inhibition of *Micrococcus* at the highest concn tested, 100 μg/ml.

Experimental Section

All melting points were observed on a Thomas-Hoover Uni-Melt and are uncorrected. Satisfactory ir spectra were recorded for all compds using a Perkin-Elmer Model 337 spectrophotometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

5*H*-Nitroso-10,11-dihydrodibenz[*b*,*f*]azepine.[5]—To a stirred solution of 5 g of 10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine[6] in 50 ml of DMF was added 2 g of $NaNO_2$. The stirred mixt was maintained at 2–8° and 25 ml of 2 *N* HCl was added dropwise at such a rate that the temp did not rise above 8°. After addn was complete, the cooling bath was removed, and the mixt was stirred for 1 hr allowing it to come to room temp. The reaction mixt was poured into H_2O, allowed to stand until coagulation occurred, filtered, washed with H_2O, and dried; crude yield 5.4 g (94%), mp 109–111°. Recrystn from cyclohexane raised the mp to 113–115°. *Anal.* ($C_{14}H_{12}N_2O$) C, H, N.

5*H*-Amino-10,11-dihydrodibenz[*b*,*f*]azepine (1).[5]—To a stirred slurry of 0.44 g of LAH in 20 ml of Et_2O, cooled to 0° under N_2, a soln of 2.0 g of the nitroso compd in 15 ml of THF was added dropwise. After addn was complete, the mixt was allowed to warm to room temp then cautiously warmed to 30° (occasionally on warming, the reaction became quite exothermic and required further cooling), and maintained at that temp for 30 min. The reaction mixt was hydrolyzed and ext with Et_2O, and the Et_2O soln was dried ($CaSO_4$) and evapd, yielding 1.7 g (91%) of an oil. The oil was crystd from low-boiling petr ether, 1.4 g (82%); after repeated recrystn mp 52–53°.

Hydrazides.—In a typical procedure 1.0 g of **1**, 1.0 g of 3,4-dichlorobenzoyl chloride, and 50 ml of dry C_6H_6 were alternately warmed and agitated for 30–45 min. The reaction mixt was cooled, filtered, and washed with C_6H_6. The solid material was treated with charcoal in boiling MeCOEt. The mixt was filtered and evapd, and the residue was recrystd from Me_2CO; yield 1.6 g (87%), mp 271–272°.

Hydrazones.—In a typical procedure, 150 ml of dry PhMe, 1.33 g of **1**, and 1.20 g of 2,4-dichlorobenzaldehyde were refluxed in a flask fitted with a Dean–Stark apparatus for 2 hr. The reaction mixt was concd under reduced pressure, and the resulting oil was crystd from EtOH–Et_2O. Repeated recrystn from EtOH gave pure **10**; yield 1.75 g (81%), mp 107–109°.

Fluorosulfonylurea Derivative (5).—A mixt of **1** (1.0 g), *m*-fluorosulfonylphenyl isocyanate (0.95 g), and 75 ml of $CHCl_3$ was alternately warmed and agitated for 30–45 min. The reaction mixt was cooled, filtered, and washed with $CHCl_3$. Recrystn from EtOH produced pure **5**; yield 1.9 g, mp 213–215° dec.

(5) (a) C. Hanna and F. W. Schueler, *J. Amer. Chem. Soc.*, **74**, 3693 (1952); (b) F. W. Schueler and C. Hanna, *ibid.*, **73**, 4996 (1951); (c) *Cf.* footnote *b*, Table I.

(6) B. P. Das, R. W. Woodard, L. K. Whisenant, W. F. Winecoff, III, and D. W. Boykin, Jr., *J. Med. Chem.*, **13**, 979 (1970).

