HCl·H-(*RS*)Pheψ(COCH$_2$)Gly-Leu-Met-NH$_2$ (9). The N-protected pseudopentapeptide 8 (0.39 mmol, 0.22 g) was deprotected according to the standard deprotection procedure given above. The precipitate obtained was dried in vacuo: yield 0.14 g (73.8%); mp 138–141 °C; TLC, R_f (B) 0.70, (D) 0.57; HPLC, k'(MeOH %/H$_2$O %) 7.5 (40/60). Anal. ($C_{23}H_{36}N_4O_4S$·HCl·H$_2$O) C, H, N.

Boc-pGlu-Phe-(*RS*)Pheψ(COCH$_2$)Gly-Leu-Met-NH$_2$ (10). Amine component 9 (0.28 mmol, 0.14 g) was coupled to Boc-pGlu-Phe-OH (0.28 mmol, 0.10 g) following method B, in 2 mL of DMF, using DCC (0.28 mmol, 0.057 g), HOBt (0.56 mmol, 0.076 g), and NMM (0.28 mmol, 0.031 mL): yield 0.14 g (60.8%); mp 105–108 °C dec; TLC R_f (B) 0.92, (D) 0.73; HPLC, k' (MeOH %/H$_2$O %) (a) 5.41, (b) 7.0 (60/40) [(a) and (b) refer to fast and slow peaks, respectively]; FAB MS, m/e 823 [M + H$^+$]. Anal. ($C_{42}H_{58}N_6O_9S$) C, H, N.

pGlu-Phe-(*RS*)Pheψ(COCH$_2$)Gly-Leu-Met-NH$_2$ (II). The Boc-protected pseudohexapeptide 10 (0.16 mmol, 0.13 g) was deprotected by the method described above. The residue obtained was twice reprecipitated from absolute methanol, centrifuged at 2500 rpm, collected, and dried in vacuo, yielding 0.1 g (86.5%) of product: mp 262–265 °C dec; TLC R_f (B) 0.88, (D) 0.86; HPLC, k'(MeOH %/H$_2$O %) (a) 2.9, (b) 3.45 (60/40) [(a) and (b) refer to fast and slow peaks, respectively]; FAB MS, m/e 723 [M + H$^+$]. Amino acid analysis: Glu: 1.00; Phe: 1.00; Leu: 1.00; Met: 1.00; X = 1.00 (X, the pseudo ketomethylene unit is detected at a t_R similar to that of His, established by an independent control run performed with a buffered sample of 6). Anal. ($C_{37}H_{50}N_6O_7S$) C, H, N.

Biological Assays. Isolated Guinea Pig Ileum Assay. This was done as previously described.[6]

Rat Diencephalon Membrane System. Diencephalons from seven male albino rats were homogenized in 25 mL of ice-cold Hepes buffer (50 mM, pH 7.4), with 10 strokes of a Teflon-glass homogenizer at 800 rpm, and centrifuged at 1000g for 10 min. The supernatant was recentrifuged at 17000g for a further 10 min. The resulting pellet was suspended with a Dounce homogenizer in cold buffer and centrifuged again at 17000g for 10 min. The final pellet was washed with cold buffer and resuspended in 5 mL of buffer (1–3 mg/mL of protein).

Assay of Peptidase Acting on the C-Terminal Sequence of Substance P. The degradation of N^{α}([^{125}I]-desaminoiodotyrosyl)SP$_{6-11}$ and its inhibition by the above-mentioned compounds by rat diencephalon membrane preparation was assayed as previously described.[16] High concentrations (10^{-6} M each) of phosphoramidon and captopril, potent inhibitors displaying affinities in the nanomolar range toward angiotensin converting enzyme and enkephalinase, respectively,[12,13] were included in the assay in order to detect SP degrading activities distinct from these two enzymes. The inhibition constants, K_i, of peptides I and II were determined as described before.[20]

Acknowledgment. This research was supported by a grant from the National Council for Research and Development, Israel, and G. S. F., Munchen, Germany, to M. C. and C. G. We also express our deep gratitude to Prof. H. Schwarz and Dr. K. Eckart (Berlin) for the FAB MS analyses and to Dr. S. Blum and her staff for the microanalytical service.

