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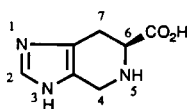
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New derivatives of the naturally occurring amino acid 4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylic acid (spinacine) are reported. These include amide, ester, 5-alkyl and acyl, and regiospecific *N*^{im}-alkyl and aralkyl derivatives. Synthesis *via* the Pictet-Spengler reaction on *N*^{im}-substituted histidines is described. Cyclic hydantoin derivatives of spinacines are included.

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Recently, non-peptide agents that bind to subclasses of angiotensin II receptors have been described [1-5]. One class of agent [1] that are derived from a rarely studied naturally occurring amino acid called "spinacine" (**1**) bind to the Type 2 (AT₂) subclass of angiotensin II receptors [2,3]. This paper describes the basic chemistry of spinacine derivatives.



1, Spinacine

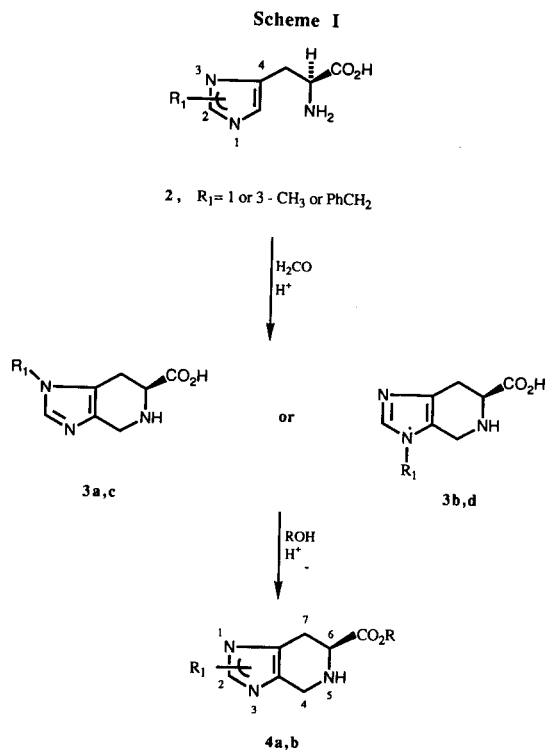
Historically, the reaction of L-histidine and formaldehyde to give spinacine ((*S*)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylic acid) was first reported by Wellisch in 1913 [6]. Subsequently, this amino acid was isolated from natural sources such as green leaves of spinach [7], hence the name spinacine. It was also identified in extracts of the crab *crango vulgaris* [8] and the liver of shark *acanthias* [9]. Over the years, conditions for the histidine-formaldehyde reaction have been extensively studied [10-14]. In addition, the reaction of histidine with a variety of other carbonyl compounds such as pyridoxal [15] and salicylaldehyde (under mildly basic conditions) [16], benzaldehyde [17], trifluoroacetaldehyde [18], cyclohexanone [19] and α -ketoglutaric acid [20] to give 4-substituted spinacines has been given considerable attention. The reported chemistry of the parent compound spinacine, however, is sparse. Only two simple derivatives, the methyl and ethyl esters [6,21] and 5-methyl spinacine [22], could be found.

In this paper we wish to report the synthesis of some new derivatives of spinacine including the amide, ester, 5-methyl, 5-benzyl, 5-acyl and 1- and 3-methyl and benzyl compounds (Schemes I-IV and Table). In addition, the preparation and reactions of some cyclic hydantoin derivatives are described (Scheme III).

In the synthesis of spinacines, when regiochemical control is desired for introduction of substituents at the imidazole N(1) and N(3) positions, it is usually beneficial to

perform regioselective reactions on histidine first, followed by cyclization to the modified spinacine. This strategy is useful because in histidine the difference between the steric environments of imidazole N(1) and N(3) allows regioselective N(1 or 3) derivitization, whereas, in spinacine N(1) and N(3) are indistinguishable in terms of chemical reactivity.

Scheme I describes the first of three approaches we developed to prepare spinacine derivatives. It involves the direct cyclization, mentioned above, of an appropriately *N*^{im}-substituted histidine **2** with methylal (formaldehyde dimethyl acetal), or aqueous formaldehyde directly, and hydrochloric acid (Pictet-Spengler reaction). These specific regioisomers of histidine derivatives (**2**, R₁ = methyl or benzyl) are prepared by regioselective syntheses reported by Beyerman [23] and by Hodges [24]. Under the cyclization conditions optical activity is retained. In one



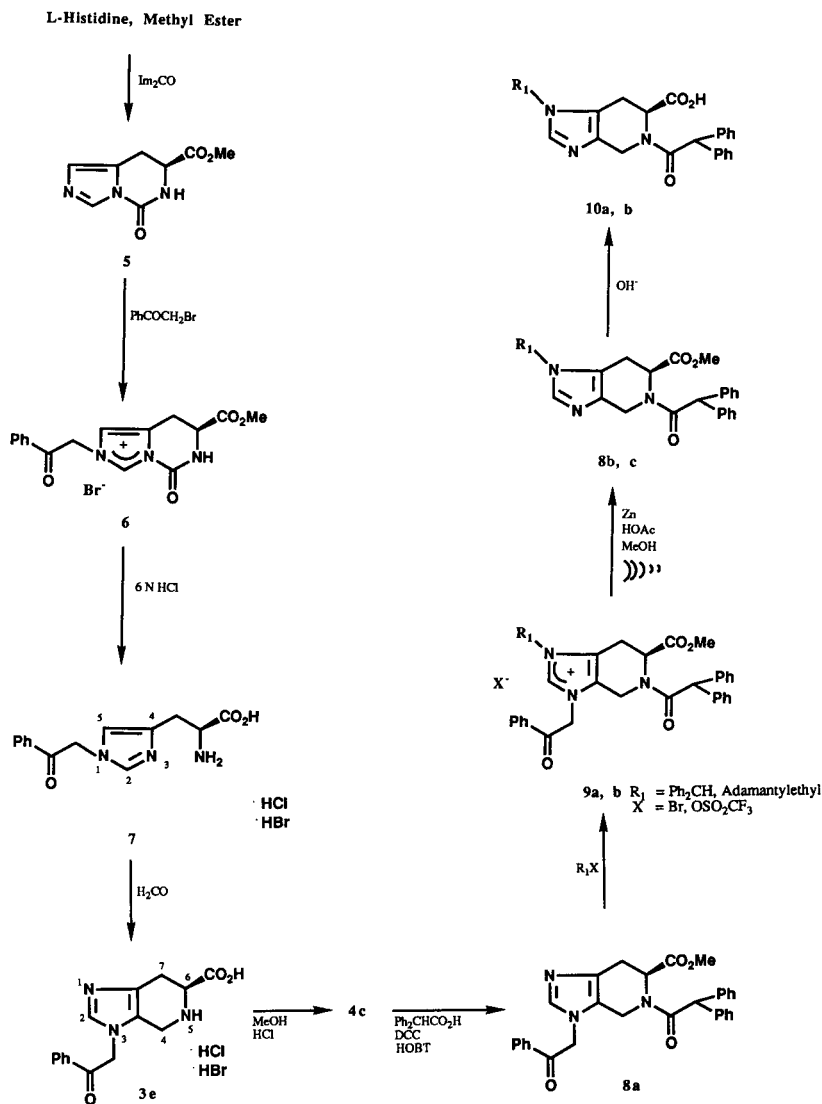
case, the pure regioispecific (*S*)-3-benzylspinacine **3d** (see Experimental) is easily isolated, in fair yield, as the least soluble dihydrochloride salt, on workup of the Pictet-Spengler reaction mixture, even though a commercial mixture of 1- and 3-benzyl-L-histidines (Vega, Sigma) is used as a starting material. Esters **4a** and **4b** of the regioisomers are obtained by treatment of **3** with alcohols and hydrogen chloride.