Analogs of Amphetamine. 6. 2,5-Dimethoxy-4-methyl- and 2,5-Dimethoxy-α,4-dimethylphenylalanines[1a]

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As a continuation of studying the effects of substitution on biological activities of amphetamine and 2,5-dimethoxy-4-methylamphetamine (DOM, STP), two amino acids, 2,5-dimethoxy-4-methylphenylalanine (**1**)[1b] and 2,5-dimethoxy-4,α-dimethylphenylalanine (**2**) were synthesized.

Heating a mixture of 2,5-dimethoxytolualdehyde, hippuric acid, and NaOAc afforded the oxazolone **3**, which was converted to the phenylpyruvic acid **4**. Compd **1** was obtained from **4** by the formation of the α-oxime **5** followed by catalytic reduction to generate the α-amino group. The phenylpyruvic acid **4** can be prepared from the 2-methyloxazolone **6**. Decomposition of **6** gave AcOH which can be easily removed from **4**. The disadvantage of this route was the low yield from the condensation of 2,5-dimethoxytolualdehyde with *N*-acetylglycine; in addition, **6** did not crystallize from solution and an extraction was, therefore, necessary. An attempt was made to prepare **1** from **3** *via* the α-benzamidophenylacrylic acid **7**. The benzoyl group of **8** was found to resist hydrolysis in either refluxing NaOH or H_2SO_4. Hydrolysis under pressure was not tried because of the awareness of a possible cleavage of the MeO group on the molecule.

For the synthesis of **2**, the substituted phenylacetone **5**[2] was converted to the hydantoin **8** by heating with $(NH_4)_2CO_3$ and KCN. Refluxing of **8** with aq Ba $(OH)_2$ then gave the α-methylphenylalanine **2**. Both **1** and **2** were further characterized by the *N*-benzoyl derivatives (**9** and **10**) and by the Me esters (**11** and **12**).

At a concn as high as 1×10^{-2} *M* neither **1** nor **2** inhibited DOPA decarboxylase in mouse brains, while α-methyldopa, a known inhibitor of the enzyme, had an I_{50} value of 3.3×10.4 *M*. Decarboxylation of **2** to DOM (STP) did not occur in brain, as demonstrated by the failure to detect DOM in either *in vitro* or *in vivo* studies.

Experimental Section[3]

4-(2,5-Dimethoxy-4-methylbenzylidene)-2-phenyl-5-oxazolone (3).—A mixt of 25 g (0.14 mole) of 2,5-dimethoxytolualdehyde, 37.4 g (0.21 mole) of hippuric acid, 34.4 g (0.42 mole) of NaOAc (anhyd), 100 ml of Ac_2O, and 80 ml of AcOH was heated on the steam bath for 45 min, during which period the mixt gradually turned orange. The resulting mixt was poured onto 1500 g of crushed ice, and the solid, upon standing overnight, was filtered: yield, 45.4 g; mp 204–205°. For purification, the product was recrystd from DMF at 100° to yield 25 g (55%) of bright orange solid, mp 210–211°. *Anal.* ($C_{19}H_{17}NO_4$) C, H, N.

4-(2,5-Dimethoxy-4-methylbenzylidene)-2-methyl-5-oxazolone (6).—A mixt of 9.0 g (50 mmoles) of 2,5-dimethoxytolualdehyde, 5.8 g (50 mmoles) of *N*-acetylglycine, 4.1 g (50 mmoles) of NaOAc, and 12.8 g (125 mmoles) of Ac_2O was warmed on the steam bath until a soln resulted. The soln was refluxed for 1 hr. After cooling 50 ml of H_2O was added, and the mixt was extd with 50 ml of $CHCl_3$. The ext was washed with H_2O (four 100-ml portions), dried (Na_2SO_4), and evapd to yield 14.0 g of gummy solid. Recrystn from EtOH gave 4.2 g (32%) of golden shining solid, mp 121–122°. *Anal.* ($C_{14}H_{15}NO_4$) C, H, N.