Resolution of Flecainide Acetate, *N*-(2-Piperidylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide Acetate, and Antiarrhythmic Properties of the Enantiomers

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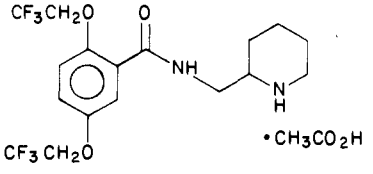
The antiarrhythmic agent flecainide acetate was resolved by fractional crystallization of its diastereomeric α-bromocamphor-π-sulfonate salts. Optical purity of the two enantiomers was shown to be >99% by an NMR technique using the chiral shift reagent Eu(hfbc)$_3$. Antiarrhythmic effects of flecainide and its enantiomers were assessed in two different animal models, chloroform-induced ventricular fibrillation in mice and ouabain-induced ventricular tachycardia in dogs. The two enantiomers were highly effective in suppressing both of these experimental arrhythmias and appeared to be essentially equipotent. No significant differences were found either between the two enantiomers or between the enantiomers and racemic flecainide.

Flecainide acetate (Tambocor, I), *N*-(2-piperidylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide acetate, is a clinically effective new agent used in the treatment of cardiac arrhythmias. The synthesis,[1] animal pharmacology,[2,3] metabolism,[4] and clinical properties[5] of racemic flecainide acetate have been previously described. In this paper we report a resolution of flecainide and an evaluation of the antiarrhythmic properties of both enantiomers compared to racemic flecainide acetate.



I

Resolution. Racemic flecainide acetate was converted to its free base and resolved by fractional crystallization of the diastereomeric salts formed by addition of 1 equiv of ammonium (+)-α-bromocamphor-π-sulfonate to a solution of flecainide in methanol. Repeated crystallizations, first from isopropyl alcohol and then ethyl acetate, yielded a single diastereomeric salt, $[\alpha]^{26}_D$ +43.5°. Decomposition

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(1) Banitt, E. H.; Bronn, W. R.; Coyne, W. E.; Schmid, J. R. *J. Med. Chem.* **1977**, *20*, 821.
(2) Schmid, J. R.; Seebeck, B. D.; Henrie, C. L.; Banitt, E. H.; Kvam, D. C. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1975**, *34*, 775.
(3) Kvam, D. C.; Banitt, E. H.; Schmid, J. R. *Am. J. Cardiol.* **1984**, *53*, 22B.
(4) Conard, G. J.; Ober, R. E. *Am. J. Cardiol.* **1984**, *53*, 41B.
(5) Anderson, J. L.; Stewart, J. R.; Perry, B. A.; Van Hamersveld, D. D.; Johnson, T. A.; Conard, G. C.; Chang, S. F.; Kvam, D. C.; Pitt, B. *N. Engl. J. Med.* **1981**, *305*, 473.

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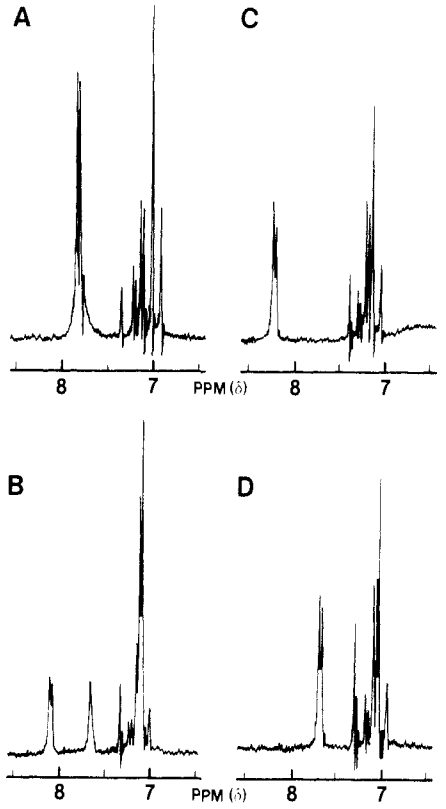

