tillation counting. Specific [^{3}H]pirenzepine was determined with bovine striatal membranes. Bovine brains were obtained from a local abattoir and transported to the laboratory packed in ice. The striata were dissected immediately and stored frozen (-80 °C) until the day of assay. For assay, the tissue was thawed, weighed, and homogenized (polytron setting 5.5; 30 s) in 20 volumes (w/v) of assay buffer (HEPES·KOH; 0.05 M; pH 7.7). The tissue was washed as described for the [^{3}H]QNB assay, and the final pellet was resuspended in sufficient buffer to yield a tissue concentration of 5 mg/mL. One milliliter aliquots of the suspension were added in triplicate to tubes containing [^{3}H]pirenzepine and various concentrations of the drugs of interest. Final ligand concentration in the assay was 1 nM, and atropine (10^{-6} M) was used to determine nonspecific binding. Incubations were continued for 60 min at 23 °C, and reaction was terminated by vacuum filtration as described previously; however, filters were presoaked at 23 °C for 45–60 min in a solution (0.04%; v/v) of polyethylimine in assay buffer. Filters were rinsed rapidly with 2 × 5 mL of ice-cold buffer, and radioactivity was determined by liquid scintillation counting.

Functional Assays. Male Sprague–Dawley rats (200–250 g) were sacrificed by decapitation, and the cerebral cortices and hearts were removed for PI and AC assays, respectively.

PI Hydrolysis. Accumulated inositol phosphates (IP) were measured as previously described.[18] Briefly, cross-chopped slices (350 × 350 μm) of rat cerebral cortex prepared on a McIlwain tissue chopper were transferred to 20 volumes of Krebs-bicarbonate buffer and incubated for 60 min at 37 °C with gentle shaking. Thereafter, 50-μL aliquots of packed slices were incubated with 5.0 mM LiCl and 0.32 μM myo-2-[^{3}H]inositol for 30 min. Antagonists were added 20 min prior to carbachol addition, and incubations were continued for 60 min. Reactions were terminated by addition of 940 μL of chloroform/methanol (1:2 v/v). Water-soluble inositol phosphates were extracted by a batch technique with a Dowex anion exchange resin. Labeled IPs were eluted with 1.0 M ammonium formate/0.1 M formic acid.

Adenylate Cyclase (AC). Rat heart membranes were prepared immediately prior to use by modification of a procedure described previously.[18] Crudely minced rat heart tissue was homogenized in 10 mM triethanolamine hydrochloride and 145 mM NaCl (pH 7.4) on ice with a Brinkmann Polytron PT 10/35 (setting 5.5, 20 s). The homogenate was filtered through four layers of cheesecloth and centrifuged (30000*g*) for 20 min at 4 °C. The pellet was resuspended in the original volume of buffer using the polytron and centrifuged, and the process was repeated three times to yield a particulate membrane fraction.

For AC assay, about 120 μg of membrane protein was added to a reaction mixture containing a final concentration of 50 mM triethanolamine hydrochloride (pH 7.4), 5.0 mM $MgSO_4$, 50 μM ATP, 50 μM AMP, 1.0 mM dithiothreitol, 1.0 mM 3-isobutyl-1-methylxanthine (IBMX), 10 mM creatine phosphate, 1.4 mg/mL creatine phosphokinase, 90 mM NaCl, 30 μM GTP, and 1.7 μCi of [^{32}P]ATP in a 100-μL final volume. Incubations were carried out for 15 min at 37 °C. Reactions were terminated with 150 μL of a stock solution containing 100 μL of 2% SDS, 40 mM ATP, 1.4 mM cAMP and 50 μL of [^{3}H]cAMP (200 000 cpm) in Tris·HCl, pH 7.4. [^{32}P]cAMP was isolated by column chromatography according to the procedure of Solomon.[22]

[^{3}H]Myoinositol (16 Ci/mmol) was purchased from Amersham (Arlington Heights, IL). [^{32}P]ATP (800 Ci/mmol), [^{3}H]cAMP (33.5 Ci/mmol), [^{3}H]QNB (30.1 Ci/mmol), and [^{3}H]pirenzepine (76 Ci/mmol) were purchased from New England Nuclear (Boston, MA).

Data Analysis. Inhibition constants (IC_{50}'s) were calculated with the EBDA program. Apparent affinity constants (K_i) were determined according to the method of Cheng and Prusoff.[23] Dissociation constants (K_D) for [^{3}H]pirenzepine (2.90 nM) and [^{3}H]QNB (180 pM) were determined in preliminary experiments by using saturation analysis and LIGAND. K_i values for PI assays were determined from Dixon plot analysis[15] or with the Cheng–Prusoff equation.[23] For AC, pA_2 curves were constructed, and K_i values were determined as described by Tallirida et al.[24]

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Registry No. (*R*)-**1**, 62869-69-6; (*S*)-**1**, 62869-68-5; (*R*)-**2**, 114298-73-6; (*S*)-**2**, 114375-05-2; (*Ra*,*Rb*)-**3**, 114298-75-8; (*Sa*,*Sb*)-**3**, 114298-77-0; (*Sb*,*Ra*)-**3**, 114298-79-2; (*Ra*,*Sb*)-**3**, 114298-81-6; (*R*)-(−)-3-quinuclidinol, 25333-42-0; ethyl benzilate, 52182-15-7; methyl xanthene-9-carboxylate, 39497-06-8; ethyl (*R*)-atrolactate, 29916-14-1; (*S*)-3-quinuclidinol, 34583-34-1; ethyl (*S*)-atrolactate, 2406-23-7; xanthene-9-carboxylate acid, 82-07-5; trifluoroacetic anhydride, 407-25-0.

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(24) Tallarida, R. J.; Murray, R. B. *Manual of Pharmacological Calculations with Computer Programs*; Springer-Verlag: New York, 1981.

