Phenylalkylamines with Potential Psychotherapeutic Utility. 1. 2-Amino-1-(2,5-dimethoxy-4-methylphenyl)butane

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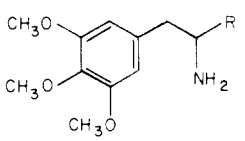
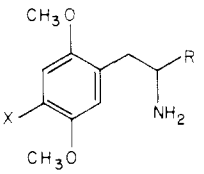
The synthesis, resolution, and asymmetric synthesis of 2-amino-1-(2,5-dimethoxy-4-methylphenyl)butane (**2e**) are described. Animal data are presented indicating that the compound can be pharmacologically differentiated from DOM and amphetamine and that it improves avoidance acquisition in the rat.

The behavorial profile of mescaline (**1a**) has prompted preparation of many derivatives.[1,2] Most studies have concentrated on the psychotomimetic effects of these molecules. Shulgin et al. have pointed out that substitution of a methyl group α to the amino function resulted in an increase in hallucinogenic potency[3] (**1b**); this effect was noted with a wide variety of ring substituents. An



1a, R = H
b, R = CH_3
c, R = C_2H_5



2a, R = H; X = CH_3
b, R = X = CH_3
c, R = CH_3; X = C_2H_5
d, R = CH_3; X = Br
e, R = C_2H_5; X = CH_3

analogy was drawn between this relationship and the activity changes found in going from phenethylamine to amphetamine.[4] Further homologation to α-ethyl (**1c**) resulted in a loss of psychotomimetic effects in man.[5]

Derivatization of the nuclear 4 position, coupled with a 2,5-dimethoxy substitution, has been found to provide particularly potent hallucinogens (**2b–d**).[6] DOM (**2b**) and DOB (**2d**) have become serious medical and law enforcement problems.[7-10] Attempts have been made to channel some of these substituted phenethylamines into medically useful paths. For example, Snyder and his associates have found that DOET (**2c**) produces, in nonmental patients, a feeling of relaxation and enhanced self-awareness which might be useful in aiding psychotherapy.[11-13]

Interestingly, DOM and DOET both produced subjective effects of mild euphoria and enhanced self-awareness; however, DOM demonstrated clear-cut psychotomimetic-hallucinogenic effects at twice the minimal detectable dose, while DOET exhibited none of these at five times the minimal dosage. Shulgin and co-workers had noted similar potential with low dosages of DOB[14] and 3,4-methylenedioxyamphetamine.[15] Hallucinogenic potential remains, however, both as a hazard and abuse liability.

Our attention was focused on the α-ethyl analogue of DOM (**2e**) by the personal observation of one of us (A.T.S.) that treatment with this compound might result in improved performance properties without hallucinogenic liability. The α-H homologue **2a** has been reported in animal avoidance tests[16] to be less active than **2b** and substantially stimulant in nature. In human evaluation[17] the decrease in potency is confirmed, but the psychopharmacological profile is largely one of sensory enhancement. We report herein the synthesis and some pharmacological comparisons of 2-amino-1-(2,5-dimeth-