Figure 1. Partial NMR spectra of (A) (±)-flecainide, (B) (±)-flecainide + Eu(hfbc)$_3$, (C) (+)-flecainide + Eu(hfbc)$_3$, and (D) (−)-flecainide + Eu(hfbc)$_3$. The proton at position 6 of the aromatic ring was used for optical purity determinations. It is a doublet at 7.76 ppm in (A) and a pair of doublets at 8.17 ppm ((+) enantiomer) and 7.72 ppm ((−) enantiomer) in (B).

of the salt with aqueous base provided optically pure free base, $[\alpha]^{26}_D$ +3.4°. Treatment of the optically pure free base with acetic acid afforded the acetate salt, $[\alpha]^{26}_D$ +4.6°. Although this extra step was not strictly necessary, the acetate was prepared for pharmacological evaluation so that the results could be compared directly with racemic flecainide acetate.

Flecainide enriched in (−) enantiomer was recovered from mother liquors of the initial resolution and combined with an equimolar amount of ammonium (−)-α-bromocamphor-π-sulfonate in methanol. The opposite diastereomeric salt, $[\alpha]^{26}_D$ −42.4°, was obtained after several crystallizations. Repetition of substantially the same isolation procedure used in the first resolution provided pure enantiomeric free base, $[\alpha]^{26}_D$ −3.3°, and its corresponding acetate salt, $[\alpha]^{26}_D$ −4.5°.

Optical Purity. Optical purity of the flecainide enantiomers was determined by NMR utilizing the chiral shift reagent tris[3-heptafluorobutyryl)-*d*-camphorato]-europium(III), Eu(hfbc)$_3$. All NMR spectra were obtained on the free base form of flecainide and its enantiomers in order to maximize the Eu-induced shifts. The aromatic protons of racemic flecainide free base show a typical 1,2,5-trisubstituted pattern assigned as follows: 6.90 ppm (H-3, doublet, 8.9 Hz), 7.09 ppm (H-4, double doublet, 2.7 and 8.9 Hz), 7.76 ppm (H-6, doublet, 2.7 Hz). In the presence of added Eu(hfbc)$_2$ large downfield shifts are observed for the protons α to nitrogen in the piperidine ring for both the (+) and (−) enantiomers, indicating binding of the Eu to the secondary amine. In addition, absorption of the H-6 proton is shifted downfield for the (+) enantiomer but slightly upfield for the (−) enantiomer, indicating a different orientation of the aromatic ring relative to the Eu in the two enantiomers. At a concentration of 33 wt % of shift reagent relative to free base, the H-6 proton signals of the two enantiomers are completely separated from each other as well as other peaks in the spectrum (Figure 1). The ratio of (+)/(−) isomers is readily quantitated from measurements of H-6 peak intensities. By use of this technique, the optical purity of both resolved samples was shown to be >99%.

Table I. Antagonism of Chloroform-Induced Ventricular Fibrillation in Mice by Orally Administered Flecainide Acetate (I)

compd	dose, mg/kg	no. of mice protected/ tested	ED_{50}[a], mg/kg	signs of toxicity
(±)-I	9.0	4/10	11.0 (6.7–18.2)	none
	13.0	6/10		none
	20.0	7/10		none
(+)-I	9.0	1/10	12.4 (9.7–15.9)	none
	13.0	7/10		none
	20.0	8/10		none
(−)-I	9.0	3/10	14.5 (8.9–23.6)	none
	13.0	5/10		none
	20.0	6/10		none

[a] Dose that prevented ventricular fibrillation in 50% of the mice with 95% confidence limits in parentheses.

Pharmacology. The antiarrhythmic properties of racemic flecainide and its enantiomers were determined in two separate experimental arrhythmia models. All compounds were tested as acetate salts so that direct comparisons could be made.

In preliminary work, prevention of chloroform-induced ventricular fibrillation in mice[6] was used to identify antiarrhythmic activity. Test substances were administered orally in a 4% acacia vehicle to groups of 10 mice. ED_{50} values, i.e., the dose that prevented fibrillation in 50% of the animals, along with 95% confidence limits were calculated. Results are summarized in Table I. All compounds were effective in suppressing ventricular fibrillation induced in this manner. Comparison of the ED_{50} values indicates that there is little difference in antiarrhythmic potency between racemic flecainide and either of its enantiomers. None of the compounds showed gross signs of toxicity in the dose range studied (9–20 mg/kg).