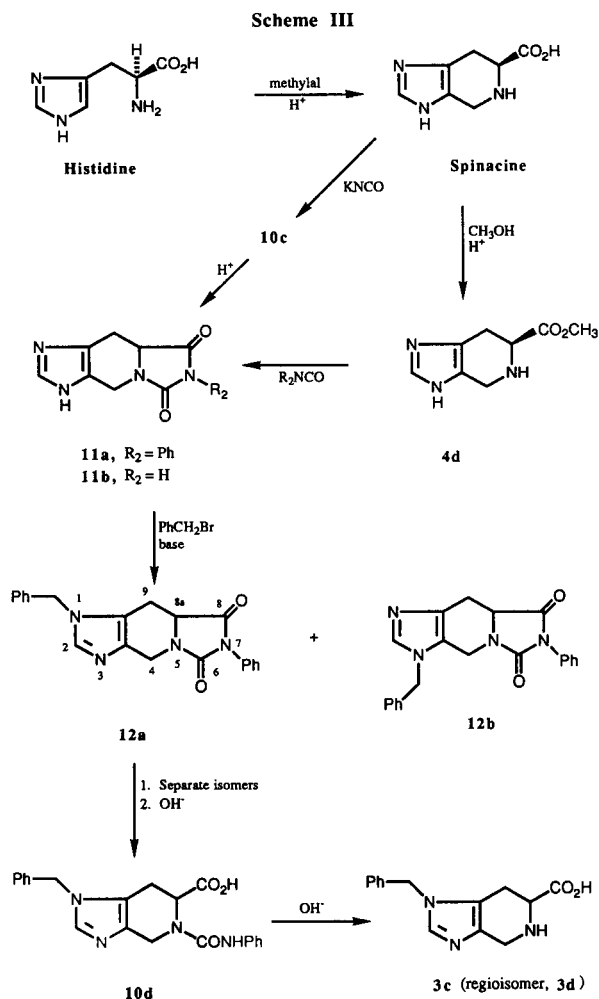
The second approach uses a variation of the first approach wherein the N(1) phenacyl protecting group is installed on histidine (Scheme II, compound **7**) *via* intermediates **5** [25] and **6** [26]. Cyclization of **7** with aqueous formaldehyde under acidic conditions gives the 3-phenacyl spinacine derivative **3e**. After esterification to **4c** and *N*(5)-acylation, a compound such as **8a** is readily alkylated by a variety of primary or secondary alkylating agents. For example, treatment of **8a** with benzhydryl

bromide, or the ester of trifluoromethanesulfonic acid and 1-adamantaneethanol, in refluxing acetonitrile, or in methylene chloride at -75° to $+25^{\circ}$ in the case of the triflate, affords the imidazolium salts **9a** and **9b**. The phenacyl group is then selectively removed by sonication in the presence of excess zinc, acetic acid and methanol. The net result is regioispecific N(1) substitution after cyclization to give **8b** and **8c**.

The third approach to *N*^{im}-substituted spinacines **3** (Scheme III) consists of a vigorous base hydrolysis of specific *N*^{im}-substituted hydantoin derivatives **12a** or **12b**. These intermediates are obtained by separation (recrystallization) of the mixed regioisomers arising from *N*^{im}-benzylation of hydantoin **11a** ($R_2 = \text{Ph}$). A disadvantage of this sequence is racemization during benzylation and hydrolysis to spinacines **3c** and **3d**; thus, many subsequent derivatives of **3** made by this method and reported

Scheme II



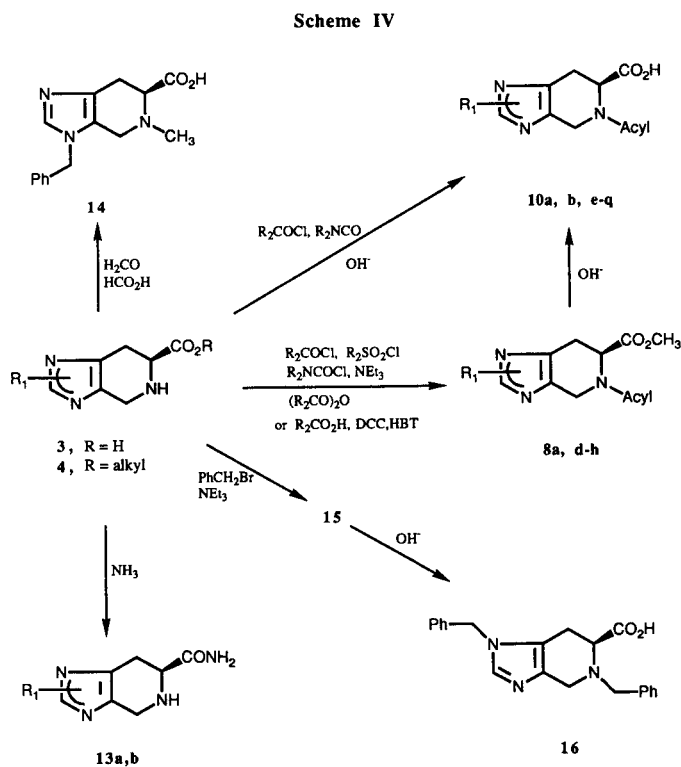


here are also racemic. Milder base hydrolysis of intermediate hydantoin **12a** leads to hydantonic acid **10d** which can be recycled, if desired, to **12a** by treatment with strong hydrochloric acid.

The intermediate hydantoin **11a** (R₂ = Ph) in Scheme III is prepared in good yield from spinacine methyl ester **4d** and phenylisocyanate. The R₂ group can be varied by this procedure. The NH hydantoin **11b** is prepared from spinacine with potassium cyanate. In this reaction the intermediate hydantonic acid **10c** forms first. It is then cyclized to **11b** by strong acid treatment.

Scheme IV shows additional products that are obtained by alkylation and acylation of various spinacines **3** or spinacine esters **4**. For instance, acylation of the amino acids **3** under Schotten-Baumann conditions (General Method D) with acid chlorides or isocyanates gives a variety of 5-acylspinacine derivatives such as amides, ureas and carbamates (**10e,f,h,i,k,l,p** and **q**). An alternate sequence to 5-acyl spinacines **10** involves first acylation of the spinacine esters **4** with acid halides or anhydrides, or coupling with carboxylic acids using DCC, to give the

5-acyl-6-carboxylic ester derivatives **8a** and **8d-h**. Subsequent base hydrolysis gives 5-acyl-6-carboxylic acid derivatives **10a,b,g,j,m-o**.

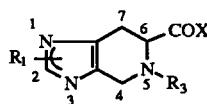


Spinacine 6-carboxamides **13a** and **13b** are obtained by treating the amino esters **4a** and **4d** with ammonia. The *N*-methylspinacine derivative **14** is generated *via* an Escheiler-Clarke methylation of 3-benzylspinacine **3d**. Finally, benzylation of the 1-benzylspinacine ester **4a** gives the 1,5-dibenzyl derivative **15** which, on base hydrolysis, yields the 1,5-dibenzylspinacine **16**.

Discussion.

Convenient procedures for the preparation of a variety of modified spinacines have been developed. Much of the work in this paper resulted from our interest in spinacines as subtype-specific angiotensin II receptor antagonists. The structure biological activity relationships for spinacines will be described elsewhere in detail beyond the scope of this publication. Spinacines can also be looked at as conformationally restricted analogs of histidine. In this regard they may have other practical uses. The chemistry for alkylation, esterification and acylation of spinacines that is described in this paper provides a number of new amino acids of potential interest in the peptide and peptidomimetic fields.

Table
Spinacine Derivatives



No.	R ₁	R ₃	X	Method
1, Spinacine	H	H	OH	A
3a	1-Me	H	OH	A
3b	3-Me	H	OH	A
3c	1-Bn [a]	H	OH	A [b]
3d	3-Bn	H	OH	A
3e	3-CH ₂ COPh	H	OH	[b]
4a	1-Bn	H	OMe	B
4b	3-Bn	H	OEt	B
4c	3-CH ₂ COPh	H	OMe	B [b]
4d	H	H	OMe	B
8a	3-CH ₂ COPh	COCHPh ₂	OMe	[b]
8b	1-CHPh ₂	COCHPh ₂	OMe	[b]
8c	1-Adamantylethyl	COCHPh ₂	OMe	[b]
8d	1-Bn	COCHPh ₂	OMe	C
8e	H	COMe	OMe	[b]
8f	1-Bn	COMe	OMe	[b]
8g	3-Bn	COMe	OMe	[b]
8h	1-Bn	SO ₂ CH ₂ Ph	OMe	C
10a	1-CHPh ₂	COCHPh ₂	OH	[b]
10b	1-Adamantylethyl	COCHPh ₂	OH	[b]
10c	H	CONH ₂	OH	[b]
10d	1-Bn	CONHPh	OH	[b]
10e	3-Bn	CONHCH(CH ₃) ₂	OH	D
10f	H	CONHPh	OH	D
10g	H	COMe	OH	E
10h	H	COPh	OH	D
10i	H	CO ₂ CH ₂ Ph	OH	D
10j	1-Bn	COMe	OH	E
10k	1-Bn	COPh	OH	D
10l	1-Bn	CO ₂ CH ₂ Ph	OH	D
10m	1-Bn	CON(Me)Ph	OH	C & E
10n	1-Bn	COCHPh ₂	OH	E
10o	1-Bn	SO ₂ CH ₂ Ph	OH	E
10p	1-Bn	COCH ₂ Ph	OH	D
10q	3-Bn	COPh	OH	D
13a	H	H	NH ₂	[b]
13b	1-Bn	H	NH ₂	[b]
14	3-Bn	Me	OH	[b]
15	1-Bn	CH ₂ Ph	OMe	[b]
16	1-Bn	CH ₂ Ph	OH	[b]