Scheme I

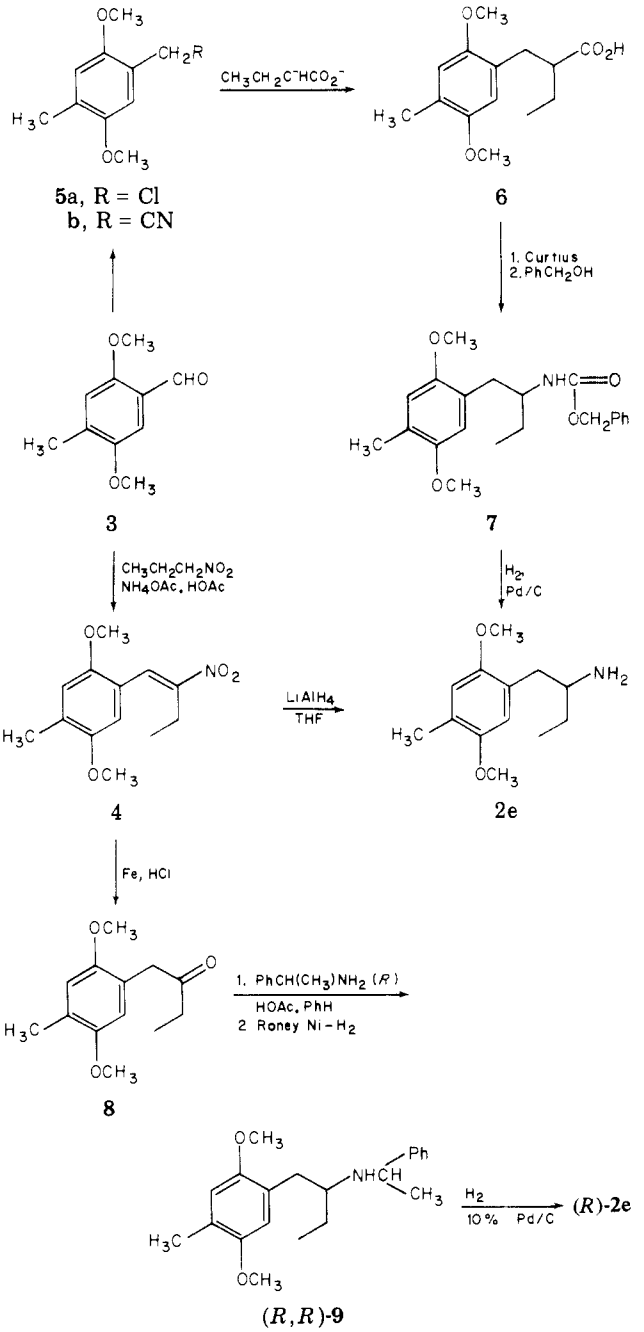


Table I. Spasmogenic Effect on Smooth Muscle of Rat Stomach Fundus

No.	ED_{50}, μg/ml (95% confidence limits)	Pot. rel to serotonin	Pot. rel to (*R*)-DOM
(*S*)-**2e**	21.8 (16.8–26.4)	0.0024	0.015
(*R*)-**2e** (BL-3912A)	20.8 (16.5–26.2)	0.0025	0.016
2a	0.021 (0.014–0.032)	0.25	1.6
(*S*)-**2b** [(*S*)-DOM]	0.077 (0.063–0.094)	0.068	0.43
(*R*)-2b [(*R*)-DOM]	0.033 (0.027–0.039)	0.16	1.0
Serotonin	0.0052 (0.0041–0.0065)	1.0	6.3

Table II. Hyperthermic Effect in the Rabbit

No.	ED, mg/kg iv	Pot. rel to LSD	Pot. rel to (*R*)-DOM
(*S*)-2e	3.6	0.0004	0.01
(*R*)-2e (BL-3912A)	0.9	0.002	0.04
2a	0.4	0.004	0.1
(*S*)-2b [(*S*)-DOM]	0.8	0.002	0.05
(*R*)-2b [(*R*)-DOM]	0.04	0.04	1.0
LSD	0.0015	1.0	27

oxy-4-methylphenyl)butane[18] (**2e**) with its two lower homologues (**2a** and **2b**).

Chemistry. Preparation of racemic **2e** proceeded readily by a standard sequence involving condensation of the appropriate aldehyde **3**[19] with nitropropane,[20] followed by reduction of the nitro olefin **4** with $LiAlH_4$ (Scheme I). Action of diborane upon the phenylacetonitrile **5b**[21,22] derived from **3** provided **2a**.[23]

The intermediate **5a** could also be utilized in an alternate synthesis of **2e**. The general method of Pfeffer[24] yielded the acid **6**, which was then degraded to the amine through the carbobenzoxy derivative **7**.

The racemic product was conveniently resolved by use of appropriately substituted tartranilic acids.[25] The resolution, though optically efficient, was time-consuming and tedious on a large scale. Need for quantities of the more active *R* isomer sufficient for toxicological and clinical work prompted a stereoselective synthesis as detailed in Scheme I.[26] The ketone **8** was converted predominately to one diastereomer of the substituted benzylamine **9**. A single recrystallization of **9** gave pure *R,R* isomer, as shown by subsequent hydrogenolysis to (*R*)-**2e** of >98% optical purity.

Optical purity checks were performed by GLC analysis of the (–)-MTPA amides[26,27] of the product amines. Although the method of synthesis, together with the order of GLC elution of the MTPA amides, is strong presumptive evidence for assignment of absolute configurations, comparison of ORD curves of the isomers of **2e** with those of amphetamine confirmed the assignment.[28,29]

Pharmacology and Discussion. The pharmacology of substituted phenylalkylamines is highly complex and it is not our purpose to present in this paper a complete pharmacological profile of **2e**. Rather, we intend to show clear-cut activity differences between **2e** and its lower homologues and to demonstrate improved performance in a simple conditioned avoidance model.

Accordingly, the serotonergic effects on smooth muscle and the hyperthermia producing properties (rabbit) of **2a** and the enantiomers of **2b** (DOM) were compared with those of the optical isomers of **2e**. The results are summarized in Tables I and II. In addition, a recent publication[30] from this laboratory contrasts the cardiovascular and gross behavioral effects of (*S*)-amphetamine, (*R*)-DOM, and (*R*)-**2e** (identified by its code number, BL-3912A).

Table III. Effect on Acquisition of Active Avoidance Response by Breeder Rats in the Shuttle Box

No.	mg/kg sc	*N*[a]	No. of trials for 80% avoidance[b]	*P*[c]
(*R*)-**2e** (BL-3912A)	1	10	>42.4 (3/10)[d]	NS[e]
	5	10	>33.4 (7/10)	<0.01
	10	9	>28.3 (7/9)	<0.01
(*S*)-**2e**	1	8	>37.4 (3/8)	NS
	5	10	>34.5 (5/10)	<0.05
	10	9	>35.9 (5/9)	<0.05
(*S*)-Amphetamine	1	5	>50 (0/5)	NS
	5	5	>50 (0/5)	NS
	10	5	>34.2 (2/5)	NS
Saline		41	>48.0 (3/41)	

[a] Number of animals. [b] Means are preceded by a sign ">" because there were animals which failed to achieve the required avoidance criterion in 50 trials. [c] Wilcoxon rank sum method with respect to saline. [d] Number of animals achieving 80% avoidance/number of animals used. [e] Not significant.

It has been suggested that stimulation of serotonin receptors may be related to psychotomimetic activity.[31,32] Marked potency differences in spasmogenicity, as it reflects serotonergic stimulation, were found between the phenyl-*sec*-butylamines **2e** and the corresponding phenylisopropylamines **2b** and the phenethylamine **2a** (see Table I). There were no significant potency differences between the optical isomers of **2e**. However, (*R*)-DOM [(*R*)-**2b**] was approximately twice as active as (*S*)-DOM. This coincides with the observation of Shulgin that (*R*)-DOM is the hallucinogenic isomer in man.[33]

The results in the rabbit hyperthermia test (Table II) are of particular interest because of the documented parallel[6] between the production of a psychotomimetic syndrome in man and this effect. (*R*)-DOM [(*R*)-**2b**] shows 25–100 times the potency of the **2e** isomers in this test, indicating low hallucinogenic potential for these phenyl-*sec*-butylamines. The potency difference between the **2e** isomers was smaller than that exhibited by the DOM isomers, but (*R*)-**2e** was more active than (*S*)-**2e**. The phenethylamine **2a** was of intermediate activity.

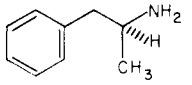
Thus it would appear that the results obtained in the rabbit hyperthermia model are more predictive of potential hallucinogenic activity than in vitro spasmogenicity, although both tests indicate low hallucinogenic potential for the **2e** isomers.

The effects of **2e** isomers upon the rate of acquisition in a conditioned avoidance model are presented in Table III. It is apparent that (*R*)-**2e** facilitated acquisition of the avoidance response as reflected in the number of trials required to achieve the 80% avoidance criterion and by the fraction of animals reaching such performance.

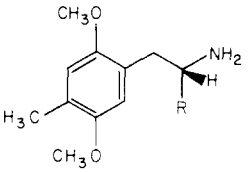
There was also an indication of a dose–response relationship in the range tested (1–10 mg/kg sc). There was no sharp activity separation between the two isomers; however, the *S* form appeared less effective. The reference agent, (*S*)-amphetamine, proved to be inactive under the testing conditions, although it produced definite signs of overt stimulation.

In summary, homologation of the side chain of DOM (α-methyl to α-ethyl) produces a drastic change in activity, as measured by two standard pharmacological tests. Both isomers of **2e** have been shown to increase acquisition rate in a simple avoidance model. It is interesting to note that the more active isomer of **2e** has the same absolute configuration as the potent hallucinogen (*R*)-DOM and opposite that of (*S*)-amphetamine (Chart I).

Chart I



(S)-(+)-amphetamine



(R)-DOM, R = CH_3
(R)-2e, R = C_2H_5

The title compounds thus present potential for improved performance unencumbered by hallucinogenic side effects and their accompanying abuse liability. (R)-2-Amino-1-(2,5-dimethoxy-4-methylphenyl)butane hydrochloride (BL-3912A) is presently in clinical trial for evaluation as a psychotherapeutic agent.

Experimental Section

Chemistry. Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Department of Bristol Laboratories. Where indicated by symbols of the elements, the analytical results obtained were within ±0.4% of the calculated values. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter using 1% solutions in 95% EtOH. GLC analyses were performed on a F & M Model 810 gas chromatograph equipped with a flame ionization detector. All products gave ir and NMR spectra consistent with their expected structures.

2,5-Dimethoxy-4-methylbenzaldehyde (3).[19] A mixture of 800 ml (8.74 mol) of $POCl_3$ and 900 ml (7.29 mol) of *N*-methylformanilide was stirred at room temperature for 50 min. 2,5-Dimethoxytoluene (304.4 g, 2.0 mol) was added all at once and the solution was warmed to 70 °C on the steam bath with rapid stirring. A vigorous, exothermic reaction occurred; the heat source was removed and the exotherm was allowed to run its course. When the reaction had moderated the mixture was stirred and heated on the steam bath for 2 h. The hot reaction mixture was then poured, with stirring, into 40 l. of ice H_2O. Stirring was continued for 2 h. The reddish solid was filtered, washed well with cold H_2O, and air-dried to give 400 g of crude product.

The crude material was suspended in 1000 ml of boiling petroleum ether (bp 60–70 °C) and the yellow supernatant was decanted from the black, tarry residue. The extraction procedure was repeated with 1000-ml portions of petroleum ether until the supernatant was colorless (total of 3–4 l. of petroleum ether). The extracts were chilled at 5 °C for 17 h. The yellow crystalline solid was filtered; concentration of the mother liquors to one-fourth volume yielded a large second crop. The solid was recrystallized from 80% MeOH–H_2O to give 277 g (77% yield) of **3** as light yellow crystals, mp 77–78 °C.

1-(2,5-Dimethoxy-4-methylphenyl)-2-nitro-1-butene (4). A mixture of 278 g (1.54 mol) of **3**, 278 ml (278.8 g, 3.13 mol) of 1-nitropropane, 110 g (1.43 mol) of NH_4OAc, and 1100 ml of glacial HOAc was refluxed for 5 h. The solution was cooled and poured into 9 l. of ice H_2O. The orange solid which separated was filtered, washed thoroughly with H_2O, and air-dried. Recrystallization from 6 l. of boiling MeOH yielded 184.5 g (48%) of the nitro olefin **4** as yellowish crystals, mp 116.5–117.5 °C. Anal. ($C_{13}H_{17}NO_4$) C, H, N.

2,5-Dimethoxy-4-methylbenzyl Chloride (5a).[21] Sodium borohydride (42 g, 1.1 mol) was added to a suspension of **3** (180 g, 1 mol) in *i*-PrOH (2 l.) The resulting mixture was refluxed for 2.5 h. The solvent was removed in vacuo and the residue partitioned between H_2O and Et_2O. The ethereal solution was washed (H_2O, saturated brine) and chilled (ice H_2O), and 500 ml of 12 N HCl was added with good stirring. Stirring was continued, without cooling, for 1 h. The two layers were separated and the aqueous layer was extracted with Et_2O. The combined ethereal solutions were washed (H_2O, saturated brine), dried (Na_2SO_4), and concentrated to give 189 g of beige crystals. Recrystallization from petroleum ether (bp 100–115 °C) gave **5a** (138 g, 69%), mp 60–67 °C. By boiling down the petroleum ether mother liquors, a second crop (about 30 g) of material suitable for use in the preparation of **5b** was obtained.

2,5-Dimethoxy-4-methylbenzonitrile (5b).[21] To a suspension of 0.7 g (14 mmol) of NaCN in 6 ml of anhydrous Me_2SO was added, dropwise, with stirring a solution of 2.0 g (10 mmol) of **5a** in 6 ml of anhydrous Me_2SO. A slight exothermic effect was noted.

The mixture was stirred for 2.5 h at ambient temperature and then poured into H_2O. The product was extracted out with Et_2O; the combined extracts were washed with H_2O and with saturated brine and dried (Na_2SO_4).

The solvent was evaporated to give a solid which was recrystallized from petroleum ether (bp 100–115 °C) to give 1.3 g (68%) of **5b**, mp 65–66 °C.

2-(2,5-Dimethoxy-4-methylbenzyl)butyric Acid (6). A solution of diisopropylamine (9.2 ml, 0.066 mol) in 90 ml of THF, under N_2, was cooled to about −20 °C with an ice–salt bath. A solution of *n*-butyllithium in *n*-hexane (41 ml of 1.6 M, 0.066 mol) was added dropwise at such a rate that the temperature did not go above 0 °C. Butyric acid (2.8 ml, 0.03 mol) was then added dropwise, again keeping the temperature below 0 °C. Hexamethylphosphoramide (6.3 ml, 0.036 mol) was added and the mixture stirred without cooling for 0.5 h.

The mixture was cooled to −15 °C and a solution of **5a** (6.0 g, 0.030 mol) in THF (10 ml) was added. The cooling bath was removed and the mixture stirred for 3 h.

The mixture was cooled (ice H_2O) and 100 ml of 10% HCl added. After removal of THF, the mixture was extracted with Et_2O. The combined Et_2O extracts were washed twice with 5% HCl and once with H_2O and then extracted with 15 N NH_4OH. The ammoniacal solution was washed with Et_2O, acidified with 12 N HCl, and then extracted with Et_2O.

Washing (H_2O, saturated brine), drying (Na_2SO_4), and concentrating the ethereal extract gave the crude acid (6.0 g). This was crystallized from petroleum ether (bp 63–75 °C) to give the acid **6** (5.9 g, 79%). Recrystallization from the same solvent gave analytically pure material, mp 92–94 °C. Anal. ($C_{14}H_{20}O_4$) C, H.

1-(2,5-Dimethoxy-4-methylphenyl)-2-carbobenzoxamidobutane (7). A suspension of **6** (10.0 g, 0.0396 mol) in 10 ml of H_2O was stirred at −15 °C and enough acetone was added to give a complete solution (~30 ml). The solution was stirred at −14 °C under N_2 with 4.24 g (0.042 mol) of triethylamine. A solution of 4.80 g (0.44 mol) of ethyl chloroformate in 35 ml of acetone was added dropwise and the solution stirred a total of 35 min. Sodium azide (2.93 g, 0.045 mol) in 25 ml of H_2O was added slowly (25 min) and the reaction was stirred an additional 45 min. The mixture was poured into 300 ml of ice H_2O and extracted with Et_2O, and the extract was washed rapidly with one portion of cold H_2O and one portion of saturated brine. Drying (Na_2SO_4) and removal of the solvent at room temperature gave a white solid. After azeotroping twice with benzene the solid was dissolved in anhydrous toluene and heated on a steam bath for 20 min (evolution of N_2 ceased in the first 10 min). Benzyl alcohol (15 ml, 0.15 mol) was added and heating continued for 10 min. The flask was allowed to remain at ambient temperature 16 h. The solvent was removed at reduced pressure giving a highly crystalline solid which was washed with petroleum ether (bp 60–71 °C) and filtered to give 12.2 g (93%) of carbamate. The solid was recrystallized from boiling CH_3CN giving 10.0 g of **7**, mp 130.5–132.5 °C. Anal. ($C_{21}H_{27}NO_4$) C, H, N.

1-(2,5-Dimethoxy-4-methylphenyl)-2-butanone (8). A mixture of 150.5 g (0.6 mol) of **4**, 248 g (4.25 mol) of 100 mesh Fe powder, 5 g of $FeCl_3 \cdot 6H_2O$, and 1160 ml of H_2O was stirred and refluxed for 30 min. Concentrated HCl (98.7 ml, 1.19 mol) was then added dropwise with stirring over 30 min. When addition was complete the mixture was stirred and refluxed for 4 h.

The mixture was cooled somewhat and made basic with 96.5 ml (1.38 mol) of 40% (w/w) NaOH solution. The mixture was then steam distilled until the distillate, which was initially strongly basic with a pronounced ammoniacal odor, became neutral. The pot mixture was filtered hot (Dicalite) and washed thoroughly with Et_2O and then with H_2O. The layers of the filtrate were separated and the aqueous layer was extracted twice with Et_2O. The steam distillate was likewise extracted twice with Et_2O. All Et_2O extracts were combined, washed with H_2O and then with saturated brine, and dried (Na_2SO_4). The solvents were evaporated to yield an amber oil which crystallized upon standing.

This was distilled under reduced pressure to give 108 g (81%) of 8 as a light yellow oil, bp 126–127 °C (1 mm), which crystallized upon standing. Anal. ($C_{13}H_{18}O_3$) C, H.

2,5-Dimethoxy-4-methylphenethylamine Hydrochloride (2a).[23] To a stirred solution at room temperature of 5.0 g (26.3 mmol) of the nitrile **5b** in 100 ml of anhydrous THF was added, at a moderate rate, 158 ml (158 mmol as BH_3) of B_2H_6 in THF solution. The solution was stirred and refluxed for 16.5 h.

The reaction mixture (some solid had separated) was cooled (0 °C) and cautiously decomposed with 50 ml of 6 N HCl. The resulting mixture was poured onto cracked ice and an excess of dilute NaOH solution; the oily product was extracted out with Et_2O. The combined extracts were washed with H_2O and then with saturated brine and dried ($MgSO_4$).

The solvents were removed under reduced pressure and the salt of the product was formed with HCl(g) in EtOH. The solution was evaporated to dryness and the residue was recrystallized from *i*-PrOH. Colorless crystals of **2a** (3.80 g, 62%), mp 214–215.5 °C, were obtained (lit.[17,23] gives mp 212–213, 211–212 °C).

(±)-2-Amino-1-(2,5-dimethoxy-4-methylphenyl)butane Hydrochloride (2e). A. To a stirred, refluxing suspension of 12.5 g (329 mmol) of $LiAlH_4$ in 600 ml of anhydrous THF was added, dropwise, a solution of 15.0 g (59.8 mmol) of the nitrobutene 4 in 150 ml of anhydrous THF. Stirring and refluxing was continued for 15 h. The mixture was then cooled and decomposed by the sequential addition of 12.5 ml of H_2O, 12.5 ml of 15% NaOH solution, and finally 37.5 ml of H_2O. The mixture was stirred for 1 h and then filtered; the filter cake was washed well with THF and the filtrate was evaporated. The oil thus obtained was dissolved in Et_2O and the salt was formed with HCl(g). The crude salt (which separated slowly from Et_2O) was filtered and recrystallized from *i*-PrOH. There was obtained 11.43 g (74%) of **2e** as colorless crystals, mp 232.5–234.5 °C (darken). Anal. ($C_{13}H_{21}NO_2$·HCl) C, H, N, Cl.

B. A mixture of 2.3 g (0.0064 mol) of the carbamate **7**, 0.4 g 10% Pd/C, and 200 ml of absolute ethanol was hydrogenated under an initial H_2 pressure of 2.5 atm. After 1 h the catalyst was filtered. The solvent was evaporated; the oily base was dissolved in ether, and the solution saturated with HCl(g). The solid was filtered (1.6 g) and recrystallized from *i*-PrOH, yielding 1.33 g (83%) of **2e**, mp 228–229.5 °C.

Resolution of 2-Amino-1-(2,5-dimethoxy-4-methylphenyl)butane (2e Isomers). A. *S* Isomer. 2-Amino-1-(2,5-dimethoxy-4-methylphenyl)butane (**2e**) (17.9 g, 80.2 mmol) and 10.82 g (40.1 mmol) of (+)-2′-nitrotartranilic acid[25] were dissolved in 85 ml of hot 95% ethanol. The solution was cooled, seeded with salt previously obtained on a test tube scale, and allowed to stand undisturbed at room temperature until crystallization was complete (at least 18 h). The solid was filtered, sucked as free of mother liquor as possible, and washed with 10 ml of cold (−15 °C) 95% EtOH in two portions. The mother liquor and washing were reserved for recovery of the *R* isomer. The product was air-dried to give 12.32 g of fluffy yellowish crystals. Two recrystallizations in a like manner from 10 ml/g of 95% ethanol gave 8.64 g (44%) of the pure (+)-2′-nitrotartranilic acid salt (**10**) of **2e**, mp 155.5–157 °C. Anal. ($C_{23}H_{31}N_3O_9$) C, H, N.

This salt was dissolved in 100 ml of hot EtOH. The solution was cooled and poured into excess dilute K_2CO_3 solution. The mixture was extracted with two portions of Et_2O; the combined Et_2O extracts were washed with dilute K_2CO_3 solution, dilute $NaHCO_3$ solution, and three portions of H_2O. Drying and evaporation of the solvent gave 3.8 g of pure (*S*)-**2e** as a light yellow oil which crystallized upon standing: $[\alpha]^{26}_{365}$ +155.3° (*c* 1.3, 95% EtOH). The salt was formed with HCl(g) in anhydrous Et_2O. The solid was filtered, washed with Et_2O, and air-dried to give 4.34 g of slightly yellowish powder.

Recrystallization from 105 ml of *i*-PrOH provided 3.70 g of pure (*S*)-**2e** hydrochloride as colorless, fluffy needles: mp 245–246 °C; $[\alpha]^{23}_{365}$ +49.8° (*c* 1.0, 95% EtOH). The overall yield was 35% of available *S* isomer. Anal. ($C_{13}H_{21}NO_2$·HCl) C, H, N, Cl.

B. *R* Isomer. The mother liquor from isolation of the *S* isomer was evaporated and the residue was converted to the free base as previously described. The oil thus obtained and 9.37 g (36.1 mmol, 0.9 molar equiv) of (+)-2′-chlorotartranilic acid[25] were dissolved in 85 ml of hot 95% EtOH. The solution was cooled, seeded with salt previously obtained on a test tube scale, and allowed to stand undisturbed at room temperature until crystallization was complete (at least 18 h). The solid was filtered, washed with 10 ml of cold (−15 °C) 95% EtOH, and air-dried; 13.22 g of light yellowish fluffy crystals was obtained. Two recrystallizations in a like manner from 10 ml/g of 95% EtOH gave 7.99 g (46%) of pure colorless (+)-2′-chlorotartranilic acid salt (**11**) of (*R*)-**2e**, mp 182.5–184 °C. Anal. ($C_{23}H_{31}ClN_2O_7$) C, H, N, Cl.

This salt was converted to the free base as described for the *S* isomer. Pure (*R*)-**2e** (3.6 g) was recovered as an almost colorless oil which crystallized upon standing: $[\alpha]^{23.5}_{365}$ −156.3° (*c* 1.3, 95% EtOH). The salt was formed with HCl(g) in Et_2O and the colorless powder (4.18 g) thus obtained was recrystallized from 110 ml of *i*-PrOH to give 3.64 g of pure (*R*)-**2e** hydrochloride as colorless, fluffy needles: mp 245–246 °C; $[\alpha]^{24}_{365}$ −49.9° (*c* 1.0, 95% EtOH). The overall yield was 35% of available *R* isomer. Anal. ($C_{13}H_{21}NO_2$·HCl) C, H, N, Cl.

C. Determination of Optical Purities. The appropriate amine hydrochloride (25–40 mg) and a 25–50% molar excess of (−)-α-methoxy-α-trifluoromethylphenylacetyl chloride[27] were mixed in 5 ml of CH_2Cl_2 and 2 ml of pyridine. The solution was incubated at room temperature for 12–24 h. The reaction mixture was diluted with Et_2O and washed with two portions each of 5% HCl, 5% $NaHCO_3$ solution, and H_2O. The solvents were evaporated under reduced pressure and the crude residual oil was subjected directly to GLC analysis.

A 6 ft × 6 mm glass column was used, with 3% OV-17 as liquid phase and 100–120 mesh Gas Chrom Q (Applied Sciences) as support. Samples were injected (port temperature 288 °C, detector temperature 300 °C) as 20 mg/ml solutions in CH_2Cl_2 onto the column at 100 °C and programmed at 4 °C/min (He flow rate ca. 75 ml/min, rotameter reading 3.0). Under these conditions retention times of ca. 35–40 min were observed, with a 1–2 min separation between isomer peaks. As had been noted for the lower homologues,[26] the amide of the *R* isomer was eluted first.

Isomer purities of >98% (peak heights) were found by this technique.

Stereoselective Synthesis of (*R*)-2-Amino-1-(2,5-dimethoxy-4-methylphenyl)butane Hydrochloride [(*R*)-2e)]. A. (*R*,*R*)-1-(2,5-Dimethoxy-4-methylphenyl)-2-(α-methylbenzylamino)butane Hydrochloride [(*R*,*R*)-9]. The ketone **8** (98.9 g, 0.445 mol), 54.0 g (0.445 mol) of (+)-α-methylbenzylamine, and 15 drops of glacial HOAc were mixed together in 450 ml of benzene and the solution was refluxed under a Dean-Stark H_2O trap until separation of H_2O was complete (36–64 h).

The benzene was removed under reduced pressure and the oily residue was dissolved in 1300 ml of absolute EtOH and hydrogenated in the presence of 65 g of W-2 Raney nickel at an initial H_2 pressure of 3 atm until no further pressure drop occurred (64–96 h). The catalyst was filtered (caution!) and the solvent was evaporated to give an oil. The crude base was dissolved in 2000 ml of Et_2O and the solution was saturated with HCl(g). The dark mixture was chilled overnight at 0 °C.