These initial results were confirmed by a second set of experiments that measured antagonism of ouabain-induced ectopic ventricular tachycardia in dogs. Doses of ouabain sufficient to produce ventricular tachycardia were administered to anesthetized dogs.[7] The arrhythmias developed slowly and were ectopic in origin (stimulation of the distal end of the severed right vagus nerve did not alter ventricular rate). After the arrhythmias had stabilized (ca. 15 min), test drugs were given intravenously in 1 mg/kg increments until the appearance of sinus rhythm. When sinus rhythm was attained, stimulation of the vagus nerve produced its characteristic response, indicating a shift of the pacemaker back to the sinoatrial node. The duration of sinus rhythm was also recorded.

Flecainide and its two stereoisomers were highly effective in suppressing ouabain arrhythmias. Full suppression was observed at doses of 1–3 mg/kg (Table II). Although not evident from the table, the duration of antiarrhythmic action was frequently transcient (<10 min) at the lowest effective dose and was always dose-related. The effects of all test compounds on blood pressure were generally

(6) Lawson, J. W. *J. Pharmacol. Exp. Ther.* **1968**, *160*, 22.
(7) Lucchesi, B. R.; Hardman, H. F. *J. Pharmacol. Exp. Ther.* **1961**, *132*, 372.

Table II. Antiarrhythmic Activity of Flecainide Acetate (I) in Ouabain-Induced Ectopic Ventricular Tachycardia in Anesthetized Male Dogs

compd	expt (body wt, kg)	conversion of arrhythmia to sinus rhythm: conversion dose,[a] mg/kg, iv	conversion of arrhythmia to sinus rhythm: duration sinus rhythm, min
(±)-I	1 (13.1)	1.0	>10
	2 (14.1)	2.0	~6
	3 (15.7)	1.0	~10
	4 (12.7)	1.0	~6
	5 (10.9)	1.0	>28
(+)-I	6 (13.3)	1.0	>20
	7 (11.7)	1.0	<10
	8 (12.8)	1.0	~1
	9 (13.6)	3.0	>12
	10 (15.6)	2.0	~6
(−)-I	11 (11.3)	2.0	<3
	12 (12.1)	1.0	~8
	13 (12.4)	1.0	~5
	14 (14.3)	1.0	>9
	15 (15.0)	3.0	<9

[a] Additional doses not recorded in this table were administered to prolong the duration of antirrhythmic action.

mild (<15%) and variable. All compounds caused a mild to moderate bradycardia (15–35%).

The results of these studies demonstrate that there is little difference in the antiarrhythmic potency or effectiveness of racemic flecainide and its enantiomers. The two enantiomers are essentially equiactive and exhibit no evidence of stereoselectivity. In addition, the dog study revealed no significant differences between enantiomers in their effects on blood pressure or ventricular rate.

Experimental Section

Melting points were obtained in open glass capillaries on a Thomas-Hoover Uni-Melt apparatus and are uncorrected. All observed rotations at the sodium D line were determined with a Perkin-Elmer Model 241 polarimeter (1-dm cells). Where analyses are indicated only by symbols of the elements, the analytical results were within ±0.4% of the theoretical values.

Resolution of (±)-*N*-(2-Piperidylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide Acetate (I). Racemic flecainide free base was isolated by treating I with excess dilute NaOH and extracting the mixture with CH_2Cl_2. The free base obtained after drying and evaporating the solvent was used without further purification.

A solution of 18.1 g (55.1 mmol) of (+)-α-bromocamphor-π-sulfonic acid ammonium salt and 22.8 g (55.1 mmol) of racemic flecainide free base in 400 mL of MeOH was heated to boiling 30 min, cooled, and concentrated to dryness. The residual diastereomeric salt mixture was crystallized from *i*-PrOH twice and then repeatedly from EtOAc to constant specific rotation, allowing the solution to cool undisturbed to room temperature overnight each time. The salt, obtained as white needles weighing 7.8 g, had mp 179.5–182 °C; $[\alpha]^{26}_D$ +43.5° (c 2.641, MeOH). Anal. ($C_{17}H_{20}F_6N_2O_3 \cdot C_{10}H_{15}BrO_4S$) C, H, N.

