Efforts Toward Combined Analgesic/Antidepressants: Synthesis and Evaluation of (3-Aryl-2,3-dihydrobenzofuran-3-yl)alkanamines

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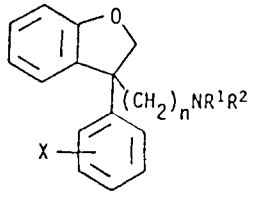
Abstract □ Several (3-aryl-2,3-dihydrobenzofuran-3-yl)alkanamines, designed as potential antidepressant agents with analgesic properties, were synthesized and pharmacologically evaluated. While two compounds (**1a**, **1f**) displayed potent antitetrabenazine activity, concomitant antinociceptive activity in the phenylquinone writhing assay was not observed.

Several clinical reports[1-3] have implied the desirability of generating a novel antidepressant which contains an analgesic component, since their evidence has closely associated depression with chronic pain. The effectiveness of several tricyclic antidepressants in alleviating pain has been demonstrated in these studies and in several reports[4,5] of novel tricyclics with combined analgesic and antidepressant properties which have recently appeared. As part of a program targeted for developing nontricyclic agents of this type, an investigation of the synthesis and pharmacological profile of a number of (3-aryl-2,3-dihydrobenzofuran-3-yl)alkanamines (**1**) was undertaken. The structural features of this series of compounds are analogous to a variety of antidepressant agents, e.g., talopram (**2**)[6] and, additionally, they can be envisioned as cyclized analogues of the diphenylmethane analgetics[7] related to methadone (**3**).



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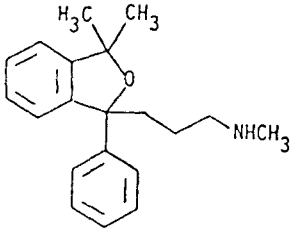

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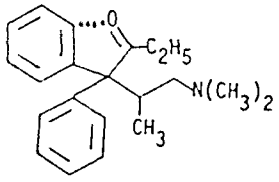

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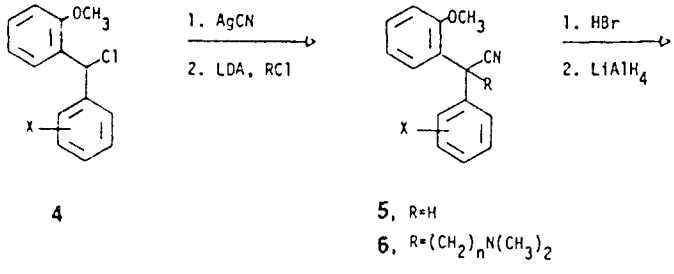
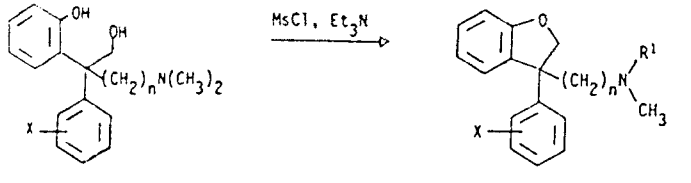
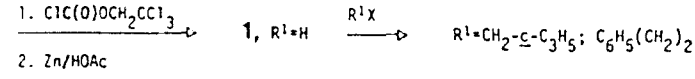
The synthetic approach to the dihydrobenzofurans (**1**) is outlined in *Scheme I*. The readily available benzhydryl chlorides (**4**) were treated with silver cyanide in acetonitrile[8] to give nitriles (**5**). Side-chain attachment was achieved via alkylation, using lithium diisopropylamide in tetrahydrofuran with the corresponding chloroalkylamine to provide aminonitriles (**6**). Refluxing 48% aqueous hydrobromic acid converted **6** to an intermediate lactone[9] (not shown), which, on subsequent reduction with lithium tetrahydridoaluminate, resulted in diols (**7**). Treating **7** with methanesulfonyl chloride and triethylamine in dichloromethane induced cyclodehydration to generate the desired dihydrobenzofuran ring (**1**, R^1 = methyl). Demethylation occurred readily via the trichloroethyl carbamate derivative, which was easily hydrolyzed with zinc in acetic acid at room temperature[10] to give secondary amines (**1**, R^1 = hydrogen). Alkylation using the appropriate alkyl halides in dimethylformamide yielded several derivatives (**1**, R^1 = cyclopropylmethyl; phenethyl). The dihydrobenzofurans (**1**) were screened for potential antidepressant and analgesic activity.



