1,2,3,4-Tetrahydro-6-methoxy-1-oxo-2-naphthalenepropionic Acid (6). Compd **5** (7 g) was added to AcOH (16.7 ml), HCl (33.4 ml), and H_2O (2.2 ml); the mixt was heated at 100° for 4 hr, then cooled, and poured into crushed ice-H_2O. The solid (5.8 g, 97%) was filtered and recrysted from Me_2CO-petr ether: mp 133–135°; λ_{max}^{MeOH} 224 (ϵ 4620) and 272 mμ (14,200). *Anal.* ($C_{14}H_{16}O_4$) C, H.

1,2,3,4-Tetrahydro-6-methoxy-1-naphthalenepropionic Acid (7). Hydrazine hydrate (2.5 ml, 80% soln) was added to a soln of **6** (3 g) and KOH (2.7 g) in 1,2-propanediol (15 ml), the mixt was heated to 120°, and H_2O was distd off. After this distillation ceased, the temperature was gradually raised to 180–190° and was maintained there under reflux for 4 hr. The reaction product was then poured into ice-H_2O, and acidified with HCl. The precipitated acid **7** (1.67 g, 59%) was filtered and recrystd from Me_2CO: mp 122–123°; λ_{max}^{MeOH} 279 (ϵ 2150) and 288 mμ (1970). *Anal.* ($C_{14}H_{18}O_3$) C, H.

4-(1,2,3,4-Tetrahydro-6-methoxy-2-naphthyl)butan-2-one (8). To a stirred soln of **7** (5 g) in anhydrous THF (70 ml) maintained at 10° under N_2 was added a soln of MeLi (50 ml, 1.6 M soln in Et_2O), dropwise over a period of 30 min. Stirring was continued for another 1.5 hr, then excess reagent was decompd with ice H_2O and the product isolated with Et_2O.** From the crude reaction product the ketone **8** was purified through a bisulfite addition product and was obtained as an oil (1.75 g, 35%). A 2,4-DNP deriv of **8** was prepd and recrystd from EtOH: mp 106–108°. *Anal.* ($C_{21}H_{24}N_4O_5$) C, H, N.

4-(1,2,3,4-Tetrahydro-6-hydroxy-2-naphthyl)butan-2-one (9). A mixt of **8** (1.18 g) and pyridine hydrochloride (1.5 g) was heated at 205° for 1 hr under N_2, then cooled, and diluted with H_2O. The pptd material was filtered and purified by column chromatography (alumina). The fractions eluted with PhH and PhH-Et_2O (8:2) were combined to give **9** (0.48 g) which was recrystallized from Me_2CO-petr ether: mp 87–89°; λ_{max}^{MeOH} 280 mμ (ϵ 2180). *Anal.* ($C_{14}H_{18}O_2$) C, H.

4-(1,2,3,4-Tetrahydro-6-hydroxy-2-naphthyl)butan-2-ol (1). To a soln of the above ketone **9** (0.262 g) in MeOH (20 ml) was added $NaBH_4$ (0.145 g), and the soln was stirred at room temp for 30 min. The excess reagent was decompd by addition of a few drops of AcOH. Most of the MeOH was evapd under vacuum and the product was isolated** with EtOAc, then purified over a column of alumina. The fractions eluted with PhH-Et_2O (8:2) were combined (0.18 g, 69%) and crystallized once from Et_2O-petr ether, mp 81–84°; λ_{max}^{MeOH} 281 mμ (ϵ 2130). *Anal.* ($C_{14}H_{20}O_2$) C, H.

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Ornithine Analogs as Potential Ornithine Decarboxylase Inhibitors 1. N-Substituted Ornithine Derivatives

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Polyamines such as spermidine, spermine, and putrescine are found to be present at higher concentrations in mammalian tissues of organs with high rates of RNA synthesis.[1] They are also present in high concentrations in regenerating rat liver[2,3] and during certain growth phases of the chick embryo.[4,5] Jänne and Raina[6a] and Russell and Snyder[6b] found that ornithine decarboxylase, the enzyme that forms putrescine from ornithine, showed a marked increase in activity in regenerating rat liver. Within 1 hr after partial hepatectomy, ornithine decarboxylase activity was tripled. In addition, some rapidly growing tumors have been found to have ornithine decarboxylase activities far greater than that of nonmalignant tissues.[7,8] A recent study[9] showed that ornithine decarboxylase activity in the rat ovary was stimulated by luteinizing hormone.

It was of interest to attempt to find inhibitors of ornithine decarboxylase in order to better understand the role of this enzyme and the polyamines resulting from its action in rapidly growing tissues. A survey of the literature failed to uncover any reports of inhibitors of ornithine decarboxylase. Thus synthetic studies were undertaken to modify the ornithine molecule in order to investigate whether these modifications would result in enzyme inhibitors. Table I summarizes the chemical data on those compounds synthesized.

