(b) Compound **11** (220 mg, 0.414 mmole) was dissolved in DMF (10 ml) containing H_2O (0.5 ml), Li_2CO_3 (0.55 g), and LiCl (0.35 g), and the mixt was brought quickly to reflux and kept refluxing vigorously for 10 min. After diln with EtOAc, the soln was filtered, and the filtrate washed (H_2O, 2 *N* HCl, and $NaHCO_3$ soln), dried, and evapd to give 100 mg of **6** (54%) (from C_6H_{14}), identical with **6** prepared from **9** in all respects.

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Specificity in Enzyme Inhibition. 2. α-Aminohydroxamic Acids as Inhibitors of Histidine Decarboxylase and 3,4-Dihydroxyphenylalanine Decarboxylase

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A recent report by Gale, *et al.*,[1] concerning the effects of hydroxamic acids on histidine decarboxylase prompts us to report on our work dealing with this system. This work is part of a continuing study on the design of active-site-directed reversible inhibitors of enzymes utilizing amino acids as substrates.[2] In order to study the specificity of inhibition of histidine decarboxylase and L-aromatic amino acid decarboxylase, derivatives of the α-amino acids phenylalanine, tyrosine, 3,4-dihydroxyphenylalanine (dopa), histidine, and tryptophan were prepared.

On the basis of both enzyme-substrate specificity and the requirement of pyridoxal as a cofactor, the hypothetical receptor site of a decarboxylase enzyme can be pictured as having 2 binding sites; a specific site, which differentiates the amino acid (active-site-directed), and a nonspecific site, which binds the amino group. It is predicted that the carboxyl group would assume little or no role in binding the substrate to the enzyme surface, since it interacts with the active site (Figure 1).

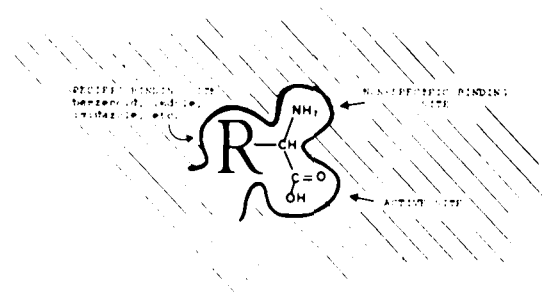


Figure 1.

Based on this model an active-site-directed inhibitor of a decarboxylase enzyme should be able to bind at the specific and the nonspecific site of the enzyme, while being unable to undergo decarboxylation at the active site. The inhibitor should possess the amino acid side chain for active-site-directed binding, along with a basic function for nonspecific binding. The carboxylic acid group should be exchanged for a function which cannot undergo decarboxylation, while still having similar structural and electronic characteristics. The inhibitor would temporarily cover the receptor, blocking the attachment of the substrate.[1] It was assumed that α-aminohydroxamic acids would meet the requirements discussed above.

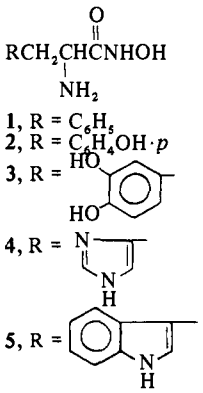
The syntheses of L-phenylalanine hydroxamic acid (**1**), L-histidine hydroxamic acid (**2**), and L-tryptophan hydroxamic acid (**3**) were based on the method of Cunningham and coworkers.[3] The general procedure involved the neutralization of amino acid ester hydrochlorides with base followed by their treatment with methanolic NH_2OH.

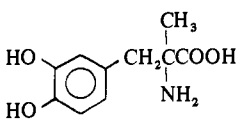
L-Tyrosine methyl ester was insoluble in MeOH under the above experimental conditions, therefore, it was necessary to run the reaction in the presence of excess KOH. DL-3,4-Dihydroxyphenylalanine methyl ester was quite susceptible to air oxidation under basic or neutral conditions, therefore it was necessary to form the hydroxamic acid under acidic conditions.