Preparation of 7-Oxaaporphine Derivatives and Evaluation of Their Dopaminergic Activity

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A series of 7-oxaaporphine derivatives was prepared. The compounds were evaluated as dopaminergic agents. None of them showed either affinity for dopamine receptors or activity in vivo in the climbing behavior (mice) and turning behavior (6-hydroxydopamine-lesioned rats) tests. The lack of activity is tentatively related to the effect of the oxygen atom on the pK_a of these molecules.

Dopamine agonists are useful in treating diseases such as Parkinsonism, Huntington's chorea, galactorrhea, and hyperprolactinemia.[1] Apomorphine (Ia, Table I) is a prototypical dopaminergic agent, but has undesirable effects such as emesis and also a short duration of action. Its pharmacology has been extensively reviewed,[2] and the in-depth studies by Cannon,[3] Neumeyer,[4] and others have

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(2) *Apomorphine and Other Dopaminomimetics*; Corsini, G. V., Gessa, G. L., Eds.; Raven: New York, 1981; Vol. 1 and 2.
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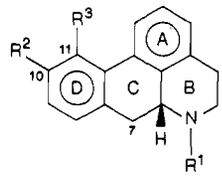
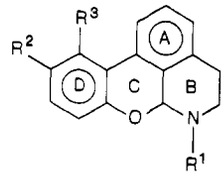
Table I. Apomorphine (Ia) and Some Derivatives



compd	R^1	R^2	R^3
Ia	CH_3	OH	OH
Ib	CH_3	H	OH
Ic	CH_3	OH	H
Id	CH_3	OCH_2O	
Ie	$CH_3CH_2CH_2$	OH	OH

Table II. 7-Oxaaporphine Derivatives (II)



compd	R^1	R^2	R^3
IIa	CH_3	H	H
IIb	CH_3	H	OH
IIc	CH_3	OH	H
IId	CH_3	OCH_2O	
IIe	$CH_3CH_2CH_2$	H	H
IIf	$CH_3CH_2CH_2$	H	OH
IIg	$CH_3CH_2CH_2$	OH	H
IIh	$CH_3CH_2CH_2$	OCH_2O	

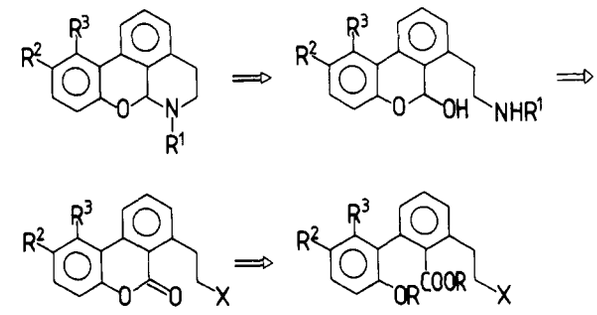
contributed to the elucidation of the structural requirements for dopaminergic activity.

It has been suggested that affinity for the dopamine receptor and in vivo biological activity of aporphine derivatives would require a hydroxyl function at the 11-position as in Ib (Table I) rather than at the 10-position as in Ic.[5]

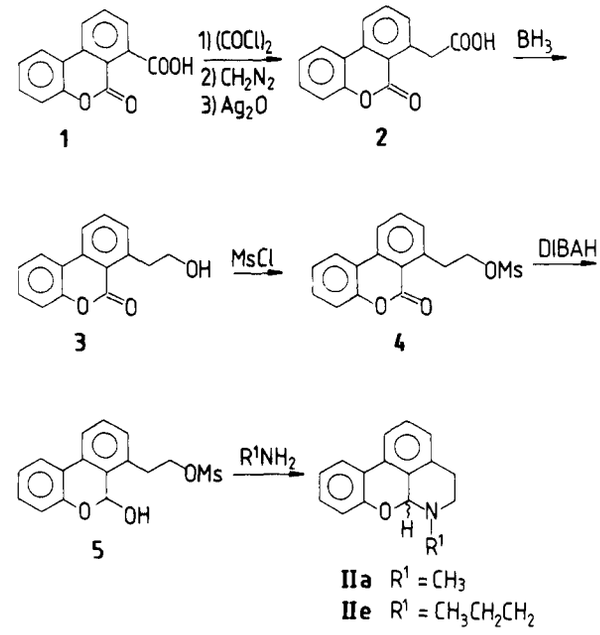
The methylenedioxy derivative Id is an orally active, long-lasting compound considered to be a prodrug of Ia.[6] Moreover, Ie is more active in vivo than Ia.[7]

Introduction of an oxygen atom into biologically active compounds such as 9-oxaergolines[8] and 2*H*-naphth[1,2-*b*]-1,4-oxazines[9] led to active analogues. Therefore, we decided to prepare the analogues IIa–h (Table II) of I where an oxygen atom has replaced the methylene group at the C-7 position. The oxygen atom at position 7 may contribute to the electron density of ring D nearly to the same extent as the C-10 hydroxy group of compounds I with the advantage of avoiding the presence of the catecholic group, which is considered responsible for the fast metabolic inactivation of apomorphine.[10] On the other hand, oxygen influences the pK_a of the amino group and also the conformation of ring B due to stereoelectronic effects.[11]

Scheme I



Scheme II



Chemistry. We intended to prepare the target compounds according to the retrosynthetic analysis outlined in Scheme I. To assess the feasibility of the last cyclization step and the stability of the final compounds, we first tried to synthesize the ring D unsubstituted compounds IIa,e from 6-oxo-6*H*-dibenzo[*b*,*d*]pyran-7-carboxylic acid (1) as shown in Scheme II.

Homologation by the Arndt–Eistert reaction and subsequent carefully controlled reduction with borane in THF gave compound **3**, which was then converted into mesylate **4**. The lactone was reduced with diisobutylaluminum hydride (DIBAH) to lactol **5**, which could be either isolated or directly converted into compounds IIa and IIe by in situ treatment with methylamine or propylamine, respectively. The use of ammonia to prepare the unsubstituted parent compounds was not successful.