Mother liquors from all recrystallizations were combined and concentrated to dryness. Dilute NaOH was added and the mixture was extracted several times with CH_2Cl_2. The combined extracts were washed with saturated NaCl solution, dried, and concentrated to dryness. Recovered free base, enriched in the (−) enantiomer, was combined with sufficient racemic free base to give 18.3 g (44.2 mmol) and dissolved in 300 mL of MeOH containing 14.5 g (44.2 mmol) of (−)-α-bromocamphor-π-sulfonic acid ammonium salt. Fractional crystallization of the diastereomeric salt mixture as described above provided 9.6 g of the sulfonate salt: mp 179–182 °C; $[\alpha]^{26}_D$ −42.4° (c 4.203, MeOH). Anal. ($C_{17}H_{20}F_6N_2O_3 \cdot C_{10}H_{15}BrO_4S$) C, H, N.

(+)-*N*-(2-Piperidylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide Acetate. Pure diastereomeric sulfonate salt from the initial resolution (7.8 g $[\alpha]^{26}_D$ +43.5°) was converted to free base by treating it with dilute NaOH and extracting the mixture several times with CH_2Cl_2. The combined extracts were washed with saturated NaCl solution and dried. Evaporation of solvent yielded 4.3 g of free base as a white powder: mp 104–105 °C; $[\alpha]^{26}_D$ +3.4° (c 3.812, MeOH). Optical purity at this stage as determined by NMR was >99%. Anal. ($C_{17}H_{20}F_6N_2O_3$) C, H, N.

The optically pure free base was converted to acetate salt by dissolving it in *i*-PrOH containing 10% molar excess AcOH, warming the solution, adding $(i\text{-Pr})_2O$ to the cloud point, and allowing crystallization to occur slowly. The product weighed 4.3 g; mp 153–155 °C; $[\alpha]^{26}_D$ +4.6° (c 3.990, MeOH). Anal. ($C_{17}H_{20}F_6N_2O_3 \cdot C_2H_4O_2$) C, H, N.

In order to prove that no racemization occurred during salt formation, a sample of acetate salt was converted back to free base. Specific rotation and optical purity (NMR) were identical with readings obtained before salt formation.

(−)-*N*-(2-Piperidylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide Acetate. Following substantially the same procedure described above for the (+) enantiomer, pure diastereomeric sulfonate salt from the second phase of the resolution (9.3 g $[\alpha]^{26}_D$ −42.4°) was converted to 5.2 g of optically pure (>99%) free base: mp 102–104 °C; $[\alpha]^{26}_D$ −3.3° (c 2.856, MeOH). Anal. ($C_{17}H_{20}F_6N_2O_3$) C, H, N.

Treatment of free base with AcOH as above yielded the product as a crystalline solid weighing 5.5 g: mp 152.5–154 °C; $[\alpha]^{26}_D$ −4.5° (c 3.231, MeOH). Anal. ($C_{17}H_{20}F_6N_2O_3 \cdot C_2H_4O_2$) C, H, N.

Optical Purity Determinations. Optical purities were measured spectrophotometrically on a Varian XL-100 NMR operating at 100 MHz using a Varian 620-i computer accessory for time-averaged CAT spectra and the chiral shift reagent Eu(hfbc)$_3$ obtained from Willow Brook Laboratories. Spectra of flecainide and its enantiomers were obtained on the free base form in $CDCl_3$. The aromatic proton at position 6 of racemic flecainide appears at 7.76 ppm and is the only resonance in the spectrum that is useful for optical purity determinations. In racemic samples containing 75:25 (w/w) of free base/shift reagent, separate H-6 peaks were clearly visible for each enantiomer. The amount of each enantiomer in mixtures was calculated from measurements of relative H-6 peak intensities. Under conditions capable of detecting impurities at the 1% level (25 CAT spectra), none of the opposite enantiomer could be detected in either resolved sample. Thus the optical purity of both enantiomers was >99%. To confirm these results, 7.9% of racemic flecainide free base was added to a sample of pure (+) enantiomer. The amount of (−) enantiomer determined by integration, 4.0%, was within experimental error of the calculated value assuming the optical purity was 100%.

