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 behavioral 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 potency3 (1b); this effect was noted with a wide variety of ring substituents. An 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 DOB14 and 3,4-methylenedioxymethamphetamine.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 tests16 to be less active than 2b and substantially stimulant in nature. In human evaluation17 the decrease in potency is confirmed, but the pharmacological profile is largely one of sensory enhancement. We report herein the synthesis and some pharmacological comparisons of 2-amino-1-(2,5-dimeth-
vascular and gross behavioral effects of (S)-amphetamine, and the enantiomers of 2b (DOM) were compared with those of amphetamine confirmed the assignment.8-9

Table II. Hyperthermic Effect in the Rabbit

<table>
<thead>
<tr>
<th>No.</th>
<th>ED, mg/kg iv</th>
<th>Pot. rel to LSD</th>
<th>Pot. rel to (R)-DOM</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S)-2e</td>
<td>3.6</td>
<td>0.0004</td>
<td>0.01</td>
</tr>
<tr>
<td>(R)-2e (BL-3912A)</td>
<td>0.9</td>
<td>0.002</td>
<td>0.04</td>
</tr>
<tr>
<td>(S)-2b [(S)-DOM]</td>
<td>0.4</td>
<td>0.004</td>
<td>0.1</td>
</tr>
<tr>
<td>(R)-2b [(R)-DOM]</td>
<td>0.04</td>
<td>0.04</td>
<td>1.0</td>
</tr>
<tr>
<td>LSD</td>
<td>0.0015</td>
<td>1.0</td>
<td>27</td>
</tr>
</tbody>
</table>

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 publication25 from this laboratory contrasts the cardiovascular and gross behavioral effects of (S)-amphetamine, oxy-4-methylphenyl)butane16 (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 31 with nitropropane,20 followed by reduction of the nitro olefin 4 with LiAlH4 (Scheme I). Action of diborane upon the phenylacetonitrile 5b21922 gave pure R,R isomer, though both tests indicate low hallucinogenic potential for these phenethylamines 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 parallel25 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 (a-methyl to a-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).
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. TLC 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-methyl benzaldehyde (3). 19 A mixture of 800 ml (8.74 mol) of POCl3 and 800 ml (7.29 mol) of N-methylaniline 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 heated 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 H2O. Stirring was continued for 2 h. The reddish oil was filtered, washed well with cold H2O, and air-dried to give 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:H2O to give 277 g (77% yield) of 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 NH2OH·HCl, and 1100 ml of glacial H2OAc was refluxed for 5 h. The solution was cooled and poured into 9 l of ice H2O. The orange solid which separated was filtered, washed thoroughly with H2O, 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. (C21H21N04) C, H, N.

2,5-Dimethoxy-4-methyl benzyl Chloride (5a). 21 Sodium borohydride (42 g, 1.1 mol) was added to a suspension of 5 (180 g, 1 mol) in i-PrOH (21 l). The resulting mixture was refluxed for 2.5 h. The solvent was removed in vacuo and the residue partitioned between H2O and Et2O. The etheral solution was washed (H2O, saturated brine) and chilled (ice H2O), 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 Et2O. The combined etheral solutions were washed (H2O, saturated brine), dried (Na2SO4), and concentrated to give 189 g of beige crystals. Recrystallization from petroleum ether (bp 100–115 °C) gave 5a (138 g, 68%), 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). 22 To a suspension of 0.7 g (14 mmol) of NaCN in 6 ml of anhydrous Me2SO was added, dropwise, with stirring solutions of 2.2 g (10 mmol) of 5a in 6 ml of anhydrous Me2SO. A slight exothermic effect was noted.

The mixture was stirred for 2.5 h at ambient temperature and then poured into H2O. The product was extracted out with Et2O; the combined extracts were washed with H2O and with saturated brine and dried (Na2SO4).

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 disopropylamine (9.2 ml, 0.066 mol) in 90 ml of THF, under N2, 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 g, 0.08 mol) was then added, again keeping the temperature below 0 °C. Hexamethyphosphoramide (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 H2O) and 100 ml of 10% HCl added. After removal of the mixture was extracted with Et2O. The combined Et2O extracts were washed twice with 5% HCl and once with H2O and then extracted with 15 N NaOH. The ammonical solution was washed with Et2O, acidified with 12 N HCl, and then extracted with Et2O. Washing (H2O, saturated brine), drying (Na2SO4), and concentrating the ethereal extract gave crude acid (6.0 g). This was crystallized from petroleum ether (bp 60–75 °C) to give the acid (5b, 79%, mp 92–94 °C. An analytical pure material, mp 92–94 °C. Anal. (C21H21N04) C, H, N.