Once the feasibility of the final step and the stability of the final compounds IIa,e were tested, we undertook the synthesis of the hydroxy-substituted analogues according to the approach shown in Scheme III. The starting compounds **6–8** were readily prepared on a large scale by ortho-lithiation of alkoxybenzenes followed by reaction with iodine.[12] Compounds **10–12** were prepared in good yield

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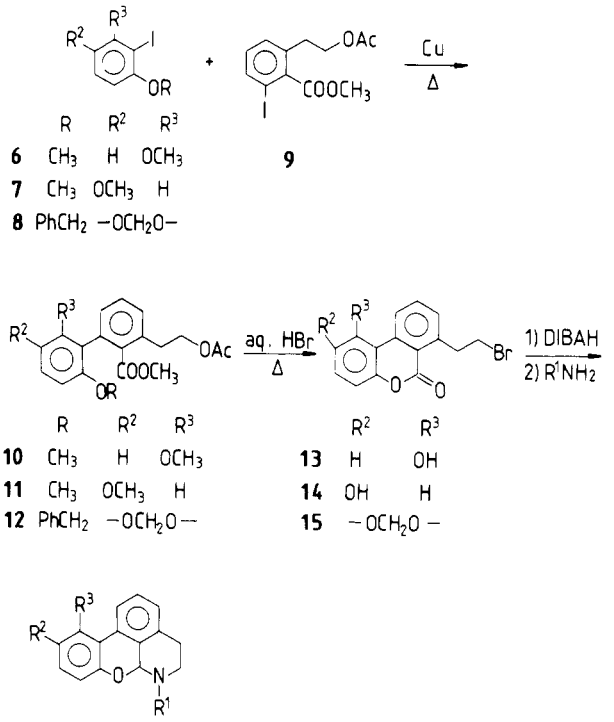
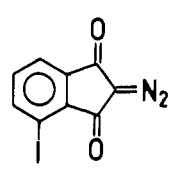
(11) Deslongchamps, P. In *Stereoelectronic Effects in Organic Chemistry*; Baldwin, J. E., Ed.; Pergamon: New York, 1983, 26.

Scheme III



(60–70%) through an Ullmann reaction and were converted to **13–15** by heating in 48% aqueous HBr. The hydrolysis of the alkoxy group occurred slowly so that the intermediates with R^2 or $R^3 = OCH_3$ could also be isolated. Compounds **13–15** were then reduced to the corresponding lactols via the same procedure used for the preparation of their unsubstituted analogues (see Scheme II). We found it very difficult to convert compounds IId,h into the dihydroxy derivatives, but the matter was not pursued further once it became apparent that IIb,f were totally devoid of dopaminergic activity.

Scheme IV shows the synthesis of the key intermediate **9**. It is worthwhile to note that the intermediate diazo ketone **18**, when treated with Ag_2O in dioxane, gave a limited yield of **19** due to the competitive formation of the indandione derivative **21** by intramolecular condensation. Formation of **21** was avoided by using the less basic silver acetate.



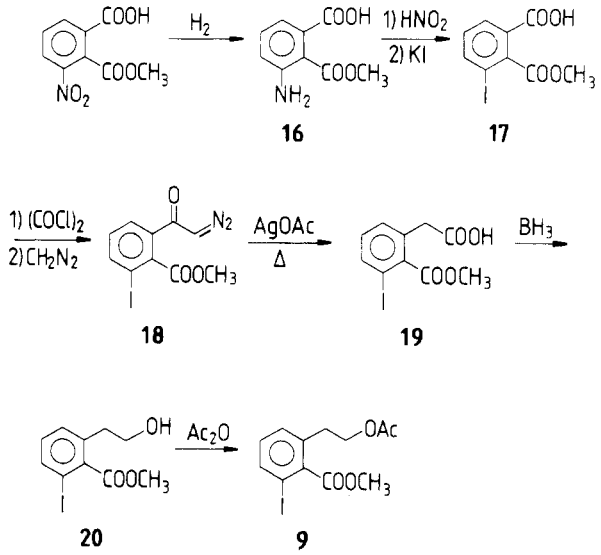
21

Biology. The compounds IIa–h were considered potential antiparkinson agents and, therefore, were tested for their D_2 receptor affinity and dopamine agonist activity. The in vitro test was performed with [^{3}H]spiperone and [^{3}H]flupenthixol as the radioactive ligands. The in vivo activity was assayed by the climbing and the turning behavior tests (see the Experimental Section).

Results and Discussion

None of the synthesized compounds II showed affinity for dopamine D_2 receptors up to 1 μM concentration, at

Scheme IV



variance with Ia and Ie for which we found IC_{50} values of 1 and 10 nM, respectively. None showed any activity in inducing climbing behavior in mice at doses up to 5 mg/kg sc or turning behavior in rats at doses up to 5 mg/kg ip. The lack of dopaminergic activity, mainly in compounds IIb,d,f,h was somewhat surprising in the light of the small modification introduced into the aporphine structure. One cause might be the change of conformation of the nitrogen lone pair because of stereoelectronic interaction with the proximal oxygen lone pairs.

In aporphine derivatives, the R^1 group at the nitrogen atom is known to be equatorial, as shown by the presence of Bohlmann bands[13] in their infrared spectra. These bands between 2800 and 2700 cm^{-1} are diagnostic of antiperiplanar hydrogen/nitrogen lone pair interaction in fused piperidine derivatives.

We compared the IR spectra of Id and IId. The presence of these bands in both compounds showed that the conformation in the two series was the same. We then investigated the basicity of the nitrogen atom since on the basis of pK_a of dopaminergic agents it has been proposed that they interact in the protonated form.[14] We found for IId a pK_a of 6.4 ± 0.1 and for Id a pK_a of 7.1 ± 0.1. Therefore at physiological pH, which is 7.3 in homogenized rat nucleus caudatus, the 7-oxaaporphines II are largely in the form of a free base at variance with aporphines, which are largely protonated,[15] and with 9-oxaergolines[8] and 2*H*-naphth[1,2-*b*]-1,4-oxazines[9] for which we have calculated pK_a values of 8.2.[16] This might be the reason for the lack of activity of our compounds.

