Synthesis and Antiinflammatory/Analgesic Activities of 11*H*-Dibenzo[*b*,*e*][1,4]dioxepinacetic Acids

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A new class of tricyclic arylacetic acids was synthesized and evaluated as antiinflammatory/analgesic agents as well as inhibitors of prostaglandin synthetase. 11*H*-Dibenzo[*b*,*e*][1,4]dioxepin-2-, -3-, -7-, and -8-acetic and α-methylacetic acids and their derivatives were prepared by cyclization of diaryl ether precursors or by condensation of catechol and an aryl dihalide. The most potent compound in the carrageenan foot edema assay was α-methyl-11*H*-dibenzo[*b*,*e*][1,4]dioxepin-8-acetic acid (1 mg/kg = 43% inhibition). The most potent enzyme inhibitors were the 2-acetic acid and the α-methyl-7-acetic acid (IC_{50} = 0.1 μM). Some of these compounds were also found to be highly ulcerogenic.

Potent analgesic and antiinflammatory activities have been reported for many tricyclic arylacetic and α-methylacetic acids having two benzo groups fused around a central seven-membered ring, including dibenzotroponones,[1] dibenzoxepins,[2] dibenzothiepins,[3] and dibenzazepins.[4] In each of these, the seven-membered ring is comprised of all carbon atoms or contains only one heteroatom. It is of interest to examine the effect of an additional heteroatom on the antiinflammatory properties of this class of acidic nonsteroidal antiinflammatory drugs (NSAIDS). Herein, we report the preparation and biological activities of the 2-, 3-, 7-, and 8-acetic acids of 11*H*-dibenzo[*b*,*e*][1,4]dioxepin (**1a–4a**, Figure 1), a fused tricyclic ring system containing two oxygen atoms in the central seven-membered ring. The measured activities are discussed in terms of a model for prostaglandin synthesis inhibition.

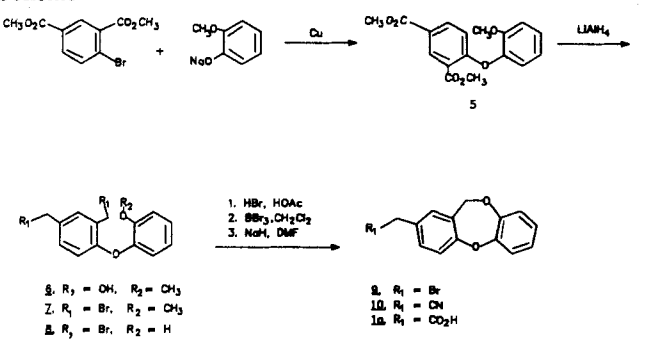
Chemistry. The compounds were initially synthesized by a method analogous to one described by Inubushi[5] and illustrated in Scheme I for the preparation of 11*H*-dibenzo[*b*,*e*][1,4]dioxepin-2-acetic acid, **1a**. Cyclization to the tricyclic ring system, **9**, was effected by treatment of a dilute solution of **8** with sodium hydride at low temperature and followed by slow warming. The 3-, 7-, and 8-acetic acids (**2a–4a**) were prepared in a similar manner.

A different method for the preparation of substituted derivatives of the 7-acetic acid was exploited and is outlined in Scheme II. Catechol was alkylated/arylated with 2-chloro-5-nitrobenzyl chloride in a "one pot" procedure to give 2-nitro-11*H*-dibenzo[*b*,*e*][1,4]dioxepin, **11**. Friedel–Crafts acylation of **11** with acetyl chloride and stannic chloride gave exclusively the 7-acetyl derivative **12**. Treatment of **12** with thallium trinitrate on K-10 support[6] gave the arylacetate ester **13**. Alkylation of **13** followed by removal of the nitro group and ester hydrolysis gave the α-methylacetic acid **3b**. Manipulation of aromatic groups on **13** gave substituted derivatives **3c–3e**.

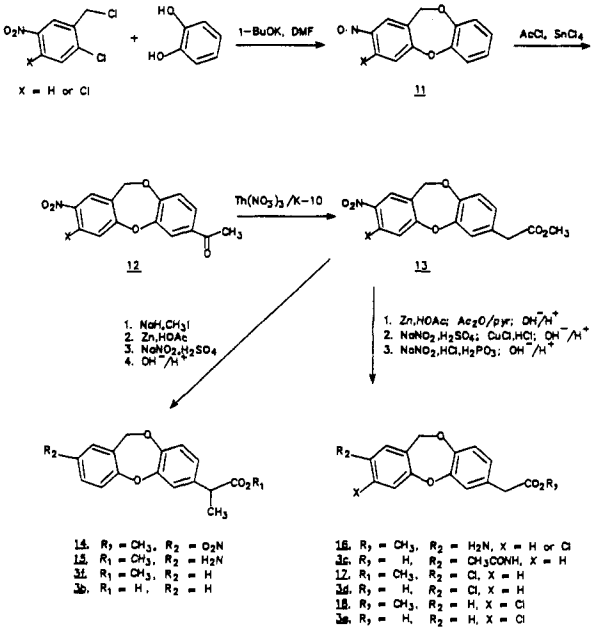
Reaction of **3b** with 1-chloroethyl ethyl carbonate ("ECOE" chloride)[7] in the presence of triethylamine gave the "ECOE" ester **3g**. Esterification of **3b** with 2-acetamidoethanol gave ester **3h**. Reduction of **3b** with borane gave the propanol derivative **3i**.

A slightly different approach was taken for the preparation of the α-methyl-8-acetic acid **4b**. The carbonyl functionality was introduced in the beginning of the synthesis by condensing methyl 2-bromobenzoate with the sodium salt of acetovanillone followed by protection of the ketone as the ethylene ketal. The remainder of the chemistry (**19** → **26** → **4b**) followed that discussed for the preparation of **3b**.

Scheme I



Scheme II



Biological Activity. The compounds were initially screened in the rat carrageenan foot edema (CFE) anti-

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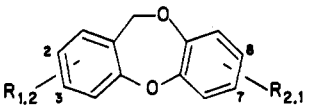
Table I. Antiinflammatory Activity and Cyclooxygenase Inhibition of Dibenzo[b,e][1,4]dioxepinacetic Acids

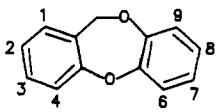


compd no.	R_1	R_2	inhibition of CFE:[a,b] dose, mg/kg 1	3	10	inhibition of cyclooxygenase: IC_{50}, μM, ±20%
1a	2-CH_2CO_2H	H	12	9	16	0.1
2a	3-CH_2CO_2H	H	NT[c]	6	5	>100
3a	7-CH_2CO_2H	H	24	10	40	1.4
3b	7-$CH(CH_3)CO_2H$	H	21	27	42	0.1
3c	7-CH_2CO_2H	2-$NHCOCH_3$	35	16	23	>100
3d	7-CH_2CO_2H	2-Cl	21	23	28	NT
3e	7-CH_2CO_2H	3-Cl	11	19	5	7.0
3f	7-$CH(CH_3)CO_2CH_3$	H	23	32	56	1.4
3g	7-$CH(CH_3)CO_2CH(CH_3)OCOC_2H_5$	H	6	15	12	NT
3h	7-$CH(CH_3)CO_2CH_2CH_2NHAc$	H	7	15	28	1.3
3i	7-$CH(CH_3)CH_2OH$	H	9	19	45	1.8
4a	8-CH_2CO_2H	H	28	53	49	10
4b	8-$CH(CH_3)CO_2H$	H	43	45	43	0.3
indomethacin			33	56	67	0.3
zomepirac			61	82	NT	NT

[a] Each point represents the mean of six rats/dose level. [b] Values ≥20% were statistically significant ($P < 0.05$). [c] Not tested.