4 **5**, R=H; **6**, $R=(CH_2)_nN(CH_3)_2$



7, n=2,3 **1**, $R^1=CH_3$



Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting-point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 727 or a Pye Unicam SP3-

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200 spectrophotometer. NMR spectra were taken at 60 MHz on either a JEOL C-60HL or a JEOL FX-60 spectrometer, and chemical shifts are given relative to internal tetramethylsilane. MS were obtained from a Finnigan Model 4000 spectrometer interfaced to a Finnigan 9610 GC and equipped with an INCOS data system. Elemental analysis was performed by Micro-Tech Laboratories, Skokie, IL. TLC were run on silica gel PF-254 plates and column chromatography was performed using silica gel 60 (E. Merçk, AG) or absorption alumina (Fisher Scientific). Preparative HPLC was performed on a Waters Prep LC/system 500 instrument using UV and RI detectors for monitoring the chromatography.

α-(2-Methoxyphenyl)benzeneacetonitrile (5a)—A mixture of α-(2-methoxyphenyl)benzyl chloride (148 g, 0.64 mol), silver cyanide (86 g, 0.64 mol), and acetonitrile (1000 mL) was refluxed for 5 h. The cooled mixture was filtered and the filtrate was concentrated. The crude product was fractionated (bp 170°C/0.5 mm) to give 70 g of an oil that solidified on standing. Recrystallization from cyclohexane yielded 50 g (35%) of yellow crystals, mp 83–85°C (Table I); IR ($CHCl_3$): 2250 cm^{-1} (C≡N); ^1H NMR ($CDCl_3$): δ 3.8 (s, 3, OCH_3), 5.6 (s, 1, CHCN), and 6.8–7.7 ppm (m, 9, ArH).

4-Dimethylamino-2-(2-methoxyphenyl)-2-phenylbutanenitrile Oxalate (6a)—To a solution of diisopropylamine (6.4 mL, 0.046 mol) in anhydrous tetrahydrofuran (50 mL) at −70°C under nitrogen was added *n*-butyllithium in hexane (0.044 mol); this mixture was stirred at −70°C for 15 min and warmed to −30°C. A solution of **5a** (9.2 g, 0.040 mol) in tetrahydrofuran (50 mL) was added in a dropwise manner and the resulting solution placed in an ice bath and warmed to 0°C. Freshly distilled dimethylaminoethyl chloride (11 mL, 0.092 mol) was added, and the mixture was heated at reflux for 1.5 h. The mixture was quenched with water (5 mL) and concentrated under reduced pressure to give a residue which was dissolved in dichloromethane (1000 mL). The solution was washed with water (2 × 200 mL), dried (magnesium sulfate), and the solvent evaporated. The free base was converted to the oxalate salt (10.8 g). Recrystallization from ethanol gave an analytical sample (Table I); ^1H NMR (Me_2SO-d_6): δ 2.4–2.6 (m, 2, CH_2), 2.7 (s, 6, NCH_3), 2.8–3.1 (m, 2, NCH_2), 3.6 (s, 3, OCH_3), 7.0–7.7 (m, 9, ArH), and 11.0 ppm (br s, 2, exchangeable); MS: $(MH)^+$ *m/z* 295.

Compounds **6b**, **6c**, and **6d** were prepared in a similar manner from **5b**, **5c**, and **5d**, respectively, and converted to either the fumarate or maleate salt. Compound **6e** was prepared in a similar manner from **5a** using dimethylaminopropyl chloride and converted to the hydrochloride salt (Table I). IR, ^1H NMR, and MS were consistent with the assigned structures.

4-Dimethylamino-2-(2-hydroxyphenyl)-2-phenylbutanol Hydrochloride (7a)—A mixture of **6a** (40 g, 0.136 mol) and 48% HBr (200 mL) was refluxed for 40 h. The cooled mixture was made basic with 50% NaOH and extracted with dichloromethane. The organic extract was washed with water and dried (magnesium sulfate). Concentration gave a brown oil that was fractionated (bp 153–160°C/0.2 mm) to yield 28.7 g (75%) of a yellow oil.