Experimental Section

Biological Methods. Assays of [^{3}H]spiperone and [^{3}H]flupenthixol binding to striatal homogenates were conducted as described in detail elsewhere.[17] Freshly dissected striata from male Sprague–Dawley rats (150–200 g) were homogenized in 30 volumes (w/v) of ice-cold 50 mM Tris·HCl buffer (pH 7.7 at 25 °C) with a Polytron PT10 homogenizer (setting 5, 20 s) and

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centrifuged at 50000*g* for 10 min at 4 °C in a Sorvall RC-2B centrifuge. The pellet was resuspended and recentrifuged. The final pellet was resuspended in Tris·HCl buffer (pH 7.1, 50 mM, at 37 °C) containing ascorbic acid (0.1%), pargyline (10 μM), NaCl (120 mM), KCl (5 mM), $CaCl_2$ (2 mM), and $MgCl_2$ (1 mM).

Nonspecific binding was defined by using 0.1 μM haloperidol in the [^{3}H]spiperone and 10 μM (+)-butaclamol in the [^{3}H]flupenthixol binding assays. Domperidone (5 nM) was added to the assay tubes in the [^{3}H]flupenthixol binding assay to exclude binding to the dopamine D_2 receptor. Membranes (100–300 μg of protein) in 1 mL of buffer were incubated for 10 min at 37 °C and rapidly filtered through glass-fiber filters (Watman GF/B) with a cell harvester M-48 R, Brandel, washed with 15 mL of buffer, suspended in 5 mL of Filter-Count (Packard), and counted in a Packard Tri-Carb 300C at about 45% efficiency.

Pharmacological Methods. Climbing Behavior. Male mice CD^R-1 (ICR) BR (22–25 g body weight) were present from the evening before in the same room in which the study was conducted. In the morning they were randomly assigned into groups of 10 animals each. The control group was injected subcutaneously with 1.3 mg/kg apomorphine (0.1% ascorbic acid) in a fixed volume (0.5 mL/100 g body weight) and the others with 5 mg/kg of the compounds II. Immediately after treatment, the animals were put into cylindrical individual cages (12 cm in diameter, 14 cm of high) with walls of vertical metal bars, 2 mm in diameter, 1 cm apart, with smooth surface. After a 5-min period of exploratory behavior, the apomorphine-treated animals tend to adopt a vertical position, holding the bars for at least 30 min and climbing up. This behavior was scored as follows: four paws on the floor = 0, forefeet holding the wall = 1, four paws holding the wall = 2. The animals were observed twice, 10 and 20 min after injection, and the scores were evaluated according to Protais.[18]

Turning Behavior in 6-Hydroxydopamine-Lesioned Rats. Male rats (290–310 g) anesthetized ip with 50 mg/kg sodium pentobarbital were placed in a Stoelting stereotaxis frame and were unilaterally injected with 6-hydroxydopamine (6-OHDA) in the substantia nigra, pars compacta (8 μg of free base in 4 μL of saline kept ice cold with 0.2% ascorbic acid at the rate of 1 μL/min). The neurotoxin was injected via a 10-μL Hamilton syringe under the following coordinates according to Paxinos and Watson:[19] A, 3.7 mm anterior to interaural line; V, 2.2 mm dorsal to interaural line; L, 2.2 mm from midline. The needle was left in place a further 5 min before being slowly withdrawn.

Following recovery from anesthesia, rats were housed one per cage and given ad libitum access to food and water. After a 3 weeks recovery, rats were injected with apomorphine (0.5 mg/kg sc) and immediately put in automated rotometer bowls with printing unit for 3 h. Only rats showing contralateral turning behavior totalling at least 250 complete turns within the control time were used for the test with the compounds. Forty selected rats were employed for testing compounds II (five rats per compound), and the substances were injected ip in a fixed volume (2 mL/kg body weight) 1 week after apomorphine. The observation for the rotational behavior lasted 6 h.

Chemistry. Melting points were determined in open capillaries with a Büchi melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Perkin-Elmer R-24B or a Brucker HX90 spectrometer. Chemical shifts are reported in parts per million (δ) relative to internal Me_4Si; IR spectra were recorded on a Perkin-Elmer 297 spectrometer. Mass spectra were recorded on a CH-7 Varian MAT spectrometer at 70 eV. Elemental analyses were performed by our analytical laboratory and agreed with theoretical values within ±0.4%. Common reagent-grade chemicals and starting materials were purchased from commercial sources and were used as received. Drying of solvents was performed by storage on 3A molecular sieves. Evaporations were made in vacuo (rotating evaporator) and were preceded by drying over sodium sulfate. Flash chromatography, with silica gel as the stationary phase and the solvent mixture reported within parentheses as the eluant, was used to purify and isolate compounds that could not be crystallized.

Determination of pK_a Values. pK_a (H_2O) values were calculated from the half-neutralization potential obtained by titration in EtOH–H_2O, 8:2, with 0.1 N HCl.[20]

(6-Oxo-6*H*-dibenzo[*b*,*d*]pyran-7-yl)acetic Acid (2). To a stirred mixture of 6-oxo-6*H*-dibenzo[*b*,*d*]pyran-7-carboxylic acid (**1**)[21] (12 g, 50 mmol) and oxalyl chloride (8.6 mL, 100 mmol) in anhydrous benzene (250 mL) was added a few drops of DMF. After 3 h the solvent was evaporated. Toluene (100 mL) was added and evaporated. The solution of the crude acyl chloride in anhydrous THF (500 mL) was added dropwise to an ice-cooled, stirred solution of diazomethane (prepared from 300 mmol of *N*-nitroso-*N*-methylurea) in diethyl ether (650 mL). The reaction mixture was stirred for a further 4 h at 0 °C and then allowed to stand overnight at room temperature. Excess diazomethane was removed by gentle heating. Solvent was evaporated, and the residue was ground with diethyl ether and filtered to give 10.9 g (83%) of the intermediate diazo ketone, mp 150–152 °C. Anal. ($C_{15}H_8N_2O_3$) C, H, N.