[a] Bn = benzyl. [b] Detailed procedure in Experimental.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary melting point apparatus, which was calibrated against known standards. The ir spectra were run on a Nicolet MX-1 spectrometer. The nmr spectra were run on a Varian XL 200 or a Bruker AM 250 spectrometer using tetramethylsilane as an inter-

nal standard. Mass spectra were run on a Finnigan 4500 or a VG Analytical 7070 E/HF spectrometer. Ionization methods used include electron impact (EI), chemical ionization with methane (CI) and fast atom bombardment with thioglycerol (FAB). In the FAB high resolution ms determination (compound **3e**) the target gas was xenon. PEG 300 was used as a reference compound with a thioglycerol matrix. Optical rotations were run on a Perkin-Elmer 241 polarimeter. HPLC analysis of commercial *N*^{im}-benzylhistidines and *N*^{im}-benzylspinacines used a C-18 column with a mobil phase of 5% acetonitrile and 95% 0.05 *M* ammonium phosphate buffer at pH 3.0 at a 2 ml/minute flow rate. The hplc analysis of *N*^{im}-methylspinacines used a C-18 column with a mobil phase of 0.005 *M* tetrabutylammonium hydroxide, pH adjusted to 7.5 with phosphoric acid, with a flow rate of 2 ml/minute. Elemental analyses (C,H,N) check to within 0.4% of calculated values.

General Method A for the Synthesis of Spinacine and Chiral, Regiospecifically *N*^{im}-Substituted Spinacines **3a-3e** via the Pictet Spengler Reaction.

A mixture of 0.10 mole of L-histidine or a chiral, regiospecifically *N*^{im}-substituted histidine (see preparation of **3d** for exception), 12 *N* hydrochloric acid (200 ml) and methylal (30 ml) was stirred at room temperature overnight. Additional methylal (30 ml) was added and the mixture was heated on the steam bath for three hours. The resulting solution was concentrated at reduced pressure. In the case of **3a** the residue was dissolved in hot methanol and the product was precipitated with ether and recrystallized similarly. In the case of **3b-d** the residue was dissolved in a minimum amount of warm water and 2-propanol or ethanol was added to precipitate the hydrochloride or dihydrochloride salt. In the case of spinacine hydrochloride **1**, the pH of a concentrated water solution of crude reaction residue was adjusted to 3.5 by the addition of pyridine before the addition of alcohol (ethanol) and precipitation of crystalline hydrochloride. The free amino acids were prepared by passage of an aqueous solution of the hydrochloride salts through a cation exchange resin (Bio-Rad AGW50-X4). The column was washed with two column volumes of water and the product was retrieved by eluting with two column volumes of concentrated ammonium hydroxide and then one of water. Concentration of the ammonia fractions at reduced pressure gave the free amino acids.

General Method B for the synthesis of Spinacine Esters **4a-d**.

A mixture of spinacine or substituted spinacines **3c** or **d** (0.40 mole), ethyl or methyl alcohol (2.5 l), and in some cases (preparation of **4c**) trimethyl orthoformate as a water scavenger, was saturated with hydrogen chloride gas. The mixture was heated at reflux with stirring overnight. The resulting solution was again treated with a stream of hydrogen chloride, at reflux, for one hour to complete the reaction. The solution was concentrated to ca. one-half volume and ether was added to precipitate the dihydrochloride salt. Recrystallization was accomplished using methanol (or ethanol) and ether. The free base was prepared by dissolving the hydrochloride in 500 ml of water, cooling to 10° adding enough solid sodium bicarbonate to neutralize and saturate the solution, and extracting with 20% methylene chloride-ethyl acetate.

General Method C for the Synthesis of 5-Acylspinacine Esters **8d** and **8h**.

An appropriate acid chloride (0.01 mole) in acetonitrile (25 ml) was added dropwise to a stirred, cooled (-10°) solution of a spinacine ester base (**4a**) (0.01 mole) and triethylamine (0.015 mole) in acetonitrile (25 ml). After one-half hour at room temperature the triethylamine hydrochloride was filtered and the solvent was distilled at reduced pressure. Ice water (50 ml) was added to the residue and the product was either filtered or extracted into ethyl acetate. The extract was washed with 2% sodium bicarbonate, dried (sodium sulfate) and concentrated to give crude product. Recrystallization from ethyl acetate-pentane or ethyl acetate gave products **8d** and **8h**.

General Method D for the Synthesis of 5-Acylspinacines **10e,f,h,i,k,l,p** and **q** via the Schotten-Baumann Reaction.

An appropriate isocyanate or acid chloride acylating agent (0.12 mole, 20% excess) was added either neat or as a dioxane solution (20 ml) over a period of fifteen minutes to a cooled (3-5°) and stirred solution of either spinacine (as the free amino acid or hydrochloride) or a substituted spinacine **3c** or **d** (as a dihydrochloride salt) (0.10 mole), dioxane or methanol (250 ml) and 2 *N* sodium hydroxide (0.10 mole when isocyanates were added and 0.22 mole when acid chlorides were added). An additional 0.10 mole of 2 *N* sodium hydroxide was added in the case of a mono-hydrochloride starting material and an additional 0.20 mole was added in the case of a dihydrochloride starting material. After fifteen minutes at 5° and one hour at 25°, the reaction mixture was filtered to remove of the urea by-product (in the case of isocyanate reactions). The filtrate was concentrated to one-third volume at reduced pressure to remove most of the organic solvent. Additional water (50 ml) was added and the aqueous solution (or mixture) was cooled to 10°. An equivalent amount of 2 *N* hydrochloric acid, or glacial acetic acid (to prevent cyclization to hydantoin in the case of products from isocyanates), to neutralize the calculated amount of remaining inorganic base (0.10 mole) was added to precipitate the product. In the case of **10h,k** and **q**, recrystallization from methanol, methanol-ether or methanol-water removed the benzoic acid by-product.

General Method E for the synthesizing 5-Acylspinacines **10g,j,m-o** by Hydrolysis of the corresponding esters.

Sodium hydroxide (1 *N*, 5.2 ml, 5.2 mmoles) at 5° was added to a solution of a 5-acylspinacine ester **8e-h** (2.6 mmoles) in methanol (10 ml) at 5°. The solution was allowed to stand at room temperature overnight. In the case of **10g**, the solution was heated at reflux for five minutes. The methanol was distilled at reduced pressure and water (5-30 ml) was added to the residue. The cooled (10°) solution was treated with 1 *N* hydrochloric acid or glacial acetic acid (5.2 mmoles) to precipitate the carboxylic acid product. In the case of **10j** the product was isolated by passing the neutralized reaction solution through a cation exchange resin (Bio-Rad AGW50), eluting with ammonium hydroxide and concentrating.

(*S*)-4,5,6,7-Tetrahydro-1*H*-Imidazo[4,5-*c*]pyridine-6-carboxylic Acid, Hydrochloride (**1**). (Spinacine Hydrochloride).

The title compound was prepared by Method A starting from L-histidine, yield, 63%, mp 286-287° dec, lit [10] mp 279-280°; $[\alpha]_D^{25}$ -131.3° (c, 2.11 water); ir (potassium bromide): 1636, 1664 cm^{-1} ; ¹H nmr (deuterium oxide): δ 3.14 (dd, 1H, H-7), 3.47 (dd, 1H, H'7), 4.25 (q, 1H, H-6), 4.46 (d, 1H, H-4), 4.63 (d, 1H, H'4), 8.74 (s, 1H, H-2); ms: (EI) *m/z* 167 (M).