Antiarrhythmic Evaluation. Prevention of $CHCl_3$-induced ventricular fibrillation in female mice weighing 18–24 g was used for preliminary estimation of antiarrhythmic activity. Control mice when exposed to $CHCl_3$ vapor until cessation of respiration exhibit ventricular fibrillation upon visual inspection of the heart. Compounds with known antiarrhythmic activity will prevent this response.[6] Flecainide and its enantiomers were administered by oral gavage using 4% acacia as vehicle. A 30-min period was allowed for absorption of the test compound during which time the mice were observed for toxic effects, and then the mice were exposed to $CHCl_3$. Compounds were tested in groups of 10 mice at dose levels of 9, 13, and 20 mg/kg and ED_{50} values were calculated according to the method of Litchfield and Wilcoxon.[8]

Secondary evaluations utilized a dog model in which ventricular tachycardia was induced by ouabain. Adult mongrel dogs weighing 8–14 kg were anesthetized by intravenous pentobarbital sodium (30 mg/kg). Experimental arrhythmias were induced by the method of Lucchesi and Hardman.[7] An initial dose of 40 μg/kg of ouabain was given intravenously and supplemented in 30 min with 20 μg/kg and every 15 min thereafter with 10 μg/kg until ectopic ventricular tachycardia occurred. The arrhythmia was allowed to stabilize for about 15 min, and then the test compound was administered by slow intravenous injection in 1.0 mg/kg increments approximately every 15 min until the end point of sinus rhythm was attained. The duration of sinus rhythm was noted and a higher dose was then given in an attempt to prolong

(8) Litchfield, J. T.; Wilcoxon, F. *J. Pharmacol. Exp. Ther.* **1949**, *96*, 99.

the period of conversion. Blood pressure was recorded in the usual fashion and a lead II electrocardiogram was recorded to visually monitor the arrhythmia.

Registry No. (±)-I, 99495-88-2; (±)-I (base), 99495-87-1; (+)-I, 99495-93-9; (+)-I (base), 99495-92-8; (+)-I ·(+)-α-bromocamphor-π-sulfonic acid, 99495-89-3; (-)-I, 99495-94-0; (-)-I (base), 99495-90-6; (-)-I ·(-)-α-bromocamphor-π-sulfonic acid, 99495-91-7; (+)-α-bromocamphor-π-sulfonic acid ammonium salt, 14575-84-9; (-)-α-bromocamphor-π-sulfonic acid ammonium salt, 55870-50-3.

Synthesis and Evaluation of 2,3-Dihydrobenzofuran Analogues of the Hallucinogen 1-(2,5-Dimethoxy-4-methylphenyl)-2-aminopropane: Drug Discrimination Studies in Rats

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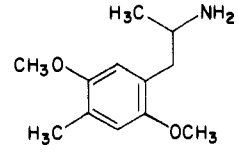
Two analogues, 6-(2-aminopropyl)-5-methoxy-2,3-dihydrobenzofuran and 6-(2-aminopropyl)-5-methoxy-2-methyl-2,3-dihydrobenzofuran, of the hallucinogenic agent 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) were synthesized and tested in the two-lever drug discrimination paradigm. In rats trained to discriminate saline from LSD tartrate (0.08 mg/kg), stimulus generalization occurred to both of the 2,3-dihydrobenzofuran analogues but at doses more than 10-fold higher than for DOM. A possible explanation for this dramatic attenuation of LSD-like activity could involve a highly directional electrophilic binding site on the receptor that cannot accept the orientation of the unshared electron pairs on the heterocyclic oxygen atom in the benzofurans.