A solution of the diazo ketone (10.5 g, 40 mmol) in 1:1 water–dioxane (300 mL) was heated at 60 °C for 5 h in presence of Ag_2O (6.6 g, 28 mmol). Then, 23% HCl (200 mL) was added, and the mixture was refluxed for 1 h. The precipitate was filtered and extracted in a Soxhlet apparatus with chloroform. Evaporation gave 6.4 g (63%) of **2**, mp 257–260 °C (from absolute EtOH): ^{1}H NMR (DMSO-d_6) δ 4.17 (s, 2 H), 7.20–7.70 (m, 4 H), 7.86 (t, 1 H), 8.30 (m, 2 H), 12.30 (br, 1 H). Anal. ($C_{15}H_{10}O_4$) C, H.

2-(6-Oxo-6*H*-dibenzo[*b*,*d*]pyran-7-yl)ethanol (3). To a stirred suspension of **2** (6.35 g, 25 mmol) in THF (370 mL) was added 1 M BH_3 in THF (35 mL) at 10 °C. The mixture was stirred for 1 h at 10 °C and then for a further 6 h at room temperature. MeOH (20 mL) was added to decompose the excess BH_3. The solution was evaporated to dryness, diluted with water, and extracted with chloroform (3 × 70 mL). The combined extracts were washed with $NaHCO_3$ and brine and evaporated. The residue was crystallized to give 5 g (83%) of **3**, mp 112–114 °C: ^{1}H NMR ($CDCl_3$) δ 2.30 (br s, 1 H), 3.35 (t, 2 H), 3.77 (t, 2 H), 6.80–7.70 (m, 7 H). Anal. ($C_{15}H_{12}O_3$) C, H.

7-[2-[(Methylsulfonyl)oxy]ethyl]-6*H*-dibenzo[*b*,*d*]pyran-6-one (4). To a stirred solution of **3** (6 g, 25 mmol) and triethylamine (4.2 mL, 30 mmol) in CH_2Cl_2 (200 mL) methanesulfonyl chloride (2.3 mL, 30 mmol) in CH_2Cl_2 (50 mL) was added dropwise at −5 °C. After 2 h the reaction was worked up to give 7.1 g (89%) of **4** as a white solid, mp 132–134 °C (from EtOAc): ^{1}H NMR ($CDCl_3$) δ 2.90 (s, 3 H), 3.60 (t, 2 H), 4.50 (t, 2 H), 7.20–8.10 (m, 7 H). Anal. ($C_{16}H_{14}SO_5$) C, H, S.

7-[2-[(Methylsulfonyl)oxy]ethyl]-6*H*-dibenzo[*b*,*d*]pyran-6-ol (5). To a stirred suspension of **4** (5 g, 1.6 mmol) in toluene (250 mL) was added 1.2 M diisobutylaluminum hydride (DIBAH) in toluene (17.5 mL, 21 mmol) at −70 °C under nitrogen. After 3 h the solution was allowed to warm to −20 °C and then water and Celite were added to the mixture. The suspension was filtered, and the precipitate was thoroughly washed with ethyl acetate. The organic solution was dried and evaporated to give 4.8 g (95%) of **5** as a pasty solid: ^{1}H NMR ($CDCl_3$) δ 2.72 (s, 3 H), 3.05 (t, 2 H), 4.30 (t, 2 H), 6.36 (s, 1 H), 6.90–7.25 (m, 5 H), 7.45–7.65 (m, 2 H).

4,5,6,6a-Tetrahydro-6-methylbenzopyrano[4,3,2-*ij*]isoquinoline (IIa). A solution of **5** (1 g, 3.1 mmol) in toluene (50 mL) and 20% $MeNH_2$ in diisopropyl ether (40 mL) was stirred overnight under nitrogen and then evaporated to dryness. Purification by flash chromatography (cyclohexane–EtOAc, 2:1) gave 0.31 g (43%) of IIa as a solid, mp 88–90 °C (from Et_2O–*n*-pentane, 1:1): ^{1}H NMR ($CDCl_3$) δ 2.62 (s, 3 H), 2.57–3.17 (m, 4 H), 4.81 (s, 1 H), 6.78–7.72 (m, 7 H); MS, *m*/*z* 237 (M^+). Anal. ($C_{16}H_{15}NO$) C, H, N.

4,5,6,6a-Tetrahydro-6-*n*-propylbenzopyrano[4,3,2-*ij*]isoquinoline (IIe). Analogously to compound IIa, with **5** (2.2 g, 6.8 mmol) and *n*-propylamine (5.6 mL, 68 mmol) as starting materials, 0.74 g (40%) of IIe was obtained as a colorless oil: ^{1}H NMR

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($CDCl_3$) δ 1.00 (t, 3 H), 1.40–1.95 (m, 2 H), 2.70–3.30 (m, 6 H), 5.25 (s, 1 H), 6.90–7.84 (m, 7 H).

2,6-Dimethoxyiodobenzene (6)[12] and 2,5-Dimethoxyiodobenzene (7).[22] These two compounds were obtained in 75% and 87% yield, respectively, by the same method described for compound 8.

5-(Benzyloxy)-4-iodo-1,3-benzodioxole (8). To a solution of 5-(benzyloxy)-1,3-benzodioxole[23] (72.5 g, 0.32 mol) in anhydrous THF (500 mL) was added 15% *n*-BuLi in hexane (220 mL, 0.35 mol) over 1.5 h at 0 °C under nitrogen. Then, a solution of iodine (89 g, 0.35 mol) in anhydrous THF (200 mL) was added dropwise over 40 min at 0 °C. After the mixture was stirred at room temperature for 2 h, MeOH (50 mL) was added dropwise, and then the solution was evaporated to dryness, taken up with water, and extracted with ethyl acetate (3 × 200 mL). The combined extracts were washed with $Na_2S_2O_3$ and then with brine. Evaporation to dryness gave 91.8 g (81%) of **8** as a brown solid, mp 63–65 °C: ^1H NMR ($CDCl_3$) δ 5.00 (s, 2 H), 5.90 (s, 2 H), 6.21 (d, 1 H, J = 8 Hz), 6.60 (d, 2 H), 7.30 (s, 5 H).