Anal. Calcd. for C₇H₉N₃O₂·HCl: C, 41.29; H, 4.95; N, 20.63. Found: C, 41.24; H, 4.74; N, 20.53.

Spinacine, Free Amino Acid, 1.5 Mole Hydrate (**1**).

The title compound was prepared by method A. The residue from concentration of the reaction solution (from 0.50 mole of histidine starting material) was redissolved in 150 ml of water and concentrated ammonium hydroxide was added to pH 8. Crystals of spinacine hydrate separated on standing. Recrystallization from 300 ml of hot water gave 48.0 g of spinacine, 1.5 mole hydrate, yield, 49%, mp 235-250° dec; $[\alpha]_D^{25}$ -182.2° (c, 1.02 water); ir (potassium bromide): 1614, 1635, 3450 cm^{-1} ; ¹H nmr (deuterium oxide): δ 3.05 (dd, 1H, H-7), 3.33 (dd, 1H, H'7), 4.12 (q, 1H, H-6), 4.32 (AB, 2H, H-4), 4.87 (s, H₂O), 7.77 (s, 1H, H-2); ms: (CI) *m/z* 168 (M + 1), 95 (base, M · HN=CH-CO₂H + 1).

Anal. Calcd. for C₇H₉N₃O₂·1.5H₂O: C, 43.29; H, 6.03; N, 21.62. Found: C, 43.45; H, 6.31; N, 21.85.

(*S*)-4,5,6,7-Tetrahydro-1-methyl-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylic Acid, Dihydrochloride (**3a**), (1-Methylspinacine).

The title compound was prepared by Method A starting from the reported 3-methyl-L-histidine [23,27,29], yield, 30%, recrystallization solvent, methanol-ether, mp 287-290° dec; $[\alpha]_D^{25}$ -95.7° (c, 1.11 water); ir (potassium bromide): 1652 (im, C=N^{*}), 1741, 1759 cm^{-1} (carboxylic acid C=O); ¹H nmr (dimethyl sulfoxide-*d*₆): δ 3.10 (dd, 1H, H-7), 3.42 (dd, 1H, H'7), 3.81 (s, 3H, CH₃), 4.31 (d, 1H, H-4), 4.50-4.90 (m, 4H, H'4, H-6, NH, OH), 9.08 (s, 1H, H-2); ms: (EI) *m/z* 181.1 (M^{*}); hplc, 99.8% (retention time 2.87 minutes).

Anal. Calcd. for C₈H₁₁N₃O₂·2HCl: C, 37.81; H, 5.16; N, 16.54. Found: C, 37.98; H, 5.13; N, 16.37.

(*S*)-4,5,6,7-Tetrahydro-3-methyl-3*H*-imidazo[4,5-*c*]pyridine-6-carboxylic Acid, Dihydrochloride (**3b**), (3-Methylspinacine).

The title compound was prepared by Method A starting from 1-methyl-L-histidine [27,29] (Vega Biochemicals: Described as 3-methyl-L-histidine in their catalog), yield, 45%, recrystallization solvent, methanol-ether; mp 262-265° dec; $[\alpha]_D^{25}$ -93.5° (c, 1.05 water); ir (potassium bromide): 1648 (im, C=N), 1755 cm^{-1} (carboxylic acid C=O); ¹H nmr (dimethyl sulfoxide-*d*₆): δ 3.12 (dd, 1H, H-7), 3.30 (dd, 1H, H'7), 3.82 (s, 3H, CH₃), 4.35 (d, 1H, H-4), 4.51 (m, 2H, H'4, H-6), 9.05 (s, 1H, H-2), 11.30 (br s, 2H, NH, OH); ms: (EI) *m/z* 181 (M); hplc, 99.3% (retention time 4.02 minutes).

Anal. Calcd. for C₈H₁₁N₃O₂·2HCl: C, 37.81; H, 5.16; N, 16.54. Found: C, 37.91; H, 5.33; N, 16.26.

(*S*)-4,5,6,7-Tetrahydro-1-(phenylmethyl)-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylic Acid, Dihydrochloride (**3c**), (1-Benzylspinacine).

The title compound was prepared by Method A and also by a variation of A using 36% aqueous formaldehyde instead of methylal as follows: A solution of 3-benzyl-L-histidine [24,27,29] (90.0 g, 0.28 mole) in water (600 ml) was treated with 36% aqueous formaldehyde (70 ml, 0.84 mole, 3 equivalents). The resulting solution was stirred one-half hour at room temperature, heated to reflux and stirred at reflux for two hours. After cooling to room temperature, the reaction mixture was treated with concentrated hydrochloric acid (10 ml) and evaporated to a thick syrup. The syrup was heated on the steam bath and ethanol was gradually added until a thick paste of precipitate formed. More ethanol was added to give a slurry which was cooled, filtered and

washed with ethanol to give 55.5 g of **3c**, yield, 60%, mp 270-271°; $[\alpha]_D^{23}$ -63.1° (c, 1.01 water); $[\alpha]_D^{23}$ -57.5° (c, 0.76 methanol); ir (potassium bromide): 1654, 1722 cm^{-1} ; ^1H nmr (dimethyl sulfoxide- d_6): δ 2.85 (dd, 1H, H-7), 3.32 (dd, 1H, H'-7), 4.30 (q, 2H, H-4), 4.52 (q, 1H, H-6), 5.48 (q, 2H, PhCH_2), 7.20-7.48 (m, 5H, Ph), 9.16 (s, 1H, H-2); ms: (CI) (m/z) 258 (M + 1).

Anal. Calcd. for $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O}_2 \cdot 2\text{HCl}$: C, 50.92; H, 5.19; N, 12.73; Cl, 21.47. Found: C, 51.25; H, 5.12; N, 12.69; Cl, 22.40.

Racemic (\pm) **3c**, Dihydrochloride.

A solution of a regiospecifically substituted spinacine hydantoin derivative **12a** (0.025 mole) in a cautiously prepared solution of water (13 ml), methanol (40 ml) and potassium hydroxide (18.0 g) was maintained at reflux for 6 hours. The methanol was distilled at reduced pressure, water (15 ml) was added and the mixture was heated on the steam bath to dissolve all solid. The cooled solution was extracted with ether to remove aniline-of-hydrolysis. Ice chips (50 g) were added to the aqueous phase and concentrated hydrochloric acid (ca. 30 ml) was cautiously added to pH 2. This solution was passed through a cation exchange resin (ca. 200 g, Bio-Rad AGW 50) and the column was washed with ca. three column volumes of water to remove inorganic salts. The product was eluted from the column by passage of concentrated ammonium hydroxide (ca. 200 ml) and then water (250 ml). The ammonia fractions were concentrated at reduced pressure to give the crude free amino acid **3c**. The dihydrochloride salt was prepared by dissolution in a minimum amount of water (5 ml) and addition of concentrated hydrochloric acid (5 ml) to yield crystalline material. Addition of 2-propanol (25 ml) to this mixture and filtration gave 7.00 g of racemic **3c**, yield, 85%, mp 279-281° dec. Recrystallization from water gave pure **3c**, mp 280-282°; ms: (CI) 258 (M + 1).

Anal. Calcd. for $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O}_2 \cdot 2\text{HCl}$: C, 50.92; H, 5.19; N, 12.73. Found: C, 51.06; H, 5.09; N, 12.72.

(S)-4,5,6,7-Tetrahydro-3-(phenylmethyl)-1H-imidazo[4,5-c]pyridine-6-carboxylic Acid, Dihydrochloride, 1.5 Moles Hydrate (**3d**), (3-Benzylspinacine).

The title compound was prepared by Method A starting from an approximately 20:80 (by hplc) mixture of 1 and 3-benzyl-L-histidines (Sigma Chemical Company Lot No. 22F-5042) [27,29]. In this reaction a 68% yield of pure (S)-3-benzylspinacine was isolated as the insoluble isomer from recrystallization of the crude dihydrochloride reaction product of method A from water-2-propanol [29]. 3-Benzylspinacine could also be isolated similarly in lower yield when a 50-50 mixture of 1- and 3-benzyl-L-histidines (Vega Biochemicals) was used, mp 130-135°; $[\alpha]_D^{23}$ -72.8° (c, 1.12 methanol); ir (potassium bromide): 1645, 1720, 1740 cm^{-1} ; ^1H nmr (dimethyl sulfoxide- d_6): δ 3.11 (dd, 1H, H-7), 3.31 (dd, 1H, H'-7), 4.07 (d, 1H, H-4), 4.39 (d, 1H, H'-4), 4.55 (q, 1H, H-6), 5.53 (AB, 2H, PhCH_2), 7.34-7.44 (m, 5H, Ph), 9.28 (s, 2H, H-2); ms: (EI) m/z 257 (M); hplc, 99.4% (retention time 3.71 minutes).

