor affinity of the 3,3′-diacetoxy-α,β-dialkylstilbenes and their corresponding oxides highly depends on the length of the alkyl side chains. The compounds with ethyl in α,β positions exhibited the maximum binding affinity. The same results were obtained in a series of 1,2-dialkyl-1,2-diphenylethanes.[6] Surprisingly, the receptor affinity is only slightly decreased by acetylation of the phenolic hydroxy groups. A cleavage of the acetoxy groups under the conditions of the binding assay is unlikely but cannot be excluded. In spite of the steric modification of the molecule by the transformation of the stilbenes into their oxides, the affinity to the estrogen receptor is not diminished but even slightly increased.

Furthermore, the uterotrophic and antiuterotrophic effects differ only slightly between the stilbenes and their epoxides. Contrary to our expectations, the introduction of the epoxide group into the stilbenes did not lead to a significant improvement of the antitumor activity, probably because their potential alkylating properties did not take effect as shown by the negative results in the NBP-test and in the prophage-inducing test.

The mechanism of the antitumor activity of these compounds is not clear yet. It may be due to either antiestrogenic or estrogenic properties. Our results that arise from the uterotrophic and antiuterotrophic assay we applied do not exclude that our compounds are more estrogenic if administered continuously.[9] It is well-known that estrogens also strongly inhibit the growth of hormone-dependent mammary carcinomas.[3,10] As a conclusion it can be stated that some of the described stilbene oxides are strong inhibitors of hormone-dependent mammary carcinomas but are not superior to the parent stilbenes in their antitumor activity.

Experimental Section

General Procedures. TLC 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 ^{1}H NMR spectra (Varian EM 360 A, 60 MHz), and the structures of the epoxides were confirmed additionally by mass spectroscopy (Varian MAT CH5).

Syntheses. 3,3′-Dihydroxy-α,β-dialkylstilbenes[1] (0.01 mol) were acetylated by refluxing with acetic anhydride (0.02 mol) and pyridine (0.025 mol) for 30 min. After the mixture was cooled, ice–water was added and the mixture was extracted with ether. The ether extract was washed with 1 N HCl and saturated $NaHCO_3$ solution. The solvent was removed, and the crude products were recrystallized from EtOH to give the 3,3′-diacetoxy-α,β-dialkylstilbenes in about quantitative yield.

Compounds **1–5** (0.01 mol) were epoxidized by stirring with 3-chloroperbenzoic acid (0.012 mol) in an ethereal solution under protection from light. The course of the reaction was observed by TLC. After quantitative conversion to the epoxide, the ethereal solution was washed with saturated $NaHCO_3$ solution, and the solvent was removed. The crude product was recrystallized from EtOH to give the epoxides in a yield of about 60–70%. For further data, see Table I.

Biological Methods. Estradiol Receptor Binding Assay. The method described in ref 2 was used with some 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. The effectiveness of an inhibitor was established by using the ratio of the unlabeled estradiol concentration for 50% competition to the inhibitor concentration for 50% competition. This ratio, multiplied by 100, forms the relative binding affinity (RBA).

Estrogen and Antiestrogen Assays. The Dorfman uterine weight test was carried out to determine estrogenic and antiestrogenic properties.[2] Compounds (as olive oil solutions) were injected sc daily into immature female NMRI mice (ten mice per group; age, 20 days at test beginning; body weight, 10–12 g) for 3 days. The animals were killed 24 h after the last injection. The uteri were removed, prepared, and weighed after drying at 100 °C for 24 h.

Cytotoxic Properties. The 4-(*p*-nitrobenzyl)pyridine test (NBP test) was used to determine the alkylating properties.[4] NBP (1 mL of a 5% ethanolic solution) was added to the test compounds (1 mg in 1 mL of ethanol) and also 1 mL of 0.05 M potassium biphthalate buffer, pH 4.2 (final pH 7.0). After an incubation at 50 °C for 1 h, ethanolic KOH was added and the extinction at 600 nm was measured (reference compounds: chlorambucile and propylene oxide).

In another experiment, the prophage-inducing effect in *Escherichia coli* K12 was tested.[5] The quotient at the given concentration is considered as a criterion of the alkylating properties.