The following (**16–20**) are intermediates for compound **9** (see Scheme IV).

3-Amino-2-(methoxycarbonyl)benzoic Acid Hydrochloride (16). A solution of 3-nitro-2-(methoxycarbonyl)benzoic acid[24] (40.5 g, 0.18 mol) in anhydrous ethanol (1.1 L) was hydrogenated at 1.5 atm with 5% Pd/C (4 g). After 1 h the catalyst was filtered off, and 8% ethanolic HCl (70 mL) was added. The solution was evaporated to dryness, redissolved in anhydrous ethanol, and evaporated to dryness again. The solid residue was suspended in diethyl ether and filtered to give 39.2 g (94%) of **16**, mp 201–204 °C. Anal. ($C_9H_{10}ClNO_4$) C, H, N, Cl.

3-Iodo-2-(methoxycarbonyl)benzoic Acid (17). To a well-stirred solution of **16** (21 g, 90.6 mmol) in 2% HCl (290 mL) was added a solution of $NaNO_2$ (6.9 g, 100 mmol) in water (30 mL) at 0–4 °C. After 2 h urea (0.5 g) and then KI (23 g, 138 mmol) in water (50 mL) were added, and the reaction was allowed to warm to room temperature. After 2 h the mixture was extracted with ethyl acetate (3 × 200 mL). The combined extracts were washed with brine, dried, and evaporated. The residue was taken up with diisopropyl ether and filtered to give 19.7 g (71%) of **17**, mp 150–153 °C. Anal. ($C_9H_7IO_4$) C, H, I.

α-Diazo-3-iodo-2-(methoxycarbonyl)acetophenone (18). To a stirred suspension of **17** (15.6 g, 50 mmol) in benzene (200 mL) were added oxalyl chloride (8.7 mL, 100 mmol) and a few drops of anhydrous DMF at room temperature. When gas evolution ceased, volatiles were removed, toluene (200 mL) was added, and the solution was evaporated to dryness. The crude acyl chloride, dissolved in anhydrous THF (400 mL), was added dropwise at 0 °C to a solution of diazomethane (prepared from 15.5 g of *N*-methyl-*N*-nitrosourea) and triethylamine (7 mL, 51 mmol) in diethyl ether (1 L). After 16 h at room temperature, excess diazomethane was decomposed with AcOH (2 mL). $Et_3N{\cdot}HCl$ was filtered, and the solution was evaporated to dryness. Recrystallization from ethyl acetate gave 12.8 g (76%) of **18**, mp 205–208 °C: ^1H NMR ($CDCl_3$) δ 3.97 (s, 3 H), 5.83 (s, 1 H), 7.13 (dd, 1 H), 7.50 (dd, 1 H), 7.97 (dd, 1 H); MS, m/z 330 (M^+), 302 ($M - N_2$, 100%).

2-(Methoxycarbonyl)-3-iodophenylacetic Acid (19). To a stirred suspension of AgOAc (6.5 g, 39 mmol) in water (225 mL) was added as solution of **18** (16.8 g, 51 mmol) in dioxane (225 mL). After the mixture was heated at 70 °C for 1.5 h, Na_2CO_3 (4 g) was added, and the suspension was filtered over Celite. The solution was brought to pH 3 with 1 M H_2SO_4 and was extracted with chloroform (3 × 100 mL). The combined extracts were evaporated to dryness. Purification by flash chromatography (cyclohexane–EtOAc–AcOH, 100:50:7.5) gave 13.4 g (82%) of **19** as a white crystalline solid, mp 91–93 °C (from *n*-heptane): ^1H NMR ($CDCl_3$) δ 3.56 (s, 2 H), 3.82 (s, 3 H), 6.95 (dd, 1 H), 7.10 (dd, 1 H), 7.64 (dd, 1 H), 8.20 (br, 1 H).

2-(2-Hydroxyethyl)-6-iodobenzoic Acid Methyl Ester (20). To a stirred solution of **19** (13.6 g, 42 mmol) in anhydrous THF (300 mL) was added 1 M BH_3 in THF (70 mL) dropwise at 5–10 °C. After 2 h, water (500 mL) was carefully added, and the solution was extracted with diethyl ether (3 × 100 mL). The combined extracts were evaporated to dryness to give 12.3 g (96%) of **20** as a yellow oil: ^1H NMR ($CDCl_3$) δ 2.60 (br, 1 H), 2.76 (t, 2 H), 3.67 (t, 2 H), 3.30 (s, 3 H), 6.97 (dd, 1 H), 7.13 (dd, 1 H), 7.61 (dd, 1 H).

2-(2-Acetoxyethyl)-6-iodobenzoic Acid Methyl Ester (9). Pyridine (2 mL) was added to a solution of **20** (21.1 g, 69 mmol), in acetic anhydride (100 mL). After 1 h the solution was poured onto a mixture of crushed ice and $NaHCO_3$. After complete decomposition of excess acetic anhydride, extraction with ethyl acetate gave 22.6 g (94%) of **9** as a colorless oil: ^1H NMR ($CDCl_3$) δ 2.00 (s, 3 H), 2.85 (t, 2 H), 3.87 (s, 3 H), 4.18 (t, 2 H), 6.80–7.20 (m, 2 H), 7.55 (dd, 1 H, J = 2 Hz, J = 8 Hz).

2-Diazo-4-iodo-2*H*-indan-1,3-dione (21). A solution of crude diazo ketone **18** (30.6 mmol) in 1:1 dioxane–water (800 mL) was heated at 60 °C for 3 h in the presence of Ag_2O (7 g). The reaction was extracted with ethyl acetate to give 4.9 g (54%) of **21**, mp 203–205 °C (from diisopropyl ether): ^1H NMR (DMSO-d_6–$CDCl_3$) δ 7.49 (t, 1 H, J = 6 Hz), 7.80 (dd, 1 H), 8.18 (dd, 1 H); MS, m/z 298 (M^+); IR (Nujol) 2150, 1680 cm^{-1}. Anal. ($C_9H_3IN_2O_2$) C, H, N, I.