Table I

Compound	Histidine decarboxylase: % inhibition at $3 \times 10^{-4} M$	Histidine decarboxylase: % inhibition at $3 \times 10^{-5} M$	Dopa decarboxylase: % inhibition at $3 \times 10^{-4} M$	Dopa decarboxylase: % inhibition at $3 \times 10^{-5} M$
L-Phenylalanine hydroxamic acid (**1**)	0	6	16	11
L-Tyrosine hydroxamic acid (**2**)	70	6	5	8
DL-Dihydroxyalanine hydroxamic acid (**3**)	100	51	89	18
L-Histidine hydroxamic acid (**4**)	81	31	42	5
L-Tryptophan hydroxamic acid (**5**)	82	25	13	9
α-Methyl dihydroxyphenylalanine (**6**)	0	0	100	82
1-(4-Imidazolyl)-2-amino-3-butanone (**7**)	87	50	0	0

†Taken in part from the dissertation presented by V. D. Warner, Sept 1970, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.





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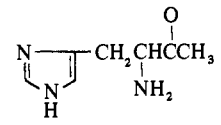

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Biological Results. Studies on the inhibition of histidine decarboxylase and L-aromatic amino acid decarboxylase (dopa decarboxylase) utilizing the α-aminohydroxamic acids were performed.[4] Phenylalanine hydroxamic acid (1) was inactive as an inhibitor of either enzyme whereas the tyrosine analog 2 was able to inhibit histidine decarboxylase but not dopa decarboxylase. The dopa hydroxamic acid 3 was the most potent inhibitor of both enzyme systems. Histidine hydroxamic acid 4 showed more specificity for inhibition of the histidine decarboxylase than for the inhibition of dopa decarboxylase while the tryptophan analog 5 had little activity in the inhibition of the dopa decarboxylase but was as active as the histidine analog in the inhibition of histidine decarboxylase. The above compounds can be compared (Table I) with α-methyldihydroxyphenylalanine (6) as a specific inhibitor of dopa decarboxylase and with 4-(4-imidazolyl)-3-amino-2-butanone (7) as a specific inhibitor of histidine decarboxylase.

Experimental Section‡

L-Phenylalanine Hydroxamic Acid (1). L-Phenylalanine methyl ester·HCl (6.7 g, 0.031 mole) was dissolved in 50 ml of H_2O, 10% NaOH was added until the soln was basic, and the free base was extracted with $CHCl_3$ (3 × 50 ml). The combined $CHCl_3$ exts were dried (Na_2SO_4), and the solvent was removed yielding 1.8 g (50%) of the free base. A NH_2OH soln was prepd by adding with cooling KOH (2.2 g, 0.034 mole) in 20 ml of MeOH to a cooled soln of NH_2OH·HCl (2.5 g, 0.036 mole) in 20 ml of MeOH and the KCl formed was removed by filtration. NH_2OH soln was added to the L-phenylalanine methyl ester, the reaction mixt was allowed to stand 8 hr at 4° and filtered, and the white solid recrystd (MeOH) yielding 1.4 g (52%), mp 186–188°. *Anal.* ($C_9H_{12}N_2O_2$) C, H, N.

L-Tyrosine Hydroxamic Acid (2). A NH_2OH soln, prepd from NH_2OH·HCl (2.2 g) as above, was added to tyrosine methyl ester (3.5 g, 0.018 mole) in 25 ml of MeOH and the pH adjusted to 9 with MeOH–KOH. The reaction mixt was allowed to stand for 12 hr at 4°, the solvent was concd to about 20 ml, and starting material crystd yielding 1.1 g (31%). The filtrate was taken to dryness and the residue recrystd (MeOH) yielding 1.6 g (45%) of 2 as a white solid, mp 178–180°. *Anal.* ($C_9H_{12}N_2O_3$) C, H, N.