Anal. Calcd. for $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O}_2 \cdot 2\text{HCl} \cdot 1.5\text{H}_2\text{O}$: C, 47.06; H, 5.64; N, 11.76; Cl, 19.84; H_2O , 7.56. Found: C, 47.08; H, 5.50; N, 11.77; Cl, 20.15; H_2O (KF) 7.47.

(S)-4,5,6,7-Tetrahydro-3-(2-oxo-2-phenylethyl)-3H-imidazo[4,5-c]pyridine-6-carboxylic Acid, 1.33 Mole Hydrochloride, 0.66 Mole Hydrobromide, 0.5 Mole Hydrate (**3e**).

A solution of **7** (32.4 g, 83 mmoles) in 1N hydrochloric acid (400 ml), was treated with 37% aqueous formaldehyde (17.5 ml, 210 mmoles). The solution was stirred for 30 minutes at room temperature and then it was heated to reflux for 2 hours. The reaction mixture was rapidly cooled to room temperature by placing it in an ice bath. Evaporation gave a colored gum that was redissolved in water (200 ml). This solution was treated with activated charcoal, filtered through celite and evaporated to give a nearly colorless gum. The gum was allowed to stand at room temperature for three days after which some crystalline material was observed at the edges. Ethanol was added to the mixture of gum and crystals and the resulting slurry was heated on a steam bath until all of the gum dissolved and product began to crystallize. The slurry was cooled on an ice bath for 4 hours and the product was collected by filtration, drying in a vacuum oven (ca. 125 mm Hg, 80°, 24 hours) to afford **3e** as a colorless, hygroscopic solid (21.8 g, 65%), mp 195-198° dec; $[\alpha]_D^{23}$ -79.8° (c, 1.05, H_2O); ir (potassium bromide): 1751, 1676 cm^{-1} ; ^1H -nmr (deuterium oxide): δ 3.18 (dd, 1H, H-7), 3.63 (dd, 1H, H'-7), 4.53 (d, 1H, H-4), 4.70 (dd, 1H, H-6), 4.82 (d, 1H, H'-4), 4.85 (s, HDO), 6.02 (s, 2H, PhCOCH_2N), 7.67 (t, 2H, 3 + 5 Ph), 7.80 (t, 1H, 4-Ph), 8.07 (d, 2H, 2 + 6 Ph), 8.90 (s, 1H, H-2); high resolution ms: (FAB) m/z observed mass 286.1191 (M + 1), theoretical mass 286.1183 (M + 1).

Anal. Calcd. for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_3 \cdot 1.33\text{HCl} \cdot 0.66\text{HBr} \cdot 0.5\text{H}_2\text{O}$: C, 45.47; H, 4.58; N, 10.61; Br, 13.31; Cl, 11.90. Found: C, 45.40; H, 4.84; N, 10.39; Br, 13.22; Cl, 11.20.

(S)-4,5,6,7-Tetrahydro-1-(phenylmethyl)-1H-imidazo[4,5-c]pyridine-6-carboxylic Acid, Methyl Ester (**4a**).

The title compound was prepared by Method B starting from **3c**, S-isomer, yield 60%, recrystallization solvent, ethyl acetate-hexane, mp 82-84°; $[\alpha]_D^{23}$ -50.0° (c, 0.68 methanol); ir (potassium bromide): 1743 cm^{-1} (ester C=O); ^1H nmr (deuteriochloroform): δ 2.62 (dd, 1H, H-7), 2.75 (dd, 1H, H'-7), 3.73 (s, 3H, OCH_3), 3.73 (m, 1H, H-6), 3.98 (AB, 2H, H-4), 5.03 (AB, 2H, PhCH_2), 7.08 (m, 2H, Ph), 7.31 (m, 3H, Ph), 7.45 (s, 1H, H-2); ms: (EI) m/z 271 (M).

Anal. Calcd. for $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_2 \cdot 0.1\text{H}_2\text{O}$: C, 65.96; H, 6.35; N, 15.39. Found: C, 65.91; H, 6.26; N, 15.25.

(S)-4,5,6,7-Tetrahydro-3-(phenylmethyl)-1H-imidazo[4,5-c]pyridine-6-carboxylic Acid, Ethyl Ester, Dihydrochloride (**4b**).

The title compound was prepared by Method B starting from **3d**, S-isomer, yield, 90%, recrystallization solvent, ethanol, mp 233-236° dec; $[\alpha]_D^{23}$ -71.2° (c, 1.13 methanol); ir (potassium bromide): 1650 (im, C=N $^+$), 1755 cm^{-1} (ester C=O); ^1H nmr (dimethyl sulfoxide- d_6): δ 1.23 (t, 3H, OCH_2CH_3), 3.14 (dd, 1H, H-7), 3.30 (dd, 1H, H'-7), 4.08 (d, 1H, H-4), 4.23 (q, 2H, OCH_2), 4.38 (d, 1-H, H'-4), 4.68 (m, 1H, H-6), 5.56 (AB, 2H, PhCH_2), 7.35-7.43 (m, 5H, Ph), 9.36 (s, 1H, H-2); ms: (EI) 285 (M).

Anal. Calcd. for $\text{C}_{16}\text{H}_{19}\text{N}_3\text{O}_2 \cdot 2\text{HCl}$: C, 53.63; H, 5.91; N, 11.73. Found: C, 53.38; H, 5.64; N, 11.66.

Free Base **4b**.

This compound was prepared from **4b** dihydrochloride as described in Method B, mp 89-90°; $[\alpha]_D^{23}$ -77.7° (c, 0.57 methanol); ir (potassium bromide): 1733 (ester C=O), 3308 cm^{-1} (NH); ^1H nmr (deuteriochloroform): δ 1.28 (t, 3H, CH_2CH_3), 2.82 (dd, 1H, H-7), 3.00 (dd, 1H, H'-7), 3.68 (m, 2H, H-4, H-6), 3.72 (d, 2H, H'-4), 4.21 (q, 2H, OCH_2CH_3), 4.99 (AB, 2H, PhCH_2), 7.05 (m, 2H, Ph), 7.32 (m, 3H, Ph), 7.44 (s, 1H, H-2); ms: (EI) m/z 285 (M).

Anal. Calcd. for $C_{16}H_{19}N_3O_2 \cdot 0.105H_2O$: C, 66.90; H, 6.74; N, 14.62. Found: C, 67.30; H, 6.66; N, 14.22.

(*S*)-4,5,6,7-Tetrahydro-3-(2-oxo-2-phenylethyl)-3*H*-imidazo[4,5-*c*]pyridine-6-carboxylic Acid, Methyl Ester, Dihydrochloride (**4c**).

A solution of **3e** (19.8 g, 49.5 mmoles) in methanol (400 ml) was treated with trimethylorthoformate (50 ml), saturated with anhydrous hydrogen chloride and heated at reflux for 6 hours. The reaction mixture was cooled to 20° and filtered to give a colorless solid which was dried in a vacuum oven (*ca.* 125 mm Hg, 70°, overnight) to afford **4c** (8.7 g, 47%), mp 242-243° dec; $[\alpha]_D^{25} -77.3^\circ$ (c 1.01, H₂O); ir (potassium bromide): 1689, 1747 cm^{-1} (ketone and ester C=O); ¹H-nmr (deuterium oxide): δ 3.42 (dd, 1H, H-7), 3.58 (dd, 1H, H'-7), 3.80 (s, 3H, OCH₃), 4.47 (q, 2H, H-4), 4.85 (s + m, HDO), 5.99 (s, 2H, PhCOCH₂N), 7.59 (t, 2H, 3 + 5 Ph), 7.76 (t, 1H, 4-Ph), 8.03 (d, 2H, 2 + 6 Ph), 8.81 (s, 1H, H-2); ms: (FAB) *m/z* 300 (M + 1).