3-(2-Acetoxyethyl)-2′,6′-dimethoxybiphenyl-2-carboxylic Acid Methyl Ester (10). A well-dispersed mixture of **9** (32 g, 92 mmol), **6** (221 g, 0.83 mol), and Cu powder (100 g, 1.56 mol) was heated at 200 °C overnight. The mixture was ground with chloroform, filtered, and thoroughly washed with the same solvent. Removal of the solvent gave a residue, which was taken up with diisopropyl ether. The insoluble material (mostly 2,2′,4,4′-tetramethoxybiphenyl) was filtered off. The solution was evaporated to dryness and purified by flash chromatography (petroleum ether–acetone, 2.5:1) to give 22.6 g (69%) of **10** as an oil: ^1H NMR ($CDCl_3$) δ 1.95 (s, 3 H), 2.96 (t, 2 H), 3.40 (s, 3 H), 4.08 (s, 6 H), 4.22 (t, 2 H), 6.46 (d, 2 H), 6.90–7.30 (m, 4 H).

3-(2-Acetoxyethyl)-2′,5′-dimethoxybiphenyl-2-carboxylic Acid Methyl Ester (11). Analogously to compound **10**, with **9** (24.2 g, 69 mmol), **7** (180 g, 0.68 mol), and Cu powder (600 g, 9.44 mol) as starting materials 14.9 g (60%) of **11** as a solid melting at 68–71 °C (diisopropyl ether) was obtained: ^1H NMR ($CDCl_3$) δ 1.95 (s, 3 H), 3.00 (t, 2 H), 3.48 (s, 3 H), 3.58 (s, 3 H), 3.68 (s, 3 H), 4.22 (t, 2 H), 6.70–7.30 (m, 6 H). Anal. ($C_{20}H_{22}O_6$) C, H.

2-[5-(Benzyloxy)-1,3-benzodioxol-4-yl]-6-(2-acetoxyethyl)benzoic Acid Methyl Ester (12). Analogously to compound **10**, with **9** (17.5 g, 50 mmol), **8** (125 g, 0.35 mol), and Cu powder (55 g, 0.85 mol) as starting materials, 12.9 g (57%) of **12** as a colorless oil was obtained: ^1H NMR ($CDCl_3$) δ 1.90 (s, 3 H), 2.96 (t, 2 H), 3.46 (s, 3 H), 4.22 (t, 2 H), 4.73 (s, 2 H), 5.70 (br, 2 H), 6.23 (d, 1 H), 6.55 (d, 1 H), 7.05–7.27 (m, 3 H); MS, m/z 448 (M^+).

7-(2-Bromoethyl)-1-hydroxy-6*H*-dibenzo[*b*,*d*]pyran-6-one (13). A suspension of **10** (10 g, 28 mmol) in acetic acid (150 mL) and 48% HBr (150 mL) was heated at 140 °C for 4 h. After cooling, the reaction mixture was poured into 2 L of ice water, and the solid was filtered. Crystallization from ethanol gave 6.8 g (76%) of **13**, mp 211–213 °C: ^1H NMR ($CDCl_3$–DMSO-d_6) δ 3.74 (br, 4 H), 6.86 (br t, 2 H), 7.06 (d, 1 H), 7.22 (d, 1 H), 7.8 (t, 1 H), 9.2 (br d, 1 H). Anal. ($C_{15}H_{11}BrO_3$) C, H, Br.

7-(2-Bromoethyl)-2-hydroxy-6*H*-dibenzo[*b*,*d*]pyran-2-one (14). Analogously to compound **13**, with **11** (14.6 g, 41 mmol) as starting material, 7.2 g (55%) of **14**, mp 196–198 °C (diisopropyl ether) was obtained: ^1H NMR ($CDCl_3$–DMSO-d_6) δ 3.65 (s, 4 H), 6.70–8.00 (m, 7 H); MS, m/z 318 (M^+). Anal. ($C_{15}H_{11}BrO_3$) C, H, Br.

8-(2-Bromoethyl)-1,3-benzodioxolo[5,4-*c*][2]benzopyran-7-one (15). A suspension of **12** (18 g, 40 mmol) in 48% HBr (250 mL) and acetic acid (400 mL) was heated for 3 h at 60 °C. Water (1 L) was added, and the solid was filtered and crystallized from 95% ethanol to give 7.8 g (54%) of **15**, mp 200–202 °C: ^1H NMR ($CDCl_3$) δ 3.70 (m, 4 H), 6.22 (s, 2 H), 6.80 (d, 1 H), 6.99 (d, 1 H), 7.47 (dd, 1 H), 7.88 (dd, 1 H), 8.49 (dd, 1 H); MS, m/z 346 (M^+), 267 (M – Br). Anal. ($C_{16}H_{11}BrO_4$) C, H, Br.

6-Methyl-4,5,6,6a-tetrahydro[1]benzopyrano[4,3,2-*ij*]isoquinolin-11-ol (IIb). To a stirred suspension of **13** (2 g, 6.28 mmol) in toluene (250 mL) under nitrogen at −70 °C was added 1.2 M DIBAH in toluene (10.3 mL, 12.5 mmol). The mixture was stirred for 8 h until a clear solution was obtained. A solution of

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20% methylamine in diisopropyl ether (30 mL) was then added, and the temperature was allowed to rise to room temperature. After being stirred overnight, the reaction mixture was diluted with water, extracted with $CHCl_3$, and evaporated, and the compound was purified by flash chromatography (increasing the polarity of the eluant from ethyl acetate–cyclohexane, 1:1, to pure ethyl acetate) to give 1.08 g (68%) of IIb, mp 158 °C dec: ^{1}H NMR (DMSO-d_6) δ 2.62 (s, 3 H), 2.55–3.10 (m, 4 H), 4.79 (s, 1 H), 6.47 (dd, 1 H), 6.60 (dd, 1 H), 6.90–7.40 (m, 3 H), 8.17 (dd, 1 H), 10.07 (s, 1 H); MS, m/z 253 (M^+) 252 (100), 210. Anal. ($C_{16}H_{15}NO_2$) C, H, N.

