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

W. PHILIP BRIAN

Organic Chemicals Division, Research and Development Department, FMC Corporation, Baltimore, Maryland 21226

Received March 16, 1971

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.

TABLE I

EFFECTIVENESS OF DERIVATIVES OF *N,N*-DIMETHYLHYDRAZINE AGAINST L1210 LEUKEMIA IN BDF_1 MICE

Compd	Dose,[a] mg/kg	Number of doses	Survivors	*T/C*, %[b]
1	400	1	6/6	100
2	400	9	6/6	110
3	400	1	0/6	
3	75	9	6/6	101

[a] Route of administration ip. [b] *T/C* is ratio of survival time of test animals to survival time of control animals.

TABLE II

DERIVATIVES OF *N,N*-DIMETHYLHYDRAZINE

No.	Compd	Mp or bp (mm), °C	% yield	$n^{25}D$	d_{25}	Analyses
1	$CH_3CCH_2COOC_2H_5$ ‖ $NN(CH_3)_2$	85 (8.1)	76	1.4750	0.9655	MR 50.1[a]
2	$CH_3CCH_2COOC(CH_3)_3$ ‖ $NN(CH_3)_2$	90 (7.5)	65	1.4640	0.9352	MR 59.0[b]
3		136–137	58			C,[c] H, N
4		139.5–140.5	24			C, H, N

[a] Calcd 48.7. [b] Calcd 57.7. [c] C: calcd, 67.81; found, 68.51.

Compds **1**, **2**, and **3** in Table II were evaluated against L1210 leukemia in BDF_1 mice.[2] Results are given in Table I.

Ethyl acetoacetate *N,N*-dimethylhydrazone (**1**) was tested against *Plasmodium berghei* in ICR/HA Swiss mice.[3] At 640 mg/kg the survival time of the mice was increased 1.8 days (mean survival time of controls was 6.2 days; mean survival time of treated animals was 8.0 days). Compd **1** showed some toxicity in this test which did not appear when it was tested against L1210 leukemia at a much higher total dosage.

Experimental Section

Ethyl Acetoacetate *N,N*-Dimethylhydrazone (1).—A mixt of 100.0 g (0.77 mole) of ethyl acetoacetate and 48.6 g (0.81 mole) of Me_2NNH_2 in 150 ml of EtOH was allowed to stand at room temp for 18 hr. At the end of this period the mixt was concd under vacuum and distd through a 30-cm vacuum-jacketed Vigreux column to give 100.3 g (75% yield) of **1**, bp 85° (8.1 mm). This material was collected in 5 fractions, $n^{25}D$ 1.4747–1.4751.

***tert*-Butyl Acetoacetate *N,N*-Dimethylhydrazone (2).**—*tert*-Butyl acetoacetate (97.1 g, 0.61 mole) and Me_2NNH_2 (38.4 g, 0.64 mole) were dissolved in 150 ml of *tert*-BuOH and the mixt was allowed to stand at room temp for 18 hr. It was concd under vacuum and the residue was distd as above. The product (**2**) (79.2 g, 65%) was collected in 4 fractions, $n^{25}D$ 1.4639–1.4641.

α-Naphthyl *N,N*-Dimethylcarbazate (3).—A mixt of α-naphthol and $C_6H_5NMe_2$ was treated with $COCl_2$ to give α-naphthyl chloroformate in 79% yield as a nearly colorless liquid, bp 101.5–104.5° (0.5 mm), $n^{25}D$ 1.5959 [lit.[4] bp 117° (1 mm)]. This was treated with Me_2NNH_2 in Et_2O and the resultant solid on extn with EtOAc and recrystn from EtOH yielded **3** (58%), mp 136–137°.

α-Naphthylacetyl *N,N*-Dimethylhydrazide (4).—α-Naphthylacetyl chloride, bp 136° (1.5 mm), $n^{25}D$ 1.6209 [lit.[5] bp 175–76° (1.5 mm)] was prepd from α-naphthylacetic acid and $SOCl_2$. It was treated with Me_2NNH_2 in a mixt of Et_2O and Et_3N and after extn with C_6H_6 and concn, the recovered solid was recrystd from EtOH to give **4** as a white solid, mp 139.5–140.5°.

Acknowledgments.—The author wishes to thank Dr. Harry B. Wood, Jr., of the Cancer Chemotherapy National Service Center for making the L1210 leukemia screening data available. He also wishes to thank Dr. B. T. Poon of the Walter Reed Army Institute of Research, Walter Reed Army Medical Center, for the data for the antimalarial test.

(2) Cancer Chemotherapy National Service Center 9062 Protocols for screening chemical agents and natural products against animal tumors and other biological systems are described in *Cancer Chemother. Rep.*, **25**, 1 (1962).

(3) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

(4) Kwan-Chung Tsou, *J. Amer. Chem. Soc.*, **76**, 6109 (1954).

(5) Instituto De Angeli Societa per Aziom (by Gianfranco Pala), British Patent 1,016,968 (1966).

Comparisons of Butyrylcholinesterase Inhibitory Potencies of Selected 3-Substituted-1-decylpiperidines with Their Electron Charge Densities†

O. ELMO MILLNER, JR.,‡ AND WILLIAM P. PURCELL*

Department of Molecular and Quantum Biology, College of Pharmacy, University of Tennessee Medical Units, Memphis, Tennessee 38103

Received January 7, 1971

Beasley, *et al.*,[1] and Purcell, *et al.*,[2] have investigated the inhibitory potencies against butyrylcholinesterase

† This research is being supported by the U. S. Army Medical Research and Development Command (DA-49-193-MD-2779), the Cotton Producers Institute (through the National Cotton Council of America), the National Science Foundation (GB-7383), and a grant from Eli Lilly and Company. Computer facilities were provided through Grant HE-09495 from the National Institutes of Health.

‡ The work reported in this paper constitutes a segment of the thesis to be submitted by O. Elmo Millner, Jr., to the Graduate School–Medical Sciences of the University of Tennessee in partial fulfillment for the degree of Doctor of Philosophy. NIH Trainee, U. S. Public Health Service Grant TO1 GM-02052 from the National Institute of General Medical Sciences, Bethesda, Md.

(1) (a) J. G. Beasley, R. P. Quintana, and G. G. Nelms, *J. Med. Chem.*, **7**, 698 (1964); (b) J. G. Beasley and W. P. Purcell, *Biochim. Biophys. Acta*, **178**, 175 (1969).

(2) (a) W. P. Purcell, J. G. Beasley, and R. P. Quintana, *ibid.*, **88**, 233 (1964); (b) W. P. Purcell, J. G. Beasley, R. P. Quintana, and J. A. Singer, *J. Med. Chem.*, **9**, 297 (1966); (c) W. P. Purcell and J. G. Beasley, *Mol. Pharmacol.*, **4**, 404 (1968).