A solution of the above benzofuranone (28.6 g, 0.102 mol) in anhydrous ether (300 mL) was added in a dropwise manner to a suspension of lithium tetrahydridoaluminate (7.74 g, 0.204 mol) in ether (150 mL) with ice bath cooling. The resulting mixture was stirred at 20°C for 2 h and quenched with sodium sulfate solution. The solids were removed by filtration and washed with ethyl acetate. The combined filtrates were washed with saturated sodium carbonate and brine, and dried (sodium sulfate). Concentration gave 28 g of a crude oil that solidified on standing. A solution of 5 g of this material in dichloromethane was added to excess ethereal hydrogen chloride. The precipitated solid was recrystallized from ethanol to give 3.2 g (57%; 43% overall) of white crystals, mp 199–201°C (Table I); IR (KBr): 3300 cm^{-1} (OH); ^1H NMR (CD_3OD): δ 2.8 (s, 6, NCH_3), 3.0–3.4 (m, 4, CH_2), 3.8–4.4 (m, 2, OCH_2), and 6.7–7.5 ppm (m, 9, ArH); MS: M^+ *m/z* 285.

Compounds **7b**, **7c**, **7d**, and **7e** were prepared in a similar manner from **6b**, **6c**, **6d**, and **6e**, respectively, and converted to the hydrochloride, fumarate, or maleate salt (Table I). IR, ^1H NMR, and MS were consistent with the assigned structures.

2-(3-Phenyl-3-dihydrobenzofuranyl)-N,N-dimethylaminoethanamine Oxalate (1a)—To a solution of **7a** (14.8 g, 0.052 mol) and triethylamine (21.5 mL, 0.156 mol) in dichloromethane (30 mL) at 5°C was added a solution of methanesulfonyl chloride (6.0 mL, 0.078 mol) in dichloromethane (50 mL). After 3 h, this mixture was diluted with dichloromethane (800 mL), washed with 10% NaOH solution (2 × 125 mL) and brine, and dried (magnesium sulfate). The solvent was evaporated to give 14 g of a crude yellow oil. A solution of 5 g of this material in dichloromethane (15 mL) was

Table I—α-(2-Methoxyphenyl)benzeneacetonitriles (5, 6) and 2-(2-Hydroxyphenyl)-2-arylalkanols (7)

Compound[a]	X	n	mp, °C	Yield, %	Formula
5a	H	—	83–85	35	$C_{15}H_{13}NO$
5b	2—F	—	97–98	14	$C_{15}H_{12}FNO$
5c	2—CH_3	—	95–95.5	44	$C_{16}H_{15}NO$
5d	4—CH_3	—	oil	62	$C_{16}H_{15}NO$
6a	H	2	177–179	68	$C_{19}H_{22}N_2O \cdot C_2H_2O_4$
6b	2—F	2	146–148	42	$C_{19}H_{21}FN_2O \cdot C_4H_4O_4$[b]
6c	2—CH_3	2	166–167.5	66	$C_{20}H_{24}N_2O \cdot C_4H_4O_4$[c]
6d	4—CH_3	2	175–176.5	55	$C_{20}H_{24}N_2O \cdot C_4H_4O_4$[c]
6e	H	3	194–195.5	38	$C_{20}H_{24}N_2O \cdot HCl$
7a	H	2	199–201	43	$C_{18}H_{23}NO_2 \cdot HCl$
7b	2—F	2	220–222	36	$C_{18}H_{22}FNO_2 \cdot ½(C_4H_4O_4)$[b]
7c	2—CH_3	2	205–207	53	$C_{19}H_{25}NO_2 \cdot HCl$
7d	4—CH_3	2	234–236	26	$C_{19}H_{25}NO_2 \cdot ½(C_4H_4O_4)$[b]
7e	H	3	182–182.5	29	$C_{19}H_{25}NO_2 \cdot C_2H_2O_4$

[a] Satisfactory analytical data (±0.4% C, H, N) were reported for all new compounds listed in the table. [b] Acid fumarate salt. [c] Acid maleate salt.