6-Methyl-4,5,6,6a-tetrahydro[1]benzopyrano[4,3,2-*ij*]isoquinolin-10-ol (IIc). Analogously to compound IIb, with **14** (1.8 g, 5.64 mmol) as starting material, 0.86 g (60%) of IIc was obtained as pale yellow crystals, mp 200–210 °C dec: ^{1}H NMR (DMSO-d_6) δ 2.60 (s, 3 H), 2.45–3.10 (m, 4 H), 4.78 (s, 1 H), 6.62–7.54 (m, 6 H); MS, m/z 253 (M^+). Anal. ($C_{16}H_{15}NO_2$) C, H, N.

7-Methyl-6a,7,8,9-tetrahydro-1,3-dioxolo[5,6][1]benzopyrano[4,3,2-*ij*]isoquinoline (IId). Analogously to compound IIb, with **15** (1.39 g, 4 mmol) as starting material, 0.83 g (74%) of IId was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.70 (s, 3 H), 2.70–3.30 (m, 4 H), 4.91 (s, 1 H), 5.98 (d, 1 H, J = 2 Hz), 6.05 (d, 1 H), 6.50 (d, 1 H, J = 8.5 Hz), 6.68 (d, 1 H), 7.00–7.40 (m, 2 H), 7.81 (dd, 1 H); MS, m/z 281 (M^+). Anal. ($C_{17}H_{15}NO_3$) C, H, N.

6-Propyl-4,5,6,6a-tetrahydro[1]benzopyrano[4,3,2-*ij*]isoquinolin-11-ol (IIf). Analogously to compound IIb, with **13** (3 g, 9.4 mmol) and excess *n*-propylamine as starting materials, 2 g (77%) of IIf was obtained as a solid, mp 150 °C dec: ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3 H), 1.64 (m, 2 H), 2.95 (m, 6 H), 5.13 (s, 1 H), 6.54 (d, 2 H), 6.90–7.40 (m, 3 H), 8.02 (dd, 1 H), 10.10 (br, 1 H); MS, m/z 281 (M^+), 280 (100). Anal. ($C_{18}H_{19}NO_2$) C, H, N.

6-Propyl-4,5,6,6a-tetrahydro[1]benzopyrano[4,3,2-*ij*]isoquinolin-10-ol (IIg). Analogously to compound IIb, with **14** (1.3 g, 4.1 mmol) and excess *n*-propylamine as starting materials, 0.7 g (64%) of IIg, mp 164–166 °C, was obtained: ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 0.90 (t, 3 H), 1.62 (m, 2 H), 2.70–3.20 (m, 6 H), 4.96 (s, 1 H), 6.66 (dd, 1 H), 6.76 (d, 1 H), 7.10–7.50 (m, 4 H), 8.91 (s, 1 H); MS, m/z 281 (M^+), 280, 251. Anal. ($C_{18}H_{19}NO_2$) C, H, N.

7-Propyl-6a,7,8,9-tetrahydro-1,3-dioxolo[5,6][1]benzopyrano[4,3,2-*ij*]isoquinoline (IIh). Analogously to compound IIb, with **15** (1.4 g, 4 mmol) and excess *n*-propylamine as starting materials, 0.84 (68%) of IIh was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 3 H), 1.67 (m, 2 H), 2.70–3.20 (m, 6 H), 5.14 (s, 1 H), 6.02 (d, 1 H, J = 1.5 Hz), 6.11 (d, 1 H), 6.53 (d, 1 H), 6.70 (d, 1 H), 7.13 (d, 1 H), 7.30 (t, 1 H), 7.83 (d, 1 H); MS, m/z 309. Anal. ($C_{19}H_{19}NO_3$) C, H, N.

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Synthesis and Estrogen Receptor Selectivity of 1,1-Bis(4-hydroxyphenyl)-2-(*p*-halophenyl)ethylenes

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A series of triarylethylenes (**1a–e**) were synthesized and evaluated for their ability to compete with [^{3}H]estradiol for high-affinity estrogen receptors (ER) in immature rat uterine cytosol. All compounds showed affinity comparable to that of estradiol, with **1c** having the highest affinity and the lowest calculated nonspecific binding of the para-halogenated members. Compound **1a** had a higher affinity than did its chlorovinyl counterpart **1b**, indicating that a vinyl hydrogen was suitable for high ER affinity in this series. Compound **1c** was labeled with ^{3}H ortho to one or both of its hydroxyls. Its ratio of specific to nonspecific binding in rat uterine cytosol, 3.2, was 140% of that of a related triarylethylene, 4-hydroxytamoxifen, and was 24% that of estradiol. Administration of [^{3}H]-**1c** to immature female rats resulted in accumulation of ^{3}H in uterine tissue which was decreased 39% when [^{3}H]-**1c** was coadministered with estradiol. The major site of accumulation 1, 4, and 8 h after administration was in the intestinal tract. Chromatographic analysis showed that levels of **1c** were less than those of **1c** glucuronide in blood plasma, liver, and intestinal contents of rats 1 h after administration of **1c**. Uterine ^{3}H was comprised of 85% of **1c** and 11% of **1c** glucuronide. These results indicate that **1c** undergoes ER-mediated uptake in the immature female rat, but selectivity is reduced due to nonspecific accumulation of free and conjugated **1c** in uterine tissue.

The presence of estrogen receptors (ER) has become a determining factor in the choice of therapy for breast cancer.[1] Such cancers, which have significant concentrations of ER, can often be suppressed by use of hormones and antihormones.[2]

For in vivo detection of ER, a variety of steroidal and nonsteroidal compounds known to interact strongly with ER in vitro, and capable of bearing short-lived radioisotopes of fluorine, bromine, or iodine, have been evaluated for their ability to locallize in ER-containing normal and malignant tissue.[3] The aim of such studies is to identify

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