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$$n = \frac{\text{no. of plaques induced by the test compd}}{\text{no. of plaques in control}}$$

Mammary Tumor Growth Inhibition Tests. (a) DMBA-Induced, Hormone-Dependent Mammary Carcinoma of the SD Rat.[2] A single dose of 20 mg of DMBA (9,10-dimethyl-1,2-benzanthracene) was administered by gastric intubation to female SD (Sprague–Dawley) rats at an age of 50 days. After the appearance of tumors, about 4 weeks later, animals with at least one tumor with an area >140 mm^2 were classified in groups of ten. Compounds were administered in olive oil solution 6 times a week sc. The duration of treatment was 28 days. Measurement of tumor area was made twice weekly. The tumor area was defined by length × width of the tumor.

(b) Hormone-Dependent Human Mammary Carcinoma Serially Transplanted in Nude Mice.[7] Animals of a random-bred strain (NMRI nu/nu) at an age of 6 to 7 weeks were grafted with mammary carcinomas from premenopausal (female mice) and postmenopausal (castrated female or male mice) women. The premenopausal tumor was estrogen receptor positive and progesterone receptor negative; the postmenopausal tumor was estrogen receptor and progesterone receptor positive. Tumors were measured once a week by two diameters. Compounds were administered as olive oil solutions 6 times a week sc. The duration of treatment was 4–5 weeks. At the beginning of treatment, tumor size was defined as "1".

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Quantitative Structure–Activity Relationships of Aromatic Esters of 1-Methyl-4-piperidinol as Analgesics[1]

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Substituted benzoic acid esters of 1-methyl-4-piperidinol showed analgesic activity when assayed by the mouse hot-plate method, the more potent ones falling in the morphine–codeine range. To understand how substituents on the aromatic ring affect the analgesic potency, quantitative structure–activity correlations were carried out on a series of 44 derivatives. Among the various substituent parameters included in the study, L_{ortho} (length of ortho-substituents) and B_1 (minimal width of substituents) or E_s at meta and para positions gave negative correlation with the potency, while lipophilicity (especially π_{meta}) and the ability of being a hydrogen-bond acceptor enhanced the potency. Based on the QSAR results, a substitution pattern of the phenyl group was defined for optimal activity. Implications on drug–receptor interactions and the possible binding mode of these compounds were discussed.

Previous studies[2,3] have shown that substituted benzoic acid esters of 1-methyl-4-piperidinol possess analgesic activity by the hot-plate assay, with the more potent ones in the range of morphine and codeine, but, in general, they display no morphine-like physical dependence liability in monkeys.

These esters have the main structural features of many synthetic analgesics, namely, a benzene ring and a piperidine ring. However, they lack the quaternary phenyl substitution at C-4 of the piperidine ring, which is present in meperidine, prodine, and other 4-phenylpiperidine analgesics. Qualitative structure–activity correlations of some 3- and 4-substituted and 3,4-disubstituted benzoate esters were made with regard to substituent constants E_s^c and π. No significant conclusions were drawn from this limited study,[3] and it became apparent that a quantitative study applying multiple-regression analysis would be necessary in order to gain insight into the involvement of the aromatic ring in determining the analgesic potency.

Over the years, several publications have appeared[4-9] on the quantitative structure–activity relationships of narcotic analgesics, but none has dealt extensively with the effects of substituents on the aromatic moiety.

Preliminary analysis of available compounds showed an insufficient spread of substituent parameter values. Therefore, additional monosubstituted compounds were synthesized based on Craig's plots,[10] as illustrated for para-substituted compounds in Figure 1. The structure and analgesic potency of all 48 benzoic acid esters of 1-methyl-4-piperidinol are shown in Table I. The analgesic potencies ranged from an average hot-plate ED_{50} of 3.9 to 74 mg/kg (0.012 to 0.23 mmol/kg), with the exception of a few which were marginally active or inactive at 100 mg/kg.

Results and Discussion

Among the various physicochemical parameters included in the study (cf. Experimental Section), those found to be significant in correlating the structure with activity are listed in Table I. The statistically significant regression equations are given below, where n is the number of compounds, r is the multiple regression coefficient, s is the standard deviation of the regression, and f is the value of

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