N^{ϵ}-Phenyl-*dl*-ornithine (**1**) was synthesized *via* the following sequence: 3-anilinopropanol was treated with BzCl to yield *N*-benzoyl-3-anilinopropanol. The benzoylation was conducted in a 2-phase system so as to benzoylate the amino group. The iodo group was introduced after chlorination with $SOCl_2$ by using NaI in boiling acetone. Reaction of the I derivative with formamido malonate yielded diethyl *N*-phenyl-*N*-benzoyl-3-aminopropyl formamidomalonate that was hydrolyzed to the desired amino acid.

β-Methylornithine hydrochloride (**2**) was prepared *via* reductive cyclization of diethyl 2-(2-cyano-1-methylethyl)malonate over Raney Ni, formation of 4-methylpiperidine-2,3-dione 3-phenylhydrazone using $NaNO_2$ and $PhNH_2$, reduction over Raney Ni of the hydrazone to the amine and acid hydrolysis to the desired amino acid.

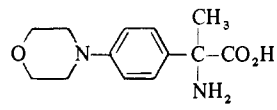
N^{α}-Methyl-N^{ϵ}-tosyl-*l*-ornithine (**4**) was synthesized *via* N^{α}-benzyl-N^{ϵ}-tosyl-*l*-ornithine,[14] that was methylated with formic acid-CH_2O, and hydrogenated over Pd/C to yield **4**.

Initially, these compounds with the exception of **3** were evaluated for their effects on ornithine decarboxylase activity in soluble supernatant preparations of livers from rats 3 hr after partial heptatectomy. The level of activity at this time is elevated about 8–10 times above basal activity.[8] Enzyme activity was determined by the formation of [^{14}C] CO_2 from [1-^{14}C] ornithine and was assayed under conditions in which activity was linear with time and enzyme concentration. The compounds were preincubated with the enzyme preparation for 10 min before the addition of [^{14}C] ornithine. They were tested in concns of 10^{-4} *M*, 10^{-5} *M*, and 10^{-6} *M*. No inhibition of enzymatic activity was obtained with any of the compounds tested.

In addition to evaluation of their ability to inhibit ornithine decarboxylase, **1**, **4**, **5**, **6**, and **7** were evaluated for anticancer activity in mice with L-1210 leukemia at a dose level of 400 mg/kg, and all were inactive. At this dose, only α-methyl-[*p*-(*N*-morpholino)phenyl]-*dl*-alanine showed any toxicity (4/6 survivors).

The antimicrobial activities of these ornithine derivatives were evaluated by an *in vitro* screen using the paper disk-agar plate method. Each disk was impregnated with 0.5 mg of test compound and laid on sensitivity agar plates streaked with dilute cultures of the test organism. Rings of inhibition after 24 hr were measured. Eight organisms were used for this test: *Staphylococcus albus*, *Escherichia coli*, *Serratia marcescens*, *Klebsiella aerobacter*, *Micrococcus luteus*, *Sacharomyces cerevisiae*, *Penicillium notatum*, and *Sporobolomyces salmoncolor*. None of

Table I

No.	Compound	Mp, °C	Formula	Analyses[a]
1	$C_6H_5NH(CH_2)_3CH(NH_2)CO_2H$	244-245	$C_{11}H_{16}N_2O_2$	*b*
2	$H_2N(CH_2)_2CH(CH_3)CH(NH_2)CO_2H \cdot HCl$	236-238	$C_6H_{14}N_2O_2 \cdot HCl$	C, H, N[c]
3	*p*-$H_3CC_6H_4SO_2NH(CH_2)_3CH(NH_2)CO_2H$	238 dec		*d*
4	*p*-$H_3CC_6H_4SO_2NH(CH_2)_3CH(NHCH_3)CO_2H$	234-236	$C_{13}H_{20}N_2O_4S$	C, H, N
5	$H_2N(CH_2)_3CH(NHCH_3)CO_2H \cdot HCl$	238-240[e]	$C_6H_{14}N_2O_2 \cdot HCl$	C, H, N
6		224-225		*f*
7	$H_3CNH(CH_2)_3CH(NH_2)CO_2H \cdot HCl$	225 dec		*g*

[a]Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values. [b]*Anal.* H, N. C, calcd, 63.44; found, 62.92. [c]C, calcd, 39.45; found, 38.69. [d]See ref 10. [e]Izumiya[11] reported mp 244-245°. [f]See ref 12. [g]See ref 13.

the ornithine analogs were active in this screen.

Since all of the ornithine derivatives with the exception of 2 had substituents on either the α- or the ε-amino group and all were inactive as inhibitors of ornithine decarboxylase, it would appear that substitution on either of the amine functions does not cause inhibition of the enzyme. Because of the method of assay for inhibition, one does not know whether any of these compounds can replace ornithine as a substrate. It would be of special interest to determine this with 2.