In our continuing investigations of the structure–activity relationships of hallucinogenic drugs, we have been directing attention to the importance of aromatic ring substituents in substituted "amphetamine" type hallucinogens. A prototype of this class of drug is 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (**1**; DOM, STP). Several years ago it was communicated by another worker that the 2,3-dihydrobenzofuran analogues of DOM **2** and **3** were highly potent hallucinogens.[1]



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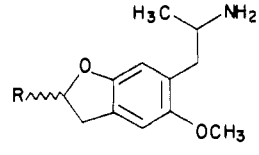


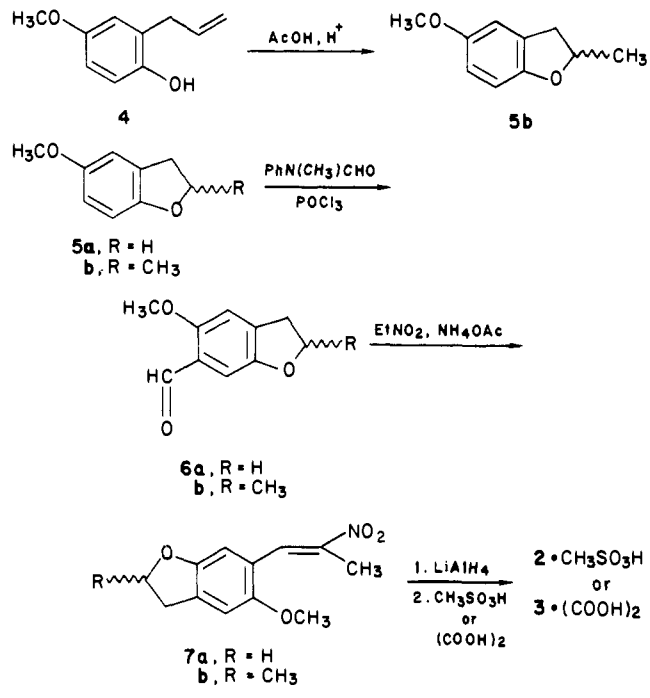
2, R = H
3, R = CH_3

We were intrigued by these reports and the possiblity that the diastereomers of **3** could be resolved to afford four isomers. These would provide useful probes of the stereochemical requirements of the binding site, if any, for the para substituent of the substituted amphetamine hallucinogens.

We therefore synthesized **2** and **3** to begin studies directed toward this goal. However, evaluation of these two compounds in the two-lever drug discrimination paradigm, in rats trained to discriminate between saline and LSD tartrate (0.08 mg/kg), revealed a dramatic attenuation of LSD-like activity in rats when compared with **1**. This report, therefore, details the synthesis of **2** and **3** and the evaluation in rats for LSD-like activity.

Chemistry. Both compounds **2** and **3** were obtained by elaboration of the 2,3-dihydrobenzofurans **5a** and **5b**. Treatment of these with phosphorus oxychloride and *N*-methylformanilide under conditions of the Vilsmeier–Haack reaction led to the corresponding benzaldehydes **6a** and **6b**, respectively. A major side reaction was formylation at the 7-position of the dihydrobenzofuran ring, but recrystallization of **6a** and **6b** from hexane effectively removed this isomeric aldehyde. Condensation of the benzaldehydes with nitroethane, followed by reduction of the resulting nitroolefin with lithium aluminum hydride and formation of the salt, gave the desired compounds **2** and **3**, as their methanesulfonate and oxalate salts, respectively.

Scheme I



Preparation of the starting 2,3-dihydrobenzofuran **5a** was accomplished following the method of Tanaka.[2]

The 2-methyl-2,3-dihydrobenzofuran **5b** was prepared by acid-catalyzed cyclization of 2-allyl-4-methoxyphenol, which was obtained by thermal Claisen rearrangement of the corresponding allyl ether. The acid-catalyzed cyclization of **4** was best accomplished following the method of Darling and Wills,[3] using reflux in glacial acetic acid containing a catalytic amount of sulfuric acid. A variety of other attempts with various acids failed, although py-

(1) Trampota, M., personal communication, 1980.

(2) Tanaka, S. *J. Am. Chem. Soc.* **1951**, *73*, 872.

(3) Darling, S. S.; Wills, K. D. *J. Org. Chem.* **1967**, *32*, 2794.

0022-2623/86/1829-0302$01.50/0