The solid was filtered, washed with Et_2O, and dried to give 115.3 g of almost colorless powder. This was recrystallized from 1200 ml of *i*-PrOH to give 99.4 g (61% yield) of pure (*R*,*R*)-**9**: mp 248–249.5 °C dec; $[\alpha]^{24.5}_{365}$ +64.8° (*c* 1.0, 95% EtOH). Anal. ($C_{21}H_{29}NO_2$·HCl) C, H, N, Cl.

B. (*R*)-2-Amino-1-(2,5-dimethoxy-4-methylphenyl)butane Hydrochloride [(*R*)-2e)]. A mixture of 99.4 g (0.273 mol) of (*R*,*R*)-**9** and 30 g of 10% Pd-on-carbon catalyst in 800 ml of 95% EtOH was hydrogenated at an initial H_2 pressure of 3 atm until no further pressure drop occurred (ca. 48 h). The catalyst was filtered and the solvent was evaporated. The crystalline residue was recrystallized twice from ca. 25 ml/g of *i*-PrOH. The amine hydrochloride (*R*)-**2e** was obtained as 54.7 g (77% yield) of colorless, fluffy needles: mp 245–246.5 °C; $[\alpha]^{26}_{365}$ −50.7° (*c* 1, 95% EtOH).

Pharmacology. Smooth Muscle Spasmogenic Effect. The smooth muscle preparation was essentially that of Vane.[34] ED_{50}'s were calculated by regression analysis as described by Finney.[35]

Rabbit Hyperthermia. The method has been described.[6] A dose causing a 1 °C increase in rectal temperature over the predose level was determined graphically by plotting the peak responses occurring within 3 h following iv drug administration. A minimum

of three doses was used with four rabbits per dose.

Avoidance Response Acquisition. Old retired male breeder rats (Long-Evans, 600–800 g) were trained for avoidance response acquisition in the shuttle box (Lehigh Valley Electronics, LVE 28). Each trial (60-s duration) consisted of a 5-s avoidance period (light present in the opposite end of the box) during which the subject had to jump over the divider ("hurdle") to the other side of the box. A 5-s foot shock (0.6 mA) was delivered if no avoidance response was made and repeated until the animal escaped. A maximum of 50 avoidance trials at 60-s intervals was presented and the number of trials required to achieve eight avoidance responses in ten consecutive trials was obtained. The drugs were administered 30 min prior to the tests. Results were evaluated statistically using the Wilcoxon rank sum test.[36]

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Aryl-*s*-tetrazines with Antiinflammatory Activity

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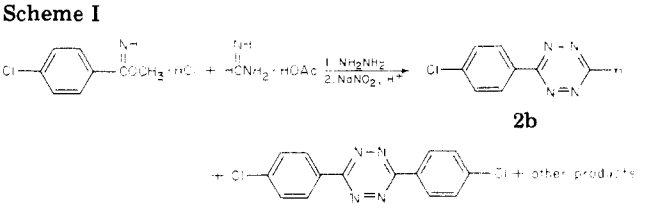
Various aryl-*s*-tetrazines and benzyl-*s*-tetrazines displayed aspirin-like activity when tested against carrageenan-induced edema in the rat, uv-induced erythema in guinea pigs, and adjuvant-induced arthritis in rats. These agents also displayed analgesic activity in the mouse writhing and paw pain tests but also lowered the red blood cell count in normal healthy rats.

From random screening 3-(*p*-chlorophenyl)-6-(1-methylhydrazino)-*s*-tetrazine (1) was found active in the carrageenan-induced edema assay in the rat. 3-(*p*-Chlorophenyl)-*s*-tetrazine (**2b**) was prepared as a potential precursor to 1 and this chemical was also active in the carrageenan test as well as the uv-induced erythema assay in the guinea pig and adjuvant-induced arthritis assay in the rat. This led to a chemical[1] and biological investigation of aryl-*s*-tetrazines as potential antiarthritic agents.

Chemistry. Aryl-*s*-tetrazines were prepared by the reaction of benzimidates and amidines with hydrazine hydrate[1-3] followed by oxidation (Scheme I). The reaction gave mixtures of the desired *s*-tetrazines, bis(aryl- and alkyl)-*s*-tetrazines, plus a number of hydrazine products.[1] The tetrazines were separated by chromatography on silica gel, eluting with methylene chloride.

Scheme I



2b

Benzimidate intermediates, which could not be easily prepared by Pinner conditions,[1,4] were prepared from amides or nitriles and methyl fluorosulfonate (Scheme II). The highly reactive intermediates were mixed first with amidines and then with hydrazine hydrate with extreme