2,5-Dimethoxy-4-methylphenylpyruvic Acid (4). Method A. From 3.—A mixt of 18.3 g (0.57 mole) of **3** and 100 ml of 10% NaOH was refluxed for 10 hr, during that period the compd slowly dissolved and the orange color faded to yellow. A Na salt, which pptd upon cooling, was redissolved by the addn of 500 ml of H_2O. The soln was satd with SO_2 to yield 4.3 g of BzOH, mp 105–110°. After filtration, the soln was heated to boiling and 50 ml of concd HCl was added. On cooling, 9.8 g (72.5%) of yellow product pptd, mp 148–151°. Recrystn from 250 ml of $PhCH_3$

(1) (a) Previous paper of the series: B. T. Ho, V. Estevez, L. W. Tansey, L. F. Englert, P. J. Creaven, and W. M. McIsaac, *J. Med. Chem.*, **14**, 158 (1971); (b) after our paper was accepted, the synthesis of **1** was reported by K. Brewster and R. M. Pinder, *J. Med. Chem.*, **14**, 650 (1971).

(2) B. T. Ho and L. W. Tansey, *ibid.*, **14**, 156 (1971).

(3) Melting points were taken on a Mel-Temp apparatus and are corrected. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values. Ir spectra of all the compds were compatible with the assigned structures.

gave 7.0 g (52%) of bright yellow, cotton-like **4**, mp 162–164°. *Anal.* ($C_{12}H_{14}O_5$) C, H.

Method B. From 6.—A mixt of 4.0 g (15 mmoles) of **6** and 100 ml of 10% NaOH was refluxed for 6 hr, during that period evoln of NH_3 was noted. Upon acidification of the resulting soln, 1.5 g (42%) of **4** was collected, mp 149–151°. This crude product was identified by its ir spectrum but was not purified further.

2,5-Dimethoxy-4-methylphenylpyruvic Acid Oxime (5).—A mixt of 6.0 g (25 mmoles) of **4**, 3.0 g (75 mmoles) of NaOH, 2.6 g (37 mmoles) of $HONH_2 \cdot HCl$, and 100 ml of H_2O was stirred overnight then poured onto 100 g of ice and 5 ml of concd HCl. The white ppt was filtered and dried: yield, 6.1 g (95%); mp 158° dec. Recrystn from 40 ml of EtOH gave 4.0 g (62%), mp 161° dec.

2,5-Dimethoxy-4-methylphenylalanine (1).—A mixt of 3.5 g (14 mmoles) of **5**, 0.5 g of 10% Pd/C, 50 ml of AcOH, and 50 ml of H_2O was shaken on a Parr hydrogenator for 30 hr. After filtration the soln was evapd under reduced pressure to dryness leaving 3.5 g of product, mp 228° dec. Recrystn from 125 ml of hot H_2O gave 3.2 g (97%), mp 235° dec. For anal., the sample was dried *in vacuo* at 100° for 6 hr; the mp became 230° (dec) after drying. *Anal.* ($C_{12}H_{17}NO_4$) C, H, N.

2-Benzamido-3-(2,5-dimethoxy-4-methylphenyl)acrylic Acid (7).—A mixt of 24 g (74 mmoles) of **3**, 200 ml of 0.5 *N* NaOH, and 500 ml of EtOH, was heated with stirring on the steam bath for 0.5 hr, during that period the solid slowly dissolved and the red color faded to yellow. After cooling, EtOH was evapd under reduced pressure, and the residue was dissolved in 500 ml of H_2O. The soln, while hot, was treated with 20 ml of concd HCl. The yellow product which pptd upon cooling was filtered: yield, 23.4 g (92%); mp 211–212°. Recrystn from 300 ml of EtOH gave 19.8 g (78%), mp 222–223°. *Anal.* ($C_{19}H_{19}NO_5$) C, H, N.