Experimental Section

Diethyl *N*-Phenyl-*N*-benzoyl-3-aminopropylformamidomalonate. Na (0.46 g, 0.02 g-atom), was dissolved in 10 ml of EtOH and to the soln was added diethyl formamidomalonate (4.06 g, 0.02 mole). Crude *N*-phenyl-*N*-benzoyl-3-aminopropyl iodide (7.3 g, 0.02 mole), dissolved in EtOH was added. The resulting soln was heated at reflux for 3 hr and evapd to near dryness. Add of H_2O gave a cryst product that was filtered off and washed (H_2O) yielding a crude product of 3.9 g. Recryst from 90% EtOH gave a pure product of white crystals; yield, 3.5 g (40%), mp 133-134°. *Anal.* ($C_{24}H_{28}N_2O$) C, H, N.

N^{ϵ}-Phenyl-*dl*-ornithine (1). Diethyl *N*-phenyl-*N*-benzoyl-3-aminopropylformamidomalonate (3.7 g, 8.4 mmoles) was boiled in HCl (6 *N*, 40 ml) for 17 hr. After cooling, the reaction mixt was ext with Et_2O 2 times to eliminate unreacted and neutral material. The reaction mixt was evapd to dryness, the residue dissolved in H_2O and the pH adjusted to 6.5 with NaOH. The free amino acid sepd and was collected after 2 hr; yield, 2.1 g (78%), mp 244-245°.

3-Amino-4-methylpiperidone (2). 4-Methylpiperid-2,3-dione-3-phenylhydrazone[15,16] (6.5 g, 0.03 mole) was dissolved in EtOH (150 ml) and hydrogenated with Raney Ni catalyst at 50-60° and the pressure was kept at 3.5 kg/cm² for 120 hr. Uptake of H_2 was close to theoretical. Most of the EtOH was evapd and the crude mix was sepd on a silica gel column. $PhNH_2$ and starting material was eluted with Et_2O. Compd 2 was eluted from the column with $CHCl_3$ satd with NH_3; yield, 2.9 g (74.5%). This material was homogeneous on silica gel tlc; $CHCl_3$-NH_3 satd.

β-Methylornithine Hydrochloride (3). 3-Amino-4-methyl-2-piperidone (1.28 g, 0.01 mole) was boiled in 6 *N* HCl (20 ml) for 16 hr. The reaction mixt was evapd to dryness. The residual yellow syrup was dissolved in H_2O (20 ml) and the pH adjusted to 5.8 with NH_4OH. H_2O was evapd and the white crystals that sepd were recrystd from EtOH and H_2O; yield, 1.0 g (45.7%), mp 236-238°.

N^{α}-Benzyl-N^{α}-methyl-N^{ϵ}-tosyl-*l*-ornithine. A mixt of N^{α}-benzyl-N^{ϵ}-tosyl-*l*-ornithine (18.8 g, 0.05 mole), HCO_2H (5.1 ml, 0.15 mole), and CH_2O soln (5 ml) was heated until it cleared. The solvent was evapd and the residue dissolved in $CHCl_3$, Me_2CO was added and after cooling overnight the ppt was filtered; yield, 16.1 g (82.5%), mp 182-183°.

N^{α}-Methyl-N^{ϵ}-*p*-toluenesulfonyl-*l*-ornithine (4). N^{α}-Benzyl-N^{α}-methyl-N^{ϵ}-tosyl-*l*-ornithine (11.7 g, 0.03 mole) was hydrogenated (3.5 kg/cm²) in 150 ml of AcOH in the presence of 3 *N* HCl overnight. The catalyst was filtered and the solvent evapd *in vacuo*. The residue was dissolved in H_2O and the pH adjusted to 6.5. After standing, the amino acid was filtered to yield 8.3 g (92%), mp 234-236°.

N^{α}-Methyl-*l*-ornithine Hydrochloride (5). A mixt of N^{α}-methyl-N^{ϵ}-*p*-toluenesulfonyl-*l*-ornithine (4 g, 0.0133 mole), and 48% HBr (35 ml) was boiled for 3 hr and cooled, and 50 ml of H_2O added. After filtering, the filtrate was evapd to dryness. The residue was dissolved in H_2O and stirred with Dowex 50 (H^+ form) (75 ml) for 1 hr. The resin was filtered, washed thoroughly with H_2O and stirred for 15 min in 5 *N* NH_4OH (100 ml). The mixt was filtered and the filtrate evapd to dryness. The residue was dissolved in H_2O and the pH adjusted to 5.8 with HCl. The soln was evapd and the residue crystd from EtOH-H_2O, yield 1.2 g (49.2%), mp 238-240°.

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