Table II—(3-Aryl-2,3-dihydrobenzofuran-3-yl)alkanamines

Compound[a]	X	n	R	mp, °C	Yield, %	Formula	TBZ, ED_{50} mg/kg ip	PQW, ED_{50} mg/kg sc
1a	H	2	CH_3	158–160	63	$C_{18}H_{21}NO \cdot C_2H_2O_4$	3.03[d]	>20
1b	2—F	2	CH_3	211–213	20	$C_{18}H_{20}FNO \cdot HCl$	>20	>10
1c	2—CH_3	2	CH_3	188–190	35	$C_{19}H_{23}NO \cdot C_4H_4O_4$[b]	>20	>10
1d	4—CH_3	2	CH_3	138–140	29	$C_{19}H_{23}NO \cdot C_4H_4O_4$[b]	>20	>10
1e	H	3	CH_3	140–141	25	$C_{19}H_{23}NO \cdot C_2H_2O_4$	>20	>20
1f	H	2	H	184–187	40	$C_{17}H_{19}NO \cdot HCl$	4.99[d]	>10
1g	H	3	H	180.0–181.5	30	$C_{18}H_{21}NO \cdot HCl$	13.68	>10
1h	H	2	CH_2—c—C_3H_5	154–156	33	$C_{21}H_{25}NO \cdot C_4H_4O_4$[b]	>20	6.27
1i	H	2	$C_6H_5(CH_2)_2$	135.5–138.0	33	$C_{25}H_{27}NO \cdot C_4H_4O_4$[b]	>20	>20
imipramine							5.5[d]	10.7
pentazocine							2.8[d]	2.4

[a] Satisfactory analytical data (±0.4% C, H, N) were reported for all new compounds listed in the table. [b] Acid fumurate salt. [c] Acid maleate salt. [d] po.

added to excess oxalic acid in ether. The precipitated solid was recrystallized from ethanol to yield 4.2 g (63%) of white crystals, mp 158–160°C (Table II); ^{1}H NMR (Me_2SO-d_6): δ 2.7 (br s, 10, NCH_2CH_2 and NCH_3), 4.6 (s, 2, OCH_2), 6.8–7.5 (m, 9, ArH), and 9.8 ppm (br s, 2, oxalate H); MS: M^+ *m/z* 267.

Compounds **1b**, **1c**, **1d**, and **1e** were prepared in a similar manner from **7b, 7c, 7d, and 7e,** respectively, and converted to the hydrochloride, fumarate, or oxalate salt (Table II). IR, ^{1}H NMR, and MS were consistent with the assigned structures.

2,3-Dihydro-N-methyl-3-phenyl-3-benzofuranethanamine Hydrochloride (1f)—A mixture of **1a** (6.0 g, 0.023 mol), β,β,β-trichloroethyl chloroformate (3.72 mL, 0.027 mol), anhydrous potassium carbonate (12.4 g, 0.090 mol), and dichloromethane (100 mL) was stirred at 20°C overnight. Water was added to dissolve the inorganic compounds, and the organic extract was washed with water and dried (magnesium sulfate). Concentration gave 7.9 g of a brown oil that was chromatographed by HPLC using 20% hexane:dichloromethane as an eluant to give 6.4 g (66%) of a light-yellow oil.

Activated zinc (14 g, 0.215 g·atm) was added to a solution of the above carbamate (22 g, 0.054 mol) in glacial acetic acid (125 mL) in several portions. After stirring for 1 h at 20°C, the reaction was diluted with dichloromethane (600 mL), filtered through Celite (Johns-Manville Corp.), and the solids were washed with dichloromethane. The combined filtrates were concentrated, and the resulting oil was taken up in dichloromethane (800 mL). This solution was washed with saturated sodium carbonate, dried (magnesium sulfate), and concentrated to an orange oil (12.9 g). This free base was converted to its hydrochloride salt in ether. Recrystallization from acetonitrile gave 9.1 g (61%; 40% overall) of a white solid, mp 184–187°C (Table II); ^{1}H NMR (Me_2SO-d_6): δ 2.2–3.0 (m, 9, CH_2, CH_3, and NH_2^+), 4.6 (s, 2, OCH_2), and 6.8–7.5 ppm (m, 9, ArH); MS: M^+ *m/z* 253.