1-(2,5-Dimethoxy-4-methylphenyl)-2-carboxybenzoximidobutane (7). A suspension of 6 (10.0 g, 0.0396 mol) in 10 ml of H2O was stirred at −13 °C and enough acetone was added to give a complete solution (~30 ml). The solution was stirred at −14 °C under N2 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 H2O was added slowly (25 min) and the reaction was stirred an additional 45 min. The mixture was poured into 300 ml of ice H2O and extracted with Et2O, and the extract was washed rapidly with one portion of cold H2O and one portion of saturated brine. Drying (Na2SO4) and removal of the solvent gave a white solid. After recrystallizing twice with benzene the solid was dissolved in anhydrous toluene and heated on a steam bath for 20 min (evolution of N2 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 (85%) of carbanate. The solid was recrystallized from boiling CH2CN giving 10.0 g of 7, mp 130.5–132.5 °C. Anal. (C21H21N04) C, H, N.

1-(2,5-Dimethoxy-4-methylbenzyl)-2-butane (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 FeCl3·6H2O, and 1160 ml of H2O was stirred and refluxed for 30 min. Concentrated HCl (98.7 ml, 1.19 mol) was added, 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 effervescing with a pronounced ammoniacal odor, became neutral. The pot mixture was filtered hot (Dicalite) and washed thoroughly with H2O and then with dry H2O. The layers of the filtrate were separated and the aqueous layer was extracted twice with Et2O. The steam distillate was likewise extracted twice with Et2O. All Et2O extracts were combined, washed with H2O and then with saturated brine, and dried (Na2SO4). The solvents were evaporated to yield an amber oil which crystallized upon standing.
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This was distilled under reduced pressure to give 105.8 g (81%) of 8 as a light yellow oil, bp 126–127 °C (1 mm), which crystallized upon standing. Anal. (C13H20N2O) C, H.

2,5-Dimethoxy-4-methylphenylamine Hydrochloride (2a).23 To a stirred solution at room temperature of 5.0 g (26.5 mmol) of the nitrite 5b in 100 ml of anhydrous THF was added, at a moderate rate, 158 ml (158 mmol as BH3) of B2H6 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 was added to the oily mixture with Et2O. The combined extracts were washed with H2O and then with saturated brine and dried (MgSO4).

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 (5.80, 62%), mp 214–215.5 °C, were obtained (lit.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 LiAlH₄ 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 H₂O, 12.5 ml of NaOH solution, and, finally, 15 ml of ¹-PrOH. The crude base 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 EtO and the salt was formed with HCl(g). The crude salt (which separated slowly from Et₂O) 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. (C₂₁H₂₉NO₂.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 37.5 ml of CH₂Cl₂ and 5.0 ml of HzO, was hydrogenated at an initial H₂ pressure of ca. 200 atm until the level was determined graphically by plotting the peak responses of the carbamate and the amine for the lower homologues,26 the amide of the (-)-α-methoxy-α-trifluoromethylphenylacetyl chloride27 were mixed in 5 ml of CH₂Cl₂ and 2 ml of pyridine. The solution was incubated at room temperature for 12–24 h. The reaction mixture was diluted with Et₂O and washed with two portions of each 5% HCl, 5% NaHCO₃ solution, and H₂O. The solvents were evaporated under reduced pressure and the crude residual oil was subjected directly to GLC analysis. The amine was eluted, 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 CH₂Cl₂ onto the column at 100 °C and programmed at 24 °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 an 1–2 min separation between isomer peaks. As had been noted for the lower homologues,26 the enantiomer R isomer was eluted first.

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

Steroselective 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) and 15 drops of glacial HOAc were mixed together in 450 ml of benzene and the solution was refluxed under reduced pressure and the crude residual oil was distilled (36–84 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 H₂ pressure of 3 atm for further periods of (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 an oil. 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; 12.22 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. (C₂₃H₂₁N₂O₂.Cl) 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: [(α)₂�⁰⁺₅₅₀ = −156.5° (c 1.3, 95% EtOH). The salt was formed with HCl(g) in Et₂O and colorless fluffy needles: mp 245–246 °C; [α]₂⁰⁺₅₅₀ = 49.9° (c 1.0, 95% EtOH). The overall yield was 35% of available R isomer. Anal. (C₁₃H₁₄N₂O₂.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-o-trifluoromethylphenylacetyl chloride27 were mixed in 5 ml of CH₂Cl₂ and 2 ml of pyridine. The solution was incubated at room temperature for 12–24 h. The reaction mixture was diluted with Et₂O and washed with two portions each of 5% HCl, 5% NaHCO₃ solution, and H₂O. The solvents were evaporated under reduced pressure and the crude residual oil was subjected directly to GLC analysis.

The amine was eluted, 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 CH₂Cl₂ 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 enantiomer R isomer was eluted first.

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


Pharmacology. Smooth Muscle Spasmogogenic Effect. The smooth muscle preparation was essentially that of Vane.24 ED₅₀'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 predrug 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

References and Notes

(1) A. T. Shulgin, Lloyd's, 36, 46 (1973).
(10) Reference 9, pp 39-51.

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 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 hydrate1-3 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.4 The tetrazines were separated by chromatography on silica gel, eluting with methylene chloride.

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