Anal. Calcd. for $C_{16}H_{19}N_3O_3 \cdot 2HCl$: C, 51.65; H, 5.14; N, 11.29; Cl, 19.05. Found: C, 51.39; H, 5.24; N, 11.27; Cl, 18.96.

The mother liquor was concentrated to a thick slurry and filtered to give a second crop which was rinsed with cold methanol and dried as above, affording an off-white solid (8.0 g, 43%) with spectral characteristics identical to the first crop, mp 218-219°; $[\alpha]_D^{25} -71.8^\circ$ (c 1.14, water). Found: C, 51.89; H, 5.46; N, 10.98; Cl, 18.93.

(*S*)-4,5,6,7-Tetrahydro-3*H*-imidazo[4,5-*c*]pyridine-6-carboxylic Acid, Methyl Ester, Dihydrochloride, Hydrate (**4d**), (Spinacine, Methyl Ester).

The title compound was prepared by Method B starting from spinacine, hygroscopic solid, yield, 91%, recrystallization solvent, methanol-ether, mp 88-110°; $[\alpha]_D^{25} -79.6^\circ$ (c, 1.08 methanol); ir (nujol): 1660, 1755, 3410 cm^{-1} ; ¹H nmr (dimethyl sulfoxide-*d*₆): δ 3.14 (dd, 1H, H-7), 3.31 (dd, 1H, H'-7), 3.81 (s, 3H, OCH₃), 4.33 (s, 2H, H-4), 4.74 (q, 1H, H-6), 9.08 (s, 1H, H-2); ms: (EI) 181 (M).

Anal. Calcd. for $C_{16}H_{19}N_3O_2 \cdot 2HCl \cdot H_2O$: C, 35.31; H, 5.56; N, 15.44. Found: C, 35.53; H, 5.52; N, 15.14.

1-(2-Oxo-2-phenylethyl)-L-histidine, Hydrochloride, Hydrobromide (**7**).

A suspension of (*S*)-5,6,7,8-Tetrahydro-7-(methoxycarbonyl)-5-oxo-2-(2-oxo-2-phenylethyl)imidazo[1,5-*c*]pyrimidinium Bromide [26] (**6**, 13.4 g, 34 mmoles) in 6*N* hydrochloric acid (250 ml) was heated at reflux for 4 hours. The resulting solution was evaporated to a gum which was dissolved in ethanol (500 ml) and evaporated to a gum once again. The residue was taken up in ethanol (50 ml), and added dropwise to vigorously stirred ethyl acetate (1.6 l). The resulting precipitate was collected by filtration under a shower of nitrogen and dried in a vacuum oven (*ca.* 125 mm Hg, 70-80°, 48 hours) to give **7** as a very hygroscopic solid (13.2 g, 99.5%), mp 145-155° dec; $[\alpha]_D^{25} +1.02$ (c 1.08, water); ir (potassium bromide): 1700, 1732 cm^{-1} (ketone and acid C=O); ¹H-nmr (deuterium oxide): δ 3.45 (d, 2H, H-7), 4.28 (t, 1H, H-6), 6.02 (s, 2H, PhCOCH₂N), 7.48 (s, 1H, H-5), 7.67-8.07 (m, H, Ph), 8.81 (s, 1H, H-2); ms: (FAB) *m/z* 274 (M + 1).

Anal. Calcd. for $C_{14}H_{15}N_3O_3 \cdot HCl \cdot HBr$: C, 43.04; H, 4.39; N, 10.76. Found: C, 42.95; H, 4.58; N, 10.72.

(*S*)-5-(Diphenylacetyl)-4,5,6,7-tetrahydro-3-(2-oxo-2-phenylethyl)-3*H*-imidazo[4,5-*c*]pyridine-6-carboxylic Acid, Methyl Ester (**8a**).

A mixture of 1,3-dicyclohexylcarbodiimide (9.3 g, 45 mmoles),

hydroxybenzotriazole hydrate (6.1 g, 45 mmoles), diphenylacetic acid (9.6 g, 45 mmoles) and acetonitrile (100 ml) was stirred at room temperature for 15 minutes to give a suspension. A mixture of **4c** (15.8 g, 42.4 mmoles), diisopropylethylamine (14.8 ml, 85 mmoles) and acetonitrile (100 ml) was stirred at room temperature for 5 minutes and then treated with the above suspension using additional acetonitrile (100 ml) to complete the transfer. The

reaction was stirred 48 hours under nitrogen. Precipitate was removed by filtration and the filtrate was evaporated. The residue was partitioned between chloroform and 0.25 *M* phosphate buffer (pH 7). The organic layer was washed with 10% sodium carbonate and phosphate buffer, dried over magnesium sulfate and evaporated. The main product was isolated by flash chromatography on silica gel, eluting first with chloroform-cyclohexane (8:2), then with chloroform, and finally with chloroform-methanol (98:2). The product fractions were pooled and evaporated. The residue was dissolved in methylene dichloride and evaporated to a foam which was dried overnight under a vacuum (0.5 mm Hg, room temperature) to give **8a** (15 g, 72%); mp 220-222°; $[\alpha]_D^{25} +12.1^\circ$ (c, 1.05 methanol); ir (potassium bromide): 1656, 1698, 1733 cm^{-1} (amide, ketone and ester C=O); ¹H nmr (dimethyl sulfoxide-*d*₆): [28] 2.56 and 2.87 (dd, 1H, H-7), 2.97 and 3.11 (d, 1H, H'-7), 3.59 and 4.22 (s, 3H, OCH₃), 4.12 and 4.22 (d, 1H, H-4), 4.81 and 4.89 (d, 1H, H'-4), 5.43-5.80 (complex, 4H, H-6, Ph₂CH, NCH₂CO), 7.26 (m, 10H, Ph), 7.47 and 7.50 (s, 1H, H-2), 7.57-7.78 (complex, 3H, Ph), 8.03 (m, 2H, Ph); ms: (EI) *m/z* 493 (M).

Anal. Calcd. for $C_{30}H_{27}N_3O_4$: C, 73.00; H, 5.52; N, 8.51. Found: C, 72.74; H, 5.31; N, 8.18.

(±)-5-(Diphenylacetyl)-4,5,6,7-tetrahydro-1-(phenylmethyl)-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylic Acid, Methyl Ester (**8d**).

The title compound was prepared by Method C from racemic **4a** base, yield, 46%, recrystallization solvent, ethyl acetate-ether, mp 127-129°; ir (potassium bromide): 1654 (amide C=O), 1739 cm^{-1} (ester C=O); ¹H nmr (deuteriochloroform): [28] δ 2.22 and 2.68 (dd, 1H, H-7), 2.95 and 3.15 (d, 1H, H'-7), 3.50 and 3.56 (s, 3H, OCH₃), 4.22 and 4.30 (d, 1H, H-4), 4.75 and 5.21 (d, 1H, H'-4), 5.00 (s, 2H, PhCH₂), 4.95 and 5.37 (s, 1H, COCHPh₂), 5.95 (d, 1H, H-6), 6.95-7.39 (m, 15H, Ph), 7.41 (s, 1H, H-2); ms: (FAB) *m/z* 466 (M + 1).

Anal. Calcd. for $C_{25}H_{27}N_3O_3$: C, 74.82; H, 5.85; N, 9.03. Found: C, 74.69; H, 6.05; N, 8.86.

(*S*)-5-Acetyl-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylic Acid, Methyl Ester, (**8e**).