Compound **1g** was prepared in a similar manner from **1e** (Table II). IR, ^{1}H NMR, and MS were consistent with the assigned structure.

N-Cyclopropylmethyl-2,3-dihydro-N-methyl-3-phenyl-3-benzofuranethanamine Fumarate (1h)—A mixture of **1f** (4.0 g, 0.016 mol), cyclopropylmethyl chloride (1.54 g, 0.017 mol), potassium carbonate (6.9 g, 0.050 mol), potassium iodide (0.2 g, 0.001 mol), and dimethylformamide (40 mL) was stirred at 65°C for 4 h. The cooled mixture was poured into water (40 mL) and extracted with ether (3 × 200 mL). The combined layers were washed with brine and dried (sodium sulfate). The yellow solution was stirred with silica gel (4 g), filtered, and concentrated. The resultant free base was converted to the fumarate salt (4.2 g). Recrystallization from acetonitrile gave 2.2 g (33%) of white crystals, mp 154–156°C (Table II); ^{1}H NMR (Me_2SO-d_6): δ 0.0–1.1 (m, 5, c-C_3H_5), 2.0–3.0 (m, 9, CH_2 and CH_3), 4.7 (s, 2, OCH_2), 6.6 (s, 2, fumaric CH), 6.7–7.6 (m, 9, ArH), and 14.3 ppm (br s, 2, fumaric OH); MS: $(MH)^+$ *m/z* 308.

Compound **1i** was prepared in a similar manner from **1f** using phenethyl bromide and converted to the fumarate salt (Table II). IR, ^{1}H NMR, and MS were consistent with the assigned structure.

Pharmacology—*Tetrabenazine Assay*[11]—The test compound was administered by intraperitoneal injection to male mice (Charles River CD-1) in groups of five. Tetrabenazine methanesulfonate (40 mg/kg, ip) was administered 30 min later and, after another 30 min, the mice were placed in individual containers. Ptosis was then evaluated on a three-point scale: eyes closed = 2; eyes half open = 1; eyes open = 0. A linear regression analysis of the ptosis scores was used to evaluate ED_{50} values and 95% confidence intervals. Data for the reference standard imipramine is included in Table II.

Phenylquinone Writhing Assay—The procedure employed was a modification of the method of Siegmund, Cadmus, and Lu.[12] Groups of five male mice (Charles River CD-1) weighing 18–24 g were administerd the test compound by subcutaneous injection at various time intervals prior to the injection of a phenyl-*p*-quinone solution (0.125% in a 5% aqueous ethanol solution). Control mice were treated with an equal volume of vehicle. After phenylquinone injection, the mice were placed in individual 1000-mL beakers and, 5 min later, the number of times the mice writhed was recorded for a 10-min period. The peak time of test drug activity was thereby determined. A dose-response study was performed in a similar manner, except that 10 animals were used at the peak time of activity. Animals were dosed and tested randomly using four doses and one control group. Drug activity is expressed as the percent inhibition of the number of times the mice writhed and an estimated ED_{50} was calculated by computerized linear-regression analysis. Data for the reference standard pentazocine is included in Table II.

Results and Discussion

All compounds listed in Tables I and II were evaluated for potential antidepressant activity with respect to their antagonism of tetrabenazine-induced ptosis (TBZ) and for analgesic activity by their inhibition of phenylquinone-induced writhing (PQW) in mice. While the intermediates (Table I) failed to display significant effects in either assay, several of the targeted dihydrobenzofurans (Table II) exhibited marked biological activity. Optimal TBZ activity of the imipramine range was observed in **1a** and its demethylated analogue **1f**. Substitution in the pendant ring[13] (**1b**, **1c**, **1d**) and lengthening of the attached side chain (**1e**, **1g**) resulted in diminished activity. In addition, replacement of a methyl with other larger groups (**1h**, **1i**) was detrimental. Unexpectedly, only the cyclopropylmethyl analogue **1h** exhibited marked PQW activity at nearly one-half the potency of pentazocine. Thus, while separate examples of significant antidepressant-like and antinociceptive properites were obtained, a simultaneous antidepressant–potent analgesic profile was not discovered in this series of compounds.

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