***N*-Benzoyl 2,5-Dimethoxy-4-methylphenylalanine (9). Method A. From 1.**—BzCl (412 mg, 3 mmoles) was added to a soln of 350 mg (1.5 mmoles) of **1** in 15 ml of H_2O containing 236 mg (6 mmoles) of NaOH; pptn occurred. After stirring overnight the mixt was poured onto 20 g of ice and 10 ml of concd HCl. The white ppt was filtered, and washed first with H_2O, then, after drying, with 400 ml of petr ether: yield, 400 mg (78%); mp 185–186°. Recrystn from 7 ml of EtOH gave 300 mg (58%), mp 184–185°. *Anal.* ($C_{19}N_{21}NO_5$) C, H, N.

Method B. From 7.—A suspension of 10 g (29 mmoles) of **7** and 0.5 g of 10% Pd/C in 200 ml of EtOH was shaken on a Parr hydrogenator for 26 hr. The flask was disassembled and an addnl 0.1 g of the catalyst was added. The reduction was contd for 24 hr. After warming on a steam bath, the mixt was filtered hot, and the filtrate was evapd under reduced pressure to give 9.2 g (92%) of white solid, mp 183–185. Recrystn from 100 ml of EtOH gave 7.8 g (78%), mp 187–188; its ir spectrum was identical with that of the product prepd by method A.

2,5-Dimethoxy-4-methylphenylalanine Methyl Ester·HCl (11).—A sample of 400 mg (1.7 mmoles) of **1** was dissolved in 25 ml of MeOH satd with HCl gas. The soln was refluxed for 8 hr, and then stirred overnight at ambient temp with an addnl 15 ml of MeOH–HCl. Evapn of MeOH gave a white solid, mp 190–191°. Recrystn from MeOH–Et_2O (1:3) gave 375 mg (76%), mp 191–192°. *Anal.* ($C_{13}H_{20}ClNO_4$) C, H, N.

4-(2,5-Dimethoxy-4-methylbenzyl)-4-methylhydantoin (8).—A mixt of 5.6 g (27 mmoles) of 1-(2,5-dimethoxy-4-methylphenyl)-2-propanone,[2] 23 g (240 mmoles) of $(NH_4)_2CO_3$, 2.3 g (35 mmoles) of KCN, 50 ml of EtOH, and 50 ml of H_2O was heated with stirring at 55–60° for 45 min. A soln was attained in a short period of time, and then within 15 min a very flocculent ppt formed. After stirring overnight at ambient temp, the white solid was collected on a filter, washed with H_2O, and dried: yield, 6.8 g (91%); mp 230–231°. Recrystn from 200 ml of EtOH gave 6.6 g (88%), mp 232–233°. *Anal.* ($C_{14}H_{18}N_2O_4$) C, H, N.

2,5-Dimethoxy-4,α-dimethylphenylalanine (2).—A mixt of 6.0 g (22 mmoles) of **8**, 16.0 g (50 mmoles) of $Ba(OH)_2$, and 150 ml of H_2O was refluxed for 48 hr; during that period the hydantoin dissolved, and slowly a ppt of $BaCO_3$ formed. After removal of the solid by filtration, the soln was dild with 600 ml of H_2O, and then acidified to pH 5 with 2 *N* H_2SO_4 (approx 75 ml). The mixt was heated to boiling and filtered hot. The filtrate was concd to 200 ml, and upon cooling 5.8 g of solid, mp 231° dec, was obtained. Recrystn of the crude product from 300 ml of H_2O gave 3.9 g of rod-shaped crystals, mp 234° dec. When the mother liquor was concd to 75 ml, an addnl 1.3 g, mp 233° dec, was collected; total yield was 5.2 g (94.5%). *Anal.* ($C_{13}H_{19}NO_4 \cdot H_2O$) C, H, N.