DL-3,4-Dihydroxyphenylalanine Hydroxamic Acid (3). A NH_2OH soln, prepd from NH_2OH·HCl (2.5 g) as above, was added under N_2 to DL-3,4-dihydroxyphenylalanine methyl ester·HCl (2.5 g, 0.010 mole) and the reaction mixt allowed to stand overnight at 4°. The solvent was removed and when Et_2O was added crystn occurred. The white solid (3) was washed with hot MeOH yielding 1.1 g (52%), mp 177–179°. *Anal.* ($C_9H_{12}N_2O_4$) C, H, N.

L-Histidine Hydroxamic Acid (4). L-Histidine methyl ester·2HCl (7.4 g, 0.031 mole) was placed in 100 ml of 5% NH_3–$CHCl_3$, allowed to stand for 1 hr, and filtered. The solvent was removed from the filtrate yielding 5.1 g (98%) of the free base. A NH_2OH soln from 2.5 g of NH_2OH·HCl was added to the L-histidine methyl ester and the reaction mixt allowed to stand 12 hr at 4°. It was taken to dryness yielding a white solid which was washed with $CHCl_3$ (3 × 25 ml) and recrystd (MeOH) yielding 2.6 g (47%), mp 159–161°. *Anal.* ($C_6H_{10}N_4O_2$) C, H, N.

L-Tryptophan Hydroxamic Acid (5). L-Tryptophan methyl ester·HCl (7.4 g, 0.031 mole) was placed in 100 ml of 5% NH_3–$CHCl_3$ allowed to stand for 1 hr, and filtered. The solvent was removed from the filtrate yielding 4.6 g (72%) of the free base. A NH_2OH soln from NH_2OH·HCl (2.5 g) was added to the L-tryptophan methyl ester, and after 12 hr at 4°, was worked up as above. The white solid (5) was recrystd (MeOH) yielding 3.2 g (67%), mp 166–168°. *Anal.* ($C_{11}H_{13}N_3O_2$) C, H, N.

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‡Melting points were det on a calibrated Thomas-Hoover capillary melting point apparatus and are corrected. Microanalyses were performed on an F and M CHN analyzer Model 185 in this department and by Midwest Microlab, Inc., Indianapolis, Ind. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4%.

Adamantyl Analogs of the Antidepressive, 5-(2-Dimethylaminoethyl)-2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5*H*)-one†

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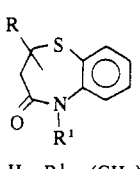
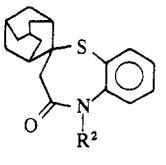
Several recent reports have described the synthesis and biological activity of a variety of adamantane derivatives.[1] We were interested in determining the effect on antidepressive activity achieved by replacing the planar phenyl ring of 5-(2-dimethylaminoethyl)-2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5*H*)-one [thiazesim (1)] with the symmetrical lipophilic adamantane moiety. This note describes the syntheses and antimuricide activity of three adamantyl analogs of 1, which had been developed in our laboratories by Krapcho, *et al.*[2]





1, R = C_6H_5; R^1 = $(CH_2)_2N(CH_3)_2$
2, R = 1-adamantyl; R^1 = $(CH_2)_2N(CH_3)_2$
3, R = 1-adamantyl; R^1 = $(CH_2)_3NC_4H_8NCH_3$
4, R = 1-adamantyl; R^1 = H

5, R^2 = H
6, R^2 = $(CH_2)_2N(CH_3)_2$

Chemistry. The reaction of adamantanone (7) with triethyl phosphonoacetate and NaH gave Δ²,α-adamantaneacetic acid, ethyl ester (8). It was determined that, by using 1.5 equiv of triethyl phosphonoacetate to an equivalent of 7 and allowing the reaction to proceed at 45°, a nearly quantitative yield of 8 could be realized. Base hydrolysis of 8 furnished Δ²,α-adamantaneacetic acid (9)[3] in 98% yield. The Michael addition of 9 to 2-aminobenzenethiol, followed by cyclization, gave the spirobenzothiazepinone 5. Alkylation of 5 with β-dimethylaminoethyl bromide gave 5′-(2-dimethylaminoethyl)spiro[adamantane-2,2′(3′*H*)-

†Thiazesim is the approved generic name for 5-(2-dimethylaminoethyl)-2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5*H*)-one.