Spinacine, methyl ester, dihydrochloride, hydrate **4d** (2.72 g, 0.01 mole) was first converted to the base by suspending in methylene chloride (75 ml) and adding a cold solution of ammonia in methylene chloride (75 ml, saturated with ammonia at 5-10°). After stirring for five minutes the ammonium chloride was filtered and the filtrate was concentrated at reduced pressure to remove the solvent and all of the ammonia, wt, 1.81 g (quantitative yield). The free base of **4d** was redissolved in methylene chloride (15 ml) and the solution cooled to 10°. Acetic anhydride (1.23 g, 0.012 mole) was added. The solution was allowed to warm to room temperature and after four hours ether was added until slightly turbid. The solution was treated with hydrogen chloride gas until complete precipitation of a tacky hydrochloride. After decantation, the residue was dissolved in water (5 ml) and the solution was cooled to 10°. Cold, 50% potassium carbonate (10

ml was added and the product was extracted with 20% methylene chloride-ethyl acetate, the solution dried over potassium carbonate (anhydrous) and concentrated to give crude **8e**, 1.40 g. Recrystallization was effected by dissolution in ethyl acetate (20 ml) and addition of hexane until slightly turbid. The crystals were collected by filtration, wt, 1.00 g, yield, 45%, mp 156-158°; tlc (silica gel, 2:10 methanol-chloroform, R_f 0.4 (I_2)); $[\alpha]_D^{25} + 55.8^\circ$ (c, 1.03 methanol); ir (nujol): 1655, 1740, 3150 cm^{-1} ; ^1H nmr (deuteriochloroform): [28] δ 2.23 and 2.26 (s, 3H, CH_3CO), 2.95 and 3.10 (dd, 1H, H-7), 3.32 and 3.41 (d, 1H, H'-7), 3.66 and 3.70 (s, 3H, OCH_3), 4.18 and 4.55 (d, 1H, H-4), 4.68 and 5.12 (d, 1H, H'-4), 4.92 and 5.92 (d, 1H, H-6), 7.55 (s, 1H, H-2), 11.32 (br s, 1H, NH); ms: (EI) m/z 223 (M).

Anal. Calcd. for $\text{C}_{10}\text{H}_{13}\text{N}_3\text{O}_3$: C, 53.80; H, 5.87; N, 18.83. Found: C, 53.79; H, 6.02; N, 18.87.

(±)-5-Acetyl-4,5,6,7-tetrahydro-1-(phenylmethyl)-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylic Acid, Methyl Ester, 0.90 Mole Hydrate (**8f**).

Racemic ester base **4a** (2.00 g, 0.0074 mole) was added to acetic anhydride (10 ml). A mild heat of reaction ensued as all solid went into solution. After one hour at room temperature, the excess acetic anhydride was distilled at reduced pressure. Water (25 ml) was added to the residue. After five minutes stirring, ice (10 g) was added and the solution was treated with saturated sodium bicarbonate to precipitate a solid (initially a gum), wt 2.20 g. Purification was effected by dissolution in methanol (5 ml), addition of water (15 ml) and concentration to remove methanol to give crystalline **8f**, wt 1.90 g (78%), mp 86-89°; tlc (silica gel, 1:4 methanol-chloroform) R_f 0.8; ir (potassium bromide): 1647 (amide C=O), 1744 cm^{-1} (ester C=O); ^1H nmr (dimethyl sulfoxide- d_6) δ 2.10 and 2.15 (s, 3H, COCH_3), 2.68 and 2.81 (dd, 1H, H-7), 3.09 (dd, 1H, H'-7), 3.50 and 3.54 (s, 3H, OCH_3), 5.18 (AB, 2H, PhCH_2), 7.15 (m, 2H, Ph), 7.36 (m, 3H, Ph), 7.71 and 7.75 (s, 1H, H-2); ms: (EI) m/z 313 (M).

Anal. Calcd. for $\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_3 \cdot 0.90\text{H}_2\text{O}$: C, 61.95; H, 6.31; N, 12.75; H_2O , 4.92. Found: C, 61.81; H, 6.15; N, 12.55; H_2O (KF) 4.87.

(*S*)-5-Acetyl-4,5,6,7-tetrahydro-3-(phenylmethyl)-3*H*-imidazo[4,5-*c*]pyridine-6-carboxylic Acid, Ethyl Ester (**8g**).

The title compound was prepared from **4b** free base and acetic anhydride by the same procedure used to prepare **8f**, mp 90-95°; $[\alpha]_D^{25} + 48.3^\circ$ (c, 0.57 methanol); ir (film): 1653 (amide C=O), 1734 cm^{-1} (carboxylic acid C=O); ms: (EI) m/z 327 (M).

Anal. Calcd. for $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_3 \cdot 0.5\text{H}_2\text{O}$: C, 64.26; H, 6.60; N, 12.49. Found: C, 64.62; H, 6.56; N, 12.80.

(±)-4,5,6,7-Tetrahydro-1-(phenylmethyl)-5-[(phenylmethyl)sulfonyl]-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylic Acid, Methyl Ester (**8h**).

The title compound was prepared from **4a** base by method C, yield, 64%, mp 129-131°; ir (potassium bromide): 1729, 1742 (ester C=O); ^1H nmr (deuteriochloroform): δ 2.21 (dd, 1H, H-7), 2.91 (d, 1H, H'-7), 3.61 (s, 3H, OCH_3), 4.30 (s, 2H, PhCH_2SO_2), 4.34 (d, 1H, H-4), 4.60 (d, 1H, H'-4), 4.77 (d, 1H, H-6), 4.98 (AB, 2H, PhCH_2), 7.06 (m, 2H, Ph), 7.20-7.37 (m, 8H, Ph), 7.47 (s, 1H, H-2); ms: (FAB) m/z 426 (M + 1).

Anal. Calcd. for $\text{C}_{22}\text{H}_{23}\text{N}_3\text{O}_4\text{S}$: C, 62.10; H, 5.45; N, 9.88. Found: C, 62.33; H, 5.27; N, 9.88.

(*S*)-5-(Diphenylacetyl)-1-(diphenylmethyl)-4,5,6,7-tetrahydro-1*H*-

imidazo[4,5-*c*]pyridine-6-carboxylic Acid (**10a**).

A solution of **8a** (3.0 g, 6.1 mmoles) in acetonitrile (30 ml) was treated with benzhydryl bromide (2.4 g, 6.57 mmoles) and heated at reflux under nitrogen for 8 hours. The cooled solution was added dropwise to vigorously stirred ether (450 ml) and the imidazolium salt **9a** (3.9 g, 85%) was collected by filtration. This crude material was dissolved in methanol (60 ml) and treated with acetic acid (60 ml) and zinc dust (10 g). The mixture was then sonicated for two hours while bubbling a stream of nitrogen through the reaction milieu. The excess zinc was removed by filtration and rinsed with methanol (10 ml). The combined filtrate and washings were diluted with methylene chloride and treated dropwise with 10% sodium carbonate (550 ml) while stirring vigorously. The organic layer was separated, dried over magnesium sulfate and evaporated. Tlc (silica gel, chloroform-methanol, 9:1) showed two uv-active spots: $R_f = 0.95$ (acetophenone) and $R_f = 0.65$ (**8b**). The latter product was isolated by flash chromatography on silica gel, eluting with chloroform-methanol (99.5:0.5) and evaporated from methylene chloride solution, drying under vacuum (0.5 mm Hg, room temperature, 18 hours) to give a crisp foam (1.30 g, 46%); ^1H -nmr (deuteriochloroform): [28] δ 2.60 (d, 1H, H-7), 3.05 (d, 1H, H'-7), 3.57 (s, 3H, OCH_3), 4.37 (d, 1H, H-4), 4.77 (d, 1H, H'-4), 5.40 (s, 1H, COCHPh_2), 5.94 (d, 1H, H-6), 6.39 (s, 1H, Ph_2CHN), 6.90-7.50 (m, 21H, H-2 + Ar). This ester **8b** (1.30 g, 2.4 mmoles) was dissolved in a mixture of tetrahydrofuran (10 ml) and methanol (3 ml) and treated with 1*N* sodium hydroxide (2.7 ml, 2.7 mmoles). After stirring 2 hours at room temperature the reaction mixture was diluted with water (50 ml) and washed with ether. The aqueous layer was acidified by dropwise addition of 1*N* hydrochloric acid (2.7 ml, 2.7 mmoles) and the resulting precipitate was collected by filtration, rinsing with water and ether. The solid was dried (ca 125 mm Hg, 75°, overnight) to give **10a** as a colorless powder (1.15 g, 90%), mp 157-163° (glass), 220-240° dec; $[\alpha]_D^{25} + 2.0^\circ$ (c 1.02, dimethylformamide); ir (potassium bromide): 1704 cm^{-1} (acid and amide C=O); ^1H -nmr (deuteriochloroform): [28] δ 1.89 and 2.40 (dd, 1H, H-7), 3.79 and 3.94 (d, 1H, H'-7), 3.31 (br s, H_2O), 3.99 and 4.18 (d, 1H, H-4), 4.63 and 4.88 (d, 1H, H'-4), 5.21 and 5.59 (d, 1H, H-6), 5.67 and 5.68 (s, 1H, COCHPh_2), 7.71 and 7.77 (s, 1H, Ph_2CHN), 7.00-7.40 (m, 21 H, H-2 + Ar); ms: (FAB) m/z 550 (M + Na), 528 (M + 1).