Table II. Inhibition of Phenylbenzoquinone (PBQ) Writhing

compd no.	dose, mg/kg/% inhibition (±SE)	compd no.	dose, mg/kg/% inhibition (±SE)
1a	30/37 (13)	**3e**	30/26 (15)
3a	30/26 (14)	**4a**	20/45 (15)
3b	30/91 (5), 10/70 (10), 3/38 (20)	**4b**	30/70 (10)
		indomethacin	1/66 (15)
3c	30/–55 (25)	zomepirac	1/70 (15)
3d	30/82 (7)		



1a. 2-CH_2CO_2H
2a. 3-CH_2CO_2H
3a. 7-CH_2CO_2H
4a. 8-CH_2CO_2H

Figure 1. 11*H*-Dibenzo[*b*,*e*][1,4]dioxepinacetic acids.

inflammatory assay[8] (see Experimental Section). The results are shown in Table I. The more active compounds have the acetic acid moiety in the 7- and 8-positions. The respective α-methylacetic acids (**3b**, **4b**) have slightly increased antiinflammatory activity. However, the dose–response curves of **3b** and **4b** flatten out quickly, indicating a limited maximal activity. Substituents at the 2- and 3-position of **3a** (**3c–e**) had a negative effect on the activity in that series. The esters **3f–h** were prepared as prodrugs of **3b** in order to reduce gastrointestinal toxicity. Interestingly, the methyl ester **3f** exhibited increased CFE activity, while the "ECOE" ester **3g** and the acetamidoethyl ester **3h** were worse than **3b**. The propanol derivative **3i** also exhibited limited activity. The potency of these compounds in the inhibition of cyclooxygenase (CO prostaglandin synthetase) was also measured and is reported in Table I.

Table III. Gastric Hemorrhage[a]

compd no.	dose, mg/kg 10	30
3b	5/6 (4.2)	6/6 (5.8)
3f	0/6	5/6 (1.7)

[a] Number of rats with lesions/total number of rats (lesions per animal).

Several compounds were selected for evaluation of their analgesic activity, which was determined by the ability to inhibit abdominal writhing after intraperitoneal administration of phenylbenzoquinone[9] (PBQ; see Experimental Section). The results are listed in Table II. The acids **3b** and **3d** had the highest activity of those tested.

The inhibition of cyclooxygenase by this type of agent, in addition to providing the therapeutic effect, gives rise to characteristic gastrointestinal side effects, such as gastric hemorrhage, lesions, and ulcers. The protective action of prostaglandins are attributed to their inhibition of acid production and stimulation of protective mucous formation.[10] Therefore, **3b** and its methyl ester **3f** were tested for incidence of gastric hemorrhage[11] (see Experimental Section). The results, shown in Table III, show that the free acid **3b** is very ulcerogenic ($UD_{50} < 10$ mg/kg), while the methyl ester **3f** does offer some protection.

Discussion

The compounds with the most potent antiinflammatory activity in this series of tricyclic arylacetic acids are 11*H*-dibenzo[*b*,*e*][1,4]dioxepin-8-acetic acids **4a** and **4b**. The position of the acetic acid group in the aromatic rings relative to the heteroatoms/carbonyl in the central seven-membered ring is crucial for maximal antiinflammatory activity of tricyclic arylacetic acids. The order of antiinflammatory potency of the tricyclic arylacetic acids with a given nucleus generally follows that shown in Figure 2. There are certainly exceptions, but the compounds having

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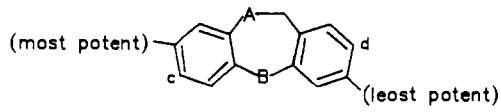

A, B = heteroatoms and/or carbonyl
c & d positions are comparable

Figure 2. Relative antiinflammatory activity of tricyclic arylacetic acids.

the acetic acid at the position "meta" to A are usually the best antiinflammatory agents compared with isomers having the acetic acid at other positions. The 11*H*-dibenzo[*b*,*e*][1,4]dioxepinacetic acids follow this observation. This generalization is not extended to analgesic activity where a difference in structural requirements has been noted.[4b]

Several models for the inhibition of prostaglandin synthetase (cyclooxygenase) by NSAIDS have been proposed.[12] One such model described by Appleton and Brown[13] suggests that arylacetic acids occupy the site on the enzyme normally taken up by arachidonic acid and the two reacting oxygen molecules. The acetic acid occupies one oxidizing position and the "meta" heteroatom or carbonyl occupies the other, as long as it is not too sterically crowded. At first glance, this model might predict that **4a** would be the best prostaglandin synthetase inhibitor followed by **3a** and **2a**. However, as seen in Table I, **1a** is the most potent inhibitor of this enzyme of the parent acetic acids followed by **3a** and **4a**. This observation can still be accommodated by the Appleton–Brown model. The oxygen at position 10 is sterically acceptable and may be better oriented in **1a** for binding to the second oxidation site of the enzyme. The correlation between enzyme inhibition and antiinflammatory activity by NSAIDs has been noted,[12] and the poor in vivo activity of **1a** and mediocre enzyme inhibition of **4a** appear to be discrepancies. Such models may be useful in designing drugs with potent enzyme inhibition, but they cannot predict the pharmacologic dynamics, such as absorption, distribution, metabolism, or excretion of these compounds.

The addition of a second heteroatom to the nucleus of the tricyclic acetic acids has resulted in the preparation of several very potent inhibitors of prostaglandin synthetase. Unfortunately, this has not translated into compounds with potent antiiinflammatory or analgesic activities. The flat dose response of the dibenzo[*b*,*e*](1,4)dioxepinacetic acids, barely reaching an ED_{50}, does not compare well with the reported antiinflammatory activities of related tricyclic arylacetic acids; e.g., 6,11-dihydro-11-oxodibenzo[*b*,*e*]oxepin-3-acetic acid (Oxepinac) has an ED_{50} = 3.7 mg/kg in the CFE assay.[2] Though some of these compounds are very potent inhibitors of cyclooxygenase, their limited antiinflammatory activity and high ulcerogenicity preclude them from further study.

Experimental Section

General Procedures. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The ^1H NMR spectra were obtained in $CDCl_3$ with tetramethylsilane as internal standard on a Varian EM-390 spectrometer. Infrared spectra were obtained as thin films on sodium chloride plates on a Perkin-Elmer 283B spectrophotometer. Mass spectra were determined on a LKB 9000 mass spectrometer. Analytical results for compounds followed by elemental symbols were ±0.4% of calculated values and were determined on a Control Equipmentl elemental analyzer 240X. Preparative HPLC was performed on a Waters Prep LC-500A apparatus with Prep-PAK 500 silica gel cartridges.

General Procedure for the Preparation of 11*H*-Dibenzo[*b*,*e*][1,4]dioxepinacetic Acids (1–4). The preparation of 11*H*-dibenzo[*b*,*e*][1,4]dioxepin-2-acetic acid (**1a**) is described and is illustrative of the procedures followed for the preparation of these compounds.

Preparation of Dimethyl 4-(2-Methoxyphenoxy)isophthalate (5). A mixture of sodium guaiacolate (23.0 g, 0.16 mol), dimethyl 4-bromoisophthalate (41.0 g, 0.15 mol), and copper powder (4.0 g, 0.06 mol) was heated to 230 °C for 3.5 h. The mixture was cooled, and ethyl acetate (200 mL) and water (50 mL) were added. The mixture was filtered through a pad of Celite, which was subsequently thoroughly washed with ethyl acetate (200 mL). The combined filtrates were successively washed with 1 N sodium hydroxide (3 × 50 mL), water 3 × 50 mL), and brine (1 × 50 mL) and dried over anhydrous magnesium sulfate. The solvent was removed by rotoevaporation to give a brown oil (25.5 g) that was purified by preparative HPLC eluting with 10% ethyl acetate in hexane. The product (**5**) was crystallized from ether/hexane as a white powder (10.35 g, 20.8% yield): mp 82–83 °C; ^1H NMR ($CDCl_3$) δ 3.74 (3 H, s), 3.89 (3 H, s), 3.91 (3 H, s), 6.67 (1 H, d, J = 8.0 Hz), 6.75–7.28 (4 H, m), 7.96 (1 H, dd, J = 8.0, 1.5 Hz), 8.53 (1 H, d, J = 1.5 Hz); IR (thin film) 1718, 1697, 1614 cm^{-1}.

Preparation of 4-(2-Methoxyphenoxy)benzene-1,3-dimethanol (6). To a stirred suspension of lithium aluminum hydride (2.66 g, 0.07 mol) in tetrahydrofuran (15 mL) at 0 °C under nitrogen atmosphere was slowly added a solution of **5** (10.00 g, 0.032 mol) in tetrahydrofuran (30 mL). After the addition was complete, the resultant suspension was refluxed for 2.5 h then cooled to 0 °C. A saturated sodium sulfate solution (5 mL) was added and the suspension stirred at 0 °C for 1 h. It was filtered through a pad of anhydrous magnesium sulfate, which was subsequently washed with ethyl acetate (50 mL). The combined filtrates were rotoevaporated to give a clear colorless oil that crystallized upon standing. Recrystallization from hot ethyl acetate/hexane gave **6** as a white powder (7.50 g, 91% yield): mp 102–103 °C; ^1H NMR ($CDCl_3$) δ 3.80 (3 H, s), 4.53 (2 H, d, J = 5.0 Hz; s upon addition of D_2O), 4.70–4.95 (4 H, m; 4.73, 2 H, s addition of D_2O), 6.55 (1 H, J = 8 Hz), 6.90 (2 H, m), 7.10 (3 H, m), 7.55 (1 H, d, J = 1.5 Hz); IR (Nujol) 3300, 1620 cm^{-1}.

Preparation of 4-(2-Methoxyphenoxy)-α,α′-dibromo-*m*-xylene (7). To a suspension of diol **6** (6.85 g, 0.026 mol) in glacial acetic acid (15 mL) was added to 30–32% solution of hydrobromic acid in glacial acetic acid (15.5 mL, 0.058 mol). The resulting clear, colorless solution was stirred at room temperature for 4.5 h. Ice water (10 mL) was added, and the solution was extractd with ether (3 × 75 mL). The combined extracts were washed successively with water (4 × 25 mL), 1 N sodium bicarbonate solution (3 × 50 mL), water (2 × 50 mL), and brine (1 × 50 mL) and dried over anhydrous sodium sulfate. Removal of the solvent by rotoevaporation gave **7** as a clear, colorless oil (9.94 g, 97.6% yield): NMR ($CDCl_3$) δ 3.73 (3 H, s), 4.37 (2 H, s), 4.60 (2 H, s), 6.52 (1 H, d, J = 8.0 Hz), 6.80–7.23 (5 H, m), 7.36 (1 H, d, J = 1.5 Hz); IR (thin film) 1620, 1600, 1595 cm^{-1}.

Preparation of 4-(2-Hydroxyphenoxy)-α,α′-dibromo-*m*-xylene (8). Boron tribromide (2.66 mL, 0.028 mol) was added to a stirred solution of **7** (9.94 g, 0.026 mol) in methylene chloride (30 mL) at −78 °C under dry nitrogen atmosphere. After stirring at −78 °C for 30 min, the solution was warmed to 0 °C for 30 min. Water (5 mL) was slowly added and the solution extracted with ether (3 × 50 mL). The combined extracts were successively washed with water (4 × 50 mL) and brine (1 × 50 mL) and dried over anhydrous sodium sulfate. Removal of the solvent gave **8** as a clear, colorless oil (8.75 g, 91% yield): NMR ($CDCl_3$) δ 4.40 (2 H, s), 4.57 (2 H, s), 5.75 (1 H, br s, disappears upon addition of D_2O), 6.55–7.28 (6 H, m), 7.36 (1 H, d, J = 1.5 Hz); IR (thin film) 3500, 1600 cm^{-1}.

Preparation of 2-(Bromomethyl)-11*H*-dibenzo[*b*,*e*][1,4]-dioxepin (9). To a solution of **8** (8.75 g, 0.023 mol) in dry dimethylformamide (85 mL) at −78 °C under dry nitrogen atmosphere was added 60% sodium hydride in oil dispersion (1.00 g,

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0.025 mol). The mixture was warmed to 0 °C and stirred for 1 h. Glacial acetic acid (1 mL) and water (1 mL) were cautiously added, and the solution was extracted with ethyl acetate (1 × 200 mL). The extract was washed successively with water (4 × 50 mL) and brine (1 × 50 mL). After drying over anhydrous sodium sulfate, the solvent was removed by rotoevaporation to give a clear, colorless oil. The product **9** was purified by column chromatography on silica gel eluted first with hexanes then with 10% ether in hexanes. It was isolated as a clear, colorless oil in low yield (0.17 g, 2.5% yield): ^{1}H NMR ($CDCl_3$) δ 4.46 (2 H, s), 5.20 (2 H, s), 6.83–7.40 (7 H, m).

Preparation of 11*H*-Dibenzo[*b*,*e*][1,4]dioxepin-2-acetonitrile (10). A mixture of bromide **9** (170 mg, 0.58 mmol) and sodium cyanide (340 mg, 6.9 mmol) in dimethyl sulfoxide (1.2 mL) was heated to 60 °C for 1 h. After cooling, ethyl acetate (100 mL) was added and the solution was washed successively with water (4 × 20 mL) and brine (1 × 20 mL) and dried over anhydrous magnesium sulfate. The solvent was removed by rotoevaporation to give **10** as a light-yellow oil (137 mg, 100% yield): ^{1}H NMR ($CDCl_3$) δ 3.60 (2 H, s), 5.10 (2 H, s), 6.70–7.20 (7 H, m); IR (thin film) 2350, 1580 cm^{-1}.

Preparation of 11*H*-Dibenzo[*b*,*e*][1,4]dioxepin-2-acetic acid (1a). A solution of nitrile **10** (137 mg, 0.58 mmol) in ethanol (10 mL) and 2.5 N sodium hydroxide (3 mL) was refluxed for 3.5 h. The solution was cooled, water (20 mL) added, and the solution extracted with ether (3 × 20 mL). The aqueous solution was acidified with 6 N hydrochloric acid and extracted with ethyl acetate (3 × 20 mL). The combined extracts were washed successively with water (2 × 10 mL) and brine (1 × 10 mL) and dried over anhydrous sodium sulfate. The solution was filtered through a pad of silica gel, which was subsequently washed with fresh ethyl acetate (50 mL). The solvent was removed from the combined filtrates by rotoevaporation to give **1a** as a white crystalline solid (55 mg, 37% yield): mp 113–115 °C; ^{1}H NMR ($CDCl_3$) δ 3.65 (2 H, s), 5.23 (2 H, s), 6.83–7.20 (7 H, m); IR (thin film) 2800–3200, 1705, 1580 cm^{-1}; mass spectrum, *m/e* 256, 211. Anal. ($C_{15}H_{12}O_4$) C, H.

The other isomers, 11*H*-dibenzo[*b*,*e*][1,4]dioxepin-3-, -7-, and -8-acetic acids (*2a-4a*), were prepared in an analogous manner. The 3-acetic acid **2a** (mp 117–118 °C) was prepared from sodium guaiacolate and dimethyl 2-bromoterephthalate. The 7-acetic acid **3a** (mp 104–105 °C) was prepared from the sodium salt of isovanillin and methyl 2-bromobenzoate. The 8-acetic acid **4a** (mp 132–134 °C) was prepared from the sodium salt of vanillin and methyl 2-bromobenzoate.

Preparation of 2-Nitro-11*H*-dibenzo[*b*,*e*][1,4]dioxepin (11). Potassium *tert*-butoxide (26.1 g, 0.23 mol) was added to an ice-cooled solution of catechol (25.6 g, 0.23 mol) in dry dimethylformamide (200 mL). After stirring at 0 °C for 30 min, 2-chloro-5-nitrobenzyl chloride (47.8 g, 0.23 mol) was added and stirring continued at room temperature for 24 h. Potassium *tert*-butoxide (26.1 g, 0.23 mol) was added and stirring continued at room temperature for 1 h. Dimethylformamide (500 mL) was added and the solution refluxed for 5 h. After cooling to 0 °C, water (100 mL) was added and the mixture successively extracted with ethyl acetate/ether (1:1, 3 × 400 mL). The combined extracts were washed with water (5 × 700 mL) and brine (1 × 200 mL) and dried over anhydrous sodium sulfate. The solvent was removed by rotoevaporation to give a thick black residue, which was purified by rapid filtration through a silica gel pad eluted with 50% ether in hexane. The filtrate was concentrated by rotoevaporation and the residue recrystallized from hot ethyl acetate to give **11** (14.2 g). The mother liquors were concentrated and purified by column chromatography on silica gel eluted with 7% ether in hexane to give additional **11** (1.7 g). The product was obtained as a bright yellow solid (15.9 g, 28% yield): mp 127–128 °C; ^{1}H NMR ($CDCl_3$) δ 5.21 (2 H, s), 6.76–7.33 (5 H, m), 8.13 (1 H, s), 8.20 (1 H, dd, *J* = 11, 3 Hz); IR (thin film) 1620, 1580, 1520 cm^{-1}; mass spectrum, *m/e* 243. Anal. ($C_{13}H_9NO_4$) C, H, N.

Preparation of 7-Acetyl-2-nitro-11*H*-Dibenzo[*b*,*e*][1,4]-dioxepin (12). To an ice-cooled solution acetyl chloride (4.82 mL, 0.068 mol) in dry nitromethene (60 mL) was added tin(IV) chloride (7.9 mL, 0.068 mol). After stirring at 0 °C for 20 min, **11** (14.2 g, 0.058 mol) was added and the solution stirred at room temperature for 24 h. Water was added and the mixture extracted with ethyl acetate (3 × 200 mL). The combined extracts were washed successively with water (3 × 200 mL) and brine (1 × 100 mL) and dried over anhydrous sodium sulfate. The solvent was removed by rotoevaporation and the black residue purified by column chromatography on silica gel eluted with 25% ether in hexanes. Recrystallization from hot ethyl acetate gave **12** as a slightly yellow soild (7.1 g, 43% yield): mp 155.5–156.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.56 (3 H, s), 5.26 (2 H, s), 6.91 (1 H, d, *J* = 8 Hz), 7.25 (1 H, d, *J* = 8 Hz), 7.53 (1 H, dd, *J* = 8, 1.5 Hz), 7.73 (1 H, d, *J* = 1,5 Hz), 8.11 (1 H, s), 8.16 (1 H, dd, *J* = 8 , 1.5 Hz); IR (thin film) 1660, 1600, 1565, 1525 cm^{-1}. Anal. ($C_{15}H_{11}NO_5$) C, H, N.

Preparation of Methyl 2-Nitro-11*H*-dibenzo[*b*,*e*][1,4]-dioxepin-7-acetate (13). A suspension of **12** (5.09 g, 0.018 mol) and thallium(III) nitrate/K-10 (60 g) in dry methylene chloride (70 mL) was stirred at room temperature for 4.5 h. The mixture was filtered, and the solids were thoroughly washed with fresh methylene chloride (200 mL). The combined filtrates were successively washed with 1 N sodium bicarbonate (3 × 50 mL), water (3 × 50 mL), and brine (1 × 50 mL) and dried over anhydrous sodium sulfate. The solvent was removed by rotoevaporation to yield a slightly yellow oil that was triturated with ether to give **13** as a light-yellow solid (5.26 g, 94% yield): mp 72–73 °C; ^{1}H NMR ($CDCl_3$) δ 3.53 (2 H, s), 3.71 (3 H, s), 5.16 (2 H, s), 6.90 (2 H, s), 7.10–7.26 (2 H, m), 8.10 (1 H, s), 8.18 (1 H, dd, *J* = 8, 1.5 Hz); IR (thin film) 1725, 1620, 1580, 1520 cm^{-1}; mass spectrum, *m/e* 315, 256. Anal. ($C_{16}H_{13}NO_6$) C, H, N.

Preparation of Methyl 2-Aminodibenzo [*b*,*e*][1,4]dioxepin-7-acetate (16). Zinc dust (7.3 g, 0.11 mol) was added to an ice-cooled solution of **13** (7.27 g, 0.023 mol) in glacial acetic acid (60 mL). After stirring at room temperature for 1.7 h, the mixture was filtered and the solids washed with ethyl acetate (200 mL) and water (50 mL). The combined filtrates were washed successively with 1 N sodium bicarbonate (3 × 50 mL), water (2 × 50 mL), and brine (1 × 50 mL) and dried over anhydrous sodium sulfate. The solvent was removed by rotoevaporation to give **16** as a dark oil (5.6 g, 85% yield): ^{1}H NMR ($CDCl_3$) δ 3.48 (2 H, s), 3.68 (3 H, s), 3.80 (2 H, br s, disappears upon addition of D_2O), 5.05 (2 H, s), 6.46–7.06 (6 H, m); IR (thin film) 3470, 1730, 1620, 1580 cm^{-1}.

Preparation of 2-Acetamidodibenzo[*b*,*e*][1,4]dioxepin-7-acetic acid (3c). A solution of **16** (0.70 g, 2.5 mmol) in methylene chloride (4 mL), pyridine (0.2 mL), and acetic anhydride (0.2 mL) was stirred at room temperature for 2 h. Ethyl acetate (30 mL) was added, and the solution was washed successively with 1 N hydrochloric acid (3 × 30 mL), water (1 × 30 mL), 1 N sodium bicarbonate (2 × 30 mL), and brine (1 × 30 mL). After drying over anhydrous magnesium sulfate, the solvent was removed by rotoevaporation and the residue purified by column chromatography on silica gel eluted with 50% ethyl acetate in hexane to give the methyl ester as an oil (0.35 g, 44% yield): ^{1}H NMR ($CDCl_3$) δ 2.06 (3 H, s), 3.50 (2 H, s), 3.70 (3 H, s), 5.03 (2 H, s), 6.76 (2 H, s), 6.96 (1 H, d, *J* = 8 Hz), 7.01 (1 H, s), 7.26 (1 H, dd, *J* = 8, 2 Hz), 7.40 (1 H, d, *J* = 2 Hz), 8.26 (1 H, s); IR (thin film) 3300, 1730, 1660, 1600 1540 cm^{-1}.

The ester was hydrolyzed in a refluxing solution of methanol (3 mL) and sodium hydroxide (43 mg, 1 equiv) for 6 h. The solution was acidified with 6 N hydrochloric acid and extracted with ethyl acetate (3 × 50 mL). The combined extracts were washed successively with water (3 × 20 mL) and brine (1 × 20 mL) and dried over anhydrous sodium sulfate. The solvent was removed by rotoevaporation and the residue triturated with hot ethyl acetate to give **3c** as a light-tan solid (0.20 g, 60% yield): mp 231–232 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.00 (3 H, s), 3.43 (2 H, s), 5.13 (2 H, s), 6.76 (2 H, s), 6.95 (1 H, s), 7.03 (1 H, d, *J* = 8 Hz), 7.43 (1 H, dd, *J* = 8, 2 Hz), 7.53 (1 H, d, *J* = 2 Hz); IR (Nujol) 3270, 1695, 1655, 1530, 1500 cm^{-1}. Anal. ($C_{17}H_{15}NO_5$) C, H, N.

Preparation of Methyl α-Methyl-2-nitro-11*H*-dibenzo-[*b*,*e*][1,4]dioxepin-7-acetate (14). Sodium hydride (60% oil dispersion, 1.5 g) was added to a stirred solution of **13** (12.8 g, 40.6 mmol) in cold dimethylformamide (50 mL). After stirring for 15 min, methyl iodide (3.6 mL, 57.8 mmol) was added and the mixture stirred at room temperature for 20 h. Water (20 mL) was added and the mixture extracted with ethyl acetate (200 mL), which was subsequently washed with water (5 × 50 mL). The extract was dried over anhydrous magnesium sulfate and the

solvent removed by rotoevaporation. The residue was purified by preparative HPLC on silica gel eluted with 10% acetate in hexane to give **14** as a pale-yellow oil (6.0 g, 45% yield): ^{1}H NMR ($CDCl_3$) δ 1.47 (3 H, d, J = 7.0 Hz), 3.69 (1 H, q, J = 7.0 Hz), 3.70 (3 H, s), 5.17 (2 H, s), 6.90 (2 H, s), 7.10–7.26 (2 H, m), 8.10 (1 H,s), 8.18 (1 H, dd, J = 8, 1.5 Hz); IR (thin film) 1728, 1620, 1575, 1522 cm^{-1}.

Preparation of Methyl 2-Amino-α-methyl-11*H*-dibenzo[*b*,*e*][1,4]dioxepin-7-acetate (15). The α-methylacetate derivative **14** was reduced by the procedure described for the preparation of **16** to give **15** as a yellow oil (91% yield): ^{1}H NMR ($CDCl_3$) δ 1.50 (3 H, d, J = 7.0 Hz), 3.67 (3 H, s), 3.63 (1 H, q, J = 7.0 Hz), 3.70 (2 H, br, s, disappears upon addition of D_2O), 5.06 (2 H, s), 6.45–7.05 (6 H, m); IR (thin film) 3460, 3380, 1725, 1620, 1580 cm^{-1}.

Preparation of Methyl α-Methyl-11*H*-dibenzo[*b*,*e*][1,4]dioxepin-7-acetate (3f). Sodium nitrite (0.76 g, 11.0 mmol) was added to a cold solution of **15** (3.1 g, 10.0 mmol) in tetrahydrofuran/methanol (1:], 11 mL) containing concentrated sulfuric acid (0.6 mL). After stirring at room temperature for 20 h, the solution was refluxed for 1.5 h. After cooling, ethyl acetate (100 mL) was added and the solution was successively washed with water (3 × 25 mL) and saturated salt solution (3 × 25 mL). The solution was dried over anhydrous magnesium sulfate and the solvent removed in vacuo. The residue was purified by column chromatography on silica gel eluted with 10% ethyl acetate in hexane to give **3f** as a clear, colorless oil (1.25 g, 42% yield): ^{1}H NMR ($CDCl_3$) δ 1.45 (3 H, d, J = 7.0 Hz), 3.60 (1 H, q, J = 7.0 Hz), 3.63 (3 H, s), 5.10 (2 H, s), 6.73, 6.76 (2 H, s), 6.90–7.33 (4 H, m); IR (thin film) 1730, 1601, 1560 cm^{-1}. Anal. ($C_{17}H_{16}O_4$) C, H.

Preparation of α-Methyl-11*H*-dibenzo[*b*,*e*][1,4]dioxepin-7-acetic acid (3b). The ester **3f** was hydrolyzed by the method described for the preparation of **3c** to give **3b**: mp 95–97 °C; ^{1}H NMR δ 1.48 (3 H, d, J = 7 Hz), 3.63 (1 H, q, J = 7 Hz), 5.20 (2 H, s), 6.86–7.33 (7 H, m); IR (thin film) 1705, 1600 cm^{-1}. Anal. ($C_{16}H_{14}O_4$) C, H.

Preparation of 2-Chloro-11*H*-dibenzo[*b*,*e*][1,4]dioxepin-7-acetic acid (3d). To a stirred suspension of **16** (X = Cl) (1.60 g, 5.61 mmol) in 6 N hydrochloric acid (4 mL) at 0 °C was added a solution of sodium nitrite (0.43 g, 6.1 mmol) in water (2 mL). After stirring at 0 °C for 20 min, the solution was added to a hot (75 °C) solution of cuprous chloride (0.63 g, 6.3 mmol) in 6 N hydrochloric acid (10 mL) and stirred at 75 °C for 2 h. After cooling, ethyl acetate (100 mL) was added and the solution washed with water (3 × 25 mL) and dried over anhydrous magnesium sulfate. The solvent was removed by rotoevaporation and the residue purified by column chromatography on silica gel eluted with 10% ether in hexane to give the methyl ester **17** as a clear film (0.15 g, 8.4% yield): ^{1}H NMR ($CDCl_3$) δ 3.50 (2 H, s), 3.68 (3 H, s), 5.10 (2 H, s), 6.83 (2 H, s), 6.93–7.30 (4 H, m); IR (thin film) 1735, 1675, cm^{-1}.

The methyl ester **17** was hydrolyzed by the method described for the preparation of **3c** to give **3d** after recrystallization from ethyl acetate/hexane: mp 153.5–155 °C, 62% yield. Anal. ($C_{15}H_{11}ClO_4$) C, H.

Preparation of α,2,4-Trichloro-5-nitrotoluene. Concentrated nitric acid (3.2 mL) was added to a solution of α,2,4-trichlorotoluene (10.0 g, 0.05 mol) in concentrated sulfuric acid (50 mL) at 0 °C. After stirring at room temperature for 48 h, the solution was poured onto crushed ice (80 g) and extracted with ether (3 × 75 mL). The combined extracts were washed successively with water (3 × 50 mL), 1 N sodium bicarbonate solution (2 × 50 mL), water (3 × 50 mL), and brine (1 × 50 mL). The solution was dried over anhydrous sodium sulfate and the solvent removed by rotoevaporation to give α,2,4-trichloro-5-nitrotoluene as a yellow oil (11.8 g, 95% yield): ^{1}H NMR δ 4.60 (2 H, s), 7.48 (1 H, s), 7.48 (1 H, s), 7.95 (1 H, s); IR (thin film) 1601, 1560, 1530 cm^{-1}.

Preparation of 3-Chloro-2-nitro-11*H*-dibenzo[*b*,*e*][1,4]dioxepin (11, X = Cl). Catechol and α,2,4-trichloro-5-nitrotoluene were reacted together by the same procedure described for the preparation of **11** (X = H) to give the 3-chloro derivative **11** (X = Cl): mass spectrum, m/e 279, 277, 233, 231, 141, 139.

Preparation of 7-Acetyl-3-chloro-2-nitro-11*H*-dibenzo[*b*,*e*][1,4]dioxepin (12, X = Cl). Prepared by the same procedure used to prepare **12** (X = H): ^{1}H NMR δ 2.50 (3 H, s), 5.20 (2 H, s), 6.97 (1 H, d, J = 8 Hz), 7.30 (1 H, s), 7.57 (1 H, dd, J = 2, 8 Hz), 7.73 (1 H, d, J = 2 Hz), 7.87 (1 H, s); IR (thin film) 1695, 1610, 1560 cm^{-1}.

Preparation of Methyl 3-Chloro-2-nitro-11*H*-dibenzo[*b*,*e*][1,4]dioxepin-7-acetate (13, X = Cl). Prepared by the same procedure used to prepare **13** (X = H): ^{1}H NMR δ 3.56 (2 H, s), 3.71 (3 H, s), 5.03 (2 H, s), 6.86 (2 H, s), 7.02 (1 H, s), 7.18 (1 H, s), 7.76 (1 H, s); IR (thin film) 1735, 1610, 1560 cm^{-1}; mass spectrum, m/e 351, 349, 292, 290.

Preparation of Methyl 2-Amino-3-chloro-11*H*-dibenzo[*b*,*e*][1,4]dioxepin-7-acetate (16, X = Cl). Prepared by the same procedure used to prepare **16** (X = H): ^{1}H NMR δ 3.46 (2 H, s), 3.66 (3 H, s), 4.30 (2 H, br, s), 4.96 (2 H, s), 6.40 (1 H, s), 6.73 (2 H, br, s), 7.00 (2 H, m); IR (thin film) 3350, 1730, 1610 cm^{-1}.

Preparation of 3-Chlorodibenzo[*b*,*e*][1,4]dioxepin-7-acetic acid (3e). To a mechanically stirred suspension of **16** (X = Cl) 1.26 g, 3.9 mmol) in 6 N hydrochloric acid (3 mL) at 0 °C was added a solution of sodium nitrite (0.29 g, 4.2 mmol) in water (1 mL). After stirring the solution at 0 °C for 20 min, cold 50% hypophosphorous acid (10 mL) was added and the solution stirred for 2 h. Ethyl acetate (100 mL) was added, and the solution was washed successively with water (3 × 25 mL), 1 N sodium bicarbonate solution (2 × 25 mL), and water (2 × 25 mL) and dried over anhydrous magnesium sulfate. The solvent was removed by rotoevaporation and the residue purified by column chromatography on silica gel eluted with 10% ethyl acetate in hexane to give the methyl ester as a colorless oil (0.35 g, 30% yield): ^{1}H NMR ($CDCl_3$) δ 3.48 (2 H, s), 3.65 (3 H, s), 5.03 (2 H, s), 6.77, 6.78 (2 H, s), 6.93–7.13 (4 H, m); IR (thin film) 1735, 1601, 1570 cm^{-1}.

The methyl ester was hydrolyzed by the same procedure described for the preparation of **3c** to give **3e** after recrystallization from ethyl acetate/hexane as a white solid (95% yield): mp 151–152 °C. Anal. ($C_{15}H_{11}ClO_2$) C, H.

Preparation of 4-(2-Carbomethoxyphenoxy)-3-methoxyacetophenone (19). Methyl 2-bromobenzoate and the sodium salt of acetovanillone were reacted by the procedure described for the preparation of **5** to give **19** as a white solid (48% yield): ^{1}H NMR ($CDCl_3$) δ 2.53 (3 H, s), 3.76 (3 H, s), 3.93 (3 H, s), 6.67 (1 H, d, J = 8.0 Hz), 6.96 (1 H, dd, J = 8.0, 1.0 Hz), 7.23 (1 H, dd, J = 6.0, 1.0 Hz), 7.43 (1 H, d, J = 8.0 Hz), 7.60 (1 H, d, J = 1.0 Hz), 7.93 (1 H, dd, J = 8.0, 1.0 Hz); IR (thin film) 1720, 1675, 1590 cm^{-1}.

Preparation of 2-[4-(2-Carbomethoxyphenoxy)-3-methoxyphenyl]-2-methyl-1,3-dioxolane (20). A solution of **19** (14.3 g, 48 mmol) in benzene (200 mL) and ethylene glycol (7.4 g, 120 mmol) containing p-toluene sulfonic acid (1.5 g, 7.9 mmol) was refluxed for 6 h in a flask equipped with a Dean–Stark trap to remove water. After cooling, solid sodium bicarbonate (5.0 g, 59 mmol) was added and the mixture stirred for 15 min. The solution was washed successively with saturated sodium bicarbonate solution (3 × 50 mL) and water (4 × 50 mL) and dried over anhydrous magnesium sulfate. The solvent was removed by rotoevaporation and the residue purified by preparative HPLC eluted with 15% ethyl acetate in hexane to give **20** as an oil (8.92 g, 54% yield): ^{1}H NMR ($CDCl_3$) δ 1.67 (3 H, s), 3.87 (6 H, s), 3.73–4.13 (4 H, m), 6.80–8.00 (6 H, m).

Preparation of 2-[4-[2-(Hydroxymethyl)phenoxy]-3-methoxyphenyl]-2-methyl-1,3-dioxolane (21). The ester **20** was reduced by the same procedure for the preparation of **6** to give **21** (oil, 77% yield): ^{1}H NMR ($CDCl_3$) δ 1.67 (3 H, s), 3.80 (3 H, s), 3.86–4.05 (4 H, m), 4.76 (2 H, d, J = 5.0 Hz), 6.62–7.40 (6 H, m); IR (thin film) 3400, 1602, 1590 cm^{-1}.

Preparation of 4-[2-(Bromomethyl)phenoxy]-3-methoxyacetophenone (22). Prepared from **21** by the same procedure described for the preparation of **7** to give **22** as a white solid (87% yield): mp 83–85 °C; ^{1}H NMR δ 2.56 (3 H, s), 3.90 (3 H, s), 4.60 (2 H, s), 6.70–7.70 (7 H, m); IR (thin film) 1680, 1610, 1585 cm^{-1}; mass spectrum, m/e 336, 334.

Preparation of 4-[2-(Bromomethyl)phenoxy]-3-hydroxyacetophenone (23). Prepared from **22** by the procedure described for the preparation of **8** to give **23** as a rose-colored oil (88% yield): ^{1}H NMR δ 2.46 (3 H, s), 4.58 (2 H, s), 6.28 (1 H, br s, disappears upon addition of D_2O), 6.78–7.73 (7 H, m).

Preparation of 8-Acetyl-11*H*-dibenzo[*b*,*e*][1,4]dioxepin (24). Prepared from **23** by the procedure described for the

preparation of **9** to give **24** (21% yield): ^{1}H NMR δ 2.51 (3 H, s), 5.23 (2 H, s), 7.05–7.60 (7 H, m); mass spectrum, *m/e* 240.

Preparation of Methyl 11*H*-Dibenzo[*b*,*e*][1,4]dioxepin-8-acetate (25). Prepared from 24 by the procedure described for the preparation of **13** to give **25** (85% yield): ^{1}H NMR δ 3.48 (2 H, s), 3.65 (3 H, s), 5.20 (2 H, s), 6.70–6.83 (2 H, m), 7.00–7.36 (5 H, m).

Preparation of Methyl α-Methyl-11*H*-dibenzo[*b*,*e*][1,4]-dioxepin-8-acetate (26). Prepared from **25** by the procedure described for the preparation of **14** to give **26** (39% yield): ^{1}H NMR δ 1.41 (3 H, d, J = 7 Hz), 3.58 (1 H, q, J = 7 Hz), 3.63 (3 H, s), 5.16 (2 H, s), 6.71–6.83 (2 H, m), 7.00–7.34 (5 H, m).

Preparation of α-Methyl-11*H*-dibenzo[*b*,*e*][1,4]dioxepin-8-acetic Acid (4b). Prepared from **26** by the procedure described for the preparation of **3b** to give **4b** (86% yield): mp 82–84 °C ^{1}H NMR δ 1.41 (3 H, d, J = 7 Hz), 3.58 (1 H, q, J = 7 Hz), 5.16 (2 H, s), 6.70–6.88 (2 H, m), 6.98–7.30 (5 H, m). Anal. ($C_{16}H_{14}O_4$) C, H.

Preparation of 1-Ethoxycarboethoxy α-Methyl-11*H*-dibenzo[*b*,*e*][1,4]dioxepin-7-acetate (3g). A solution of **3b** (233 mg, 0.86 mmol), triethylamine (0.14 mL, 1.03 mmol), and 1-chloroethyl ethyl carbonate (0.130 mL, 1.03 mmol) in toluene (3 mL) was refluxed for 72 h under a dry nitrogen atmosphere. After cooling, ether (60 mL) was added and the solution washed successively with water (1 × 10 mL), 1 N hydrochloric acid (2 × 10 mL), 1 N sodium bicarbonate solution (5 × 10 mL), and water (2 × 10 mL). The solution was dried over anhydrous sodium sulfate and the solvent removed by rotoevaporation. The residue was purified by column chromatography on silica gel eluted with 8% ethyl acetate in hexane to give **3g** as a slightly yellow oil (233 mg, 70% yield): ^{1}H NMR δ 1.20 (3 H, t, J = 7.0 Hz), 1.30–1.63 (6 H, m), 3.63 (2 H, q, J = 7.0 Hz), 4.07 (1 H, q, J = 7.0 Hz), 4.20 (2 H, q, J = 7.0 Hz), 5.20 (2 H, s) 6.67–7.33 (7 H, m); IR (thin film) 1750 cm^{-1}; mass spectrum, *m/e* 386, 358, 225. Anal. ($C_{21}H_{22}O_7$) C, H.

Preparation of 2-Acetamidoethyl α-Methyl-11*H*-dibenzo[*b*,*e*][1,4]dioxepin-7-acetate (3h). A solution of acid, **3b** (203 mg, 0.75 mmol), *N*-acetylethanolamine (0.08 mL, 0.87 mmol), 4-(dimethylamino)pyridine (5 mg, 0.04 mmol), and 1,3-dicyclohexylcarbodiimide (200 mg, 0.97 mmol) in methylene chloride (3 mL) was stirred at room temperature for 6 h. The suspension was filtered and the filtrate concentrated by rotoevaporation. The residue was purified by column chromatography on silica gel eluted with 90% ethyl acetate in hexane to give **3h** as a light yellow oil (185 mg, 69%): ^{1}H NMR δ 1.43 (3 H, d, J = 7.0 Hz), 1.78 (3 H, s), 3.4 (2 H, t, J = 7.0 Hz), 3.58 (1 H, q, J = 7 Hz), 4.06 (2 H, t, J = 7.0 Hz), 5.10 (2 H, s), 6.70–7.2 (7 H, m); IR (thin film) 3300, 1730, 1655 cm^{-1}; mass spectrum, *m/e* 355, 252, 225. Anal. ($C_{20}H_{21}NO_5$) Calcd: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.12; H, 6.12; N, 3.90.

Preparation of 2-(11*H*-Dibenzo[*b*,*e*][1,4]dioxepinyl)-1-propanol (3i). To a solution of acid **3b** (265 mg, 0.96 mmol) in tetrahydrofuran (5 mL) at room temperature under a dry nitrogen atmosphere was added a 1.0 M solution of borane–tetrahydrofuran complex in tetrahydrofuran (1.25 mL), and the solution was refluxed for 3 h. After cooling, ether (75 mL) was added and the solution washed successively with water (2 × 10 mL), 1 N sodium bicarbonate solution (3 × 10 mL), water (2 × 10 mL), and brine (1 × 10 mL). The solution was dried over anhydrous sodium sulfate and the solvent removed by rotoevaporation to give **3i** as a clear, colorless oil (227 mg, 92% yield): ^{1}H NMR δ 1.03 (3 H, d, J = 7 Hz), 2.15 (1 H, br t, disappears upon addition of D_2O), 2.77 (2 H, sextet, J = 7 Hz), 3.55 (2 H, d, J = 7 Hz), 5.06 (2 H, s), 6.53–7.23 (7 H, m); IR (thin film) 3530 cm^{-1}. Anal. ($C_{16}H_{16}O_3$) C, H.

Carrageenan-Induced Paw Edema in the Rat. Groups of six male Sprague–Dawley rats (purchased from Harlan–Sprague Dawley, Madison, WI) were sorted according to weight (in the range 120–190 g) and fasted overnight. Inflammation was induced by subplantar injection of 0.1 mL of 2% (w/v) carrageenan solution in 0.9% (w/v) saline into the right hindpaw. Compounds were administered perorally as a suspension in 0.25% (w/v) agar in water 1 h before carrageenan injection. The concentration of compounds was adjusted such that each animal, irrespective of weight, received 3.0 mL perorally. The volume of the injected hindpaw was immersed in a pool of mercury up to a mark placed over the lateral malleolus and then mercury displacement recorded electronically. The volume of the same paw was measured again by mercury displacement 3 h later. Increase in hindpaw volume was calculated by subtracting the paw volume measured immediately after carrageenan injection from the paw volume measured 3 h later. The mean swelling for six animals was calculated, and the effects of a compound were expressed as a percentage inhibition taking the swelling of the vehicle dosed control as 100%. The significance of the drug effects was determined by using the student's unpaired t test.

Inhibition of Cyclooxygenase. Cyclooxygenase from ram seminal vesicle microsomes (RSVM, 100000*g* pellet) was incubated in 0.125 M NaEDTA (pH 8) containing 100 μg/mL bovine serum albumin (BSA), 0.5 mM hydroquinone (HQ), 2 mM reduced glutathione, and 33 μM ^{14}C-radiolabeled arachidonic acid as substrate. Product prostaglandin E_2 (PGE_2) was measured with a Bioscan 200 imaging scanner after thin-layer chromatographic separation on silica gel GF plates eluted with ethyl acetate/glacial acetic acid (99:1) as solvent. Compounds for testing were preincubated with the enzyme for 4 min and incubated, after substrate addition, for 20 min at room temperature. The reaction was stopped with methanol containing arachidonic acid (1.3 mM) and PGE_2 (0.56 mM). The integrated peak of PGE_2 for each sample was converted to percent inhibition by comparison to controls.

Mouse Phenylbenzoquinone (POB) Induced Writhing Assay. Groups of 10 male mice (Canadian Breeding Laboratories, CD) weighing 18–22 g were food deprived overnight prior to experiments. Test compounds, suspended in 1% methylcellulose, were administered orally 60 min prior to the intraperitoneal injection of PBQ (2 mg/kg, 0.02% aqueous solution). The mice were placed in individual boxes and exactly 5 min later were observed for "writhes" (abdominal contractions, lordosis, and hindlimb extension) for a 10-min interval as a measure of pain induction. The number of writhes for each animal was recorded, and the group means and standard errors were calculated. The means obtained from the drug-treated group were compared to the vehicle control mean values and percent inhibition of writhing was calculated.

Gastric Hemorrhage Lesion Irritation Assay in the Rat. Gastric irritation was measured in male Sprague–Dawley rats weighing 120–200 g. Rats, in groups of six, were sorted according to weight and fasted overnight. Compounds were administered perorally as a suspension in 0.5% (w/v) in methocal. Four hours later the rats were killed by asphyxiation in CO_2, the stomachs removed, everted, and washed with tap water, and the lesions on the gastric mucosa counted by visual examination under 3× magnification. All lesions, regardless of size, were counted.

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Registry No. **1a**, 102492-43-3; **2a**, 102492-44-4; **3a**, 102492-45-5; **3b**, 102492-46-6; **3c**, 102492-47-7; **3c** (methyl ester), 102492-66-0; **3d**, 102492-48-8; **3e**, 102492-49-9; **3f**, 102492-50-2; **3g**, 102492-51-3; **3h**, 102492-52-4; **3i**, 102492-53-5; **4a**, 102492-54-6; **4b**, 102492-55-7; **5**, 102492-56-8; **6**, 102492-57-9; **7**, 102492-58-0; **8**, 102492-59-1; **9**, 102492-60-4; **10**, 102492-61-5; **11** (X = H), 102492-62-6; **11** (X = Cl), 102492-72-8; **12** (X = Cl), 102573-54-6; **12** (X = H), 102492-63-7; **13** (X = H), 102492-64-8; **13** (X = Cl), 102492-73-9; **14**, 102492-67-1; **15**, 102492-68-2; **16** (X = H), 102492-65-9; **16** (X = Cl), 102492-69-3; **17**, 102492-70-6; **18**, 102492-74-0; **19**, 102492-75-1; **20**, 102492-76-2; **21**, 102492-77-3; **22**, 102505-19-1; **23**, 102492-78-4; **24**, 102492-79-5; **25**, 102492-80-8; **26**, 102492-81-9; $Th(NO_3)_3$, 13746-98-0; sodium guaiacolate, 13052-77-2; dimethyl 4-bromoisophthalate, 28730-78-1; dimethyl 2-bromoterephthalate, 18643-86-2; isovanillin sodium salt, 63987-20-2; methyl 2-bromobenzoate, 610-94-6; vanillin sodium salt, 57531-76-7; 2-chloro-5-nitrobenzyl chloride, 69422-57-7; catechol, 120-80-9; α,2,4-trichloro-5-nitrotoluene, 102492-71-7; α,2,4-trichlorotoluene, 94-99-5; acetovanillone sodium salt, 16522-48-8; 1-chloroethyl ethyl carbonate, 50893-36-2; *N*-acetylethanolamine, 142-26-7; cyclooxygenase, 39391-18-9.