***N*-Benzoyl 2,5-Dimethoxy-4,α-dimethylphenylalanine (10).**—BzCl (412 g, 3 mmoles) was mixed with a soln of 379 mg (1.5 moles) of **2** and 236 mg (6 mmoles) of NaOH in 15 ml of H_2O, and the resulting soln was stirred at ambient temp for 2 hr. An addnl 412 mg of BzCl and 236 mg of NaOH was added, and the stirring was contd for 2 hr. The reaction mixt was poured onto 25 g of ice and 10 ml of concd HCl. The ppt was collected on a filter, and, after drying, was washed with 200 ml of petr ether to remove traces of BzOH: yield, 200 mg (37%); mp 161–164°. Recrystn from EtOH gave 140 mg (20%), mp 175–176°. *Anal.* ($C_{20}N_{23}NO_5$) C, H, N.

2,5-Dimethoxy-4,α-dimethylphenylalanine Methyl Ester·HCl (12).—Esterification of **2** by the procedure described in the prepn of **9** afforded a quant yield of **12**, mp 181–183°. Recrystn from MeOH–Et_2O (1:4) gave 76% of pure product, mp 183–184°. *Anal.* ($C_{14}H_{22}ClNO_4$) C, H, N.

Dopa Decarboxylase Inhibition Assay.—Mouse brains were homogenized in 10 parts of 0.25 *M* sucrose. The homogenate was centrifuged at 7000*g* for 10 min and the supernatant was used for the assay. Incubation was carried out initially at 37° for 30 min in a soln contg 0.4 ml of the enzyme, 0.1 ml (20 μg) of pyridoxal phosphate in 0.5 *M* phosphate buffer, pH 6.9, 0.1 ml (0.1 mg) of tranylcypromine sulfate soln, and the buffer to make a final vol of 1.5 ml. A mixt of 0.1 ml (0.2 mg, 10 μmoles) of *l*-dopa and 0.1 ml of *l*-dopa-^{14}C (0.5 μCi, 3.18 mCi/mmole) in a buffer was then added with varying amt of the inhibitor, and the incubation was contd for 30 min. To the resulting soln, chilled in ice, were added 1.5 g of NaCl and 10 ml of *n*-BuOH. After shaking for 15 min, the mixt was centrifuged at 600*g* for 8 min. The BuOH layer was washed with the buffer to remove unconverted dopa and then assayed for ^{14}C in a liquid scintillation spectrometer. The concn of the inhibitor at which enzyme activity was 50% inhibited (I_{50}) was detd.

Investigation on the Conversion of 2 to DOM (STP) in Mouse Brain. *In Vitro.*—^3H-labeled **2** (1 mg, 5 μmoles, 30 μCi) was incubated at 37° for 2 hr with the decarboxylase enzyme, 20 μg of pyridoxal phosphate, and the phosphate buffer. MeOH was added to the mixt, and after centrifugation the supernatant was spotted on silica gel tlc plate for the sepn of **2** and DOM [solvent, *i*-PrOH–*n*-BuOH–AcOH–H_2O (10:1:1:1); R_f values, compd **2**, 0.46; DOM, 0.86].

In Vivo.—Yale Swiss mice, 20–30 g, were administered tritiated **2** (50 mg/kg 400 μCi/kg) in saline ip. The animals were sacrificed at 30-min and 2-hr intervals following injection. The brains were homogenized in H_2O, and then exted with MeOH. Sepn and identification of **2** and DOM were performed by tlc as described in the *in vitro* studies.

Synthesis of Derivatives of *N,N*-Dimethylhydrazine and Their Physiological Activities

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Many organic compds contg the dialkylamino group exhibit some form of physiological activity. It would be interesting to determine to what degree the dialkylhydrazino group would contribute physiological effects to organic compds. The purpose of the work described in this note was to prepare derivatives of *N,N*-dimethylhydrazine and to evaluate them for their biological activity.

Biological Tests.—A general pharmacol screen of these compds did not show any significant activity.[1]

(1) This screen included CNS, cardiovascular, analgetic, hypoglycemic, antiinflammatory, antifertility, diuretic, autonomic, antiallergic, reticuloendothelial, local anesthetic, antispasmodic, and antiprotozoan properties and was carried out by Bristol Laboratories, Division of Bristol-Myers Company.