Anal. Calcd. for $\text{C}_{34}\text{H}_{29}\text{N}_3\text{O}_3 \cdot 0.33\text{H}_2\text{O}$: C, 76.52; H, 5.60; N, 7.87. Found: C, 76.62; H, 5.63; N, 7.87.

(*S*)-5-(Diphenylacetyl)-4,5,6,7-tetrahydro-1-[2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethyl]-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylic Acid (**10b**).

A solution of trifluoromethanesulfonic anhydride (6.04 ml, 35.9 mmoles) in methylene chloride (30 ml) was chilled to -75° under a nitrogen atmosphere and treated dropwise over 25 minutes with a solution composed of 1-adamantaneethanol (6.47 g, 35.9 mmoles), diisopropylethylamine (6.27 ml, 35.9 mmoles), and methylene chloride (30 ml). The resulting solution was stirred for another 15 minutes at -75° then a solution of **8a** (16.24 g, 32.8 mmoles) in methylene chloride (30 ml) was added dropwise over 30 minutes. The reaction mixture was warmed to room temperature over 5 hours then stirred for 24 hours. The resulting solution was poured into water (150 ml) and stirred vigorously for 30 minutes. The organic layer was separated, diluted with methylene chloride (100 ml), washed with water (150 ml), dried over magnesium sulfate and evaporated to give the crude im-

idazolium salt **9b** as a gum. Reductive cleavage of the phenacyl protecting group and saponification of the methyl ester **8c** as described above gave **10b** (8.40 g, 49% overall yield), mp 168-175° (glass); $[\alpha]_D^{25} + 13.7^\circ$ (c, 1.0 dimethylformamide); ir (potassium bromide): 1658, 1727 cm^{-1} (amide and acid C=O); ^1H -nmr (dimethyl sulfoxide- d_6): [28] δ 1.20-2.00 (m, 17H, alkyl), 1.35 and 2.87 (dd, 1H, H-7), 3.00 and 3.15 (d, 1H, H'-7), 3.55 (br s, H₂O), 3.84 (m, 2H, CH₂CH₂N), 3.97 and 4.20 (d, 1H, H-4), 4.74 and 4.92 (d, 1H, H'-4), 5.71 and 5.77 (s, 1H, C₆H₅), 5.39 and 5.75 (d, 1H, H-6), 7.18-7.32 (m, 8H, Ar), 7.58-7.61 (s, 1H, H-2); ms: (FAB) *m/z* 524 (M + 1).

Anal. Calcd. for C₃₃H₃₇N₃O₃·0.5H₂O: C, 74.41; H, 7.19; N, 7.89. Found: C, 74.27; H, 6.96; N, 7.72.

(*S*)-5-(Aminocarbonyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylic Acid (**10c**).

A solution of spinacine hydrate (9.25 g, 0.05 mole), potassium cyanate (8.00 g, 0.01 mole) and water (75 ml) was heated at reflux for ten minutes, cooled to 70° and glacial acetic acid (6.60 g, 0.11 mole) was added to precipitate 10.80 g of crude product. Recrystallization from hot water (200 ml) yielded 8.50 g (81%) of pure **10c**, mp 335-345°; $[\alpha]_D^{25} + 79.0^\circ$ (c, 1.22 in 0.1 *N* sodium hydroxide); ir (potassium bromide): 1610, 1660 cm^{-1} ; ^1H nmr (dimethyl sulfoxide- d_6): δ 2.50 (s, 2H, OH, NH), 2.83 (dd, 1H, H-7), 3.07 (d, 1H, H'-7), 4.15 (d, 1H, H-4), 4.43 (d, 1H, H'-4), 5.25 (m, 1H, H-6), 6.18 (s, 2H, NH₂), 7.50 (s, 1H, H-2); ms: (CI) *m/z* 193 (M + 1 - H₂O).

Anal. Calcd. for C₈H₁₀N₄O₃: C, 45.71; H, 4.80; N, 26.66. Found: C, 45.65; H, 4.84; N, 27.06.

(±)-4,5,6,7-Tetrahydro-5-[(phenylamino)carbonyl]-1-(phenylmethyl)-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylic Acid, 0.9 Mole Hydrate (**10d**).

A mixture of hydantoin **12a** (0.90 g, 2.5 mmoles), 1 *N* sodium hydroxide (10 ml, 10 mmoles) and methanol (30 ml) was heated for one-half hour at reflux. The resulting solution was concentrated at reduced pressure to remove methanol. The cooled solution was treated with glacial acetic acid (0.60 g, 10 mmoles) and the precipitated amorphous product was filtered and washed with water; wt 0.90 g. To purify, the crude solid was added to warm (40°) methanol (10 ml). Partial solution took place as crystals separated, wt 0.55 g, yield, 59% (of 0.9 mole hydrate), mp, softens 100°, resolidifies and melts at 270-280°; ir (potassium bromide): 1655, 1740 cm^{-1} .

Anal. Calcd. for C₂₁H₂₀N₄O₃·0.9H₂O: C, 64.24; H, 5.60; N, 14.27; H₂O, 4.13. Found: C, 64.20; H, 5.55; N, 14.22; H₂O (KF), 3.97.

(*S*)-4,5,6,7-Tetrahydro-5-[[1-(methylethyl)amino]carbonyl]-3-(phenylmethyl)-3*H*-imidazo[4,5-*c*]pyridine-6-carboxylic Acid (**10e**).

The title compound was prepared by Method **D** starting from **3d**, mp 188-190°, yield 40%, $[\alpha]_D^{25} + 70.9^\circ$ (c, 1.00 methanol); ir (potassium bromide): 1638, 1719 cm^{-1} ; ^1H nmr (dimethyl sulfoxide- d_6): δ 1.08 (t, 6H, *i*-Pr CH₃), 2.81 (dd, 1H, H-7), 3.05 (d, 1H, H'7), 3.81 (m, 1H, *i*-Pr CH), 4.09 (d, 1H, H-4), 4.55 (d, 1H, H'-4), 5.13 (q, 2H, PhCH₂), 5.25 (m, 1H, H-6), 6.35 (d, 1H, NH), 7.15 (m, 2H, Ph), 7.35 (m, 3H, Ph), 7.68 (s, 1H, H-2); ms: (EI) *m/z* 342 (M).

Anal. Calcd. for C₁₈H₂₂N₄O₃: C, 63.14; H, 6.48; N, 16.36. Found: C, 63.29; H, 6.17; N, 16.29.

(*S*)-4,5,6,7-Tetrahydro-5-[(phenylamino)carbonyl]-3*H*-imidazo-

[4,5-*c*]pyridine-6-carboxylic Acid (**10f**).

The title compound was prepared by Method **D** from spinacine hydrate **1** and phenyl isocyanate using methanol in the reaction medium. Precautions were taken on neutralization of the basic reaction solution. To prevent cyclization to the hydantoin, the reaction solution was cooled to 15° and neutralized with 1.2 equivalents of glacial acetic acid (corresponding to amount of sodium hydroxide of hydrolysis) to precipitate the product. Purification was effected by dissolution in 1.2 equivalents of 0.05 *N* sodium hydroxide, clarification with "celite", filtration and precipitation of the product with a slight excess (1.5 equivalents) of glacial acetic acid; yield, 80%, mp 138-140° dec; $[\alpha]_D^{25} + 38.7^\circ$ (c, 1.00 dimethylformamide); ir (potassium bromide): 1640 cm^{-1} ; ms: (CI) *m/z* 269 (M + 1 - H₂O).

Anal. Calcd. for C₁₄H₁₄N₄O₃·2H₂O: C, 52.17; H, 5.63; N, 17.38; H₂O, 11.18. Found: C, 52.35; H, 5.51; N, 17.55; H₂O (KF) 10.95.

(*S*)-5-Acetyl-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridine-6-carboxylic Acid, Hydrochloride (**10g**).

The title compound was prepared from **8e** by method **E**. The hydrochloride salt was prepared from the free amino acid (from the ion exchange column) by suspending in methanol and treating with hydrogen chloride gas. Ether was added to the resulting solution to precipitate crystalline **10g**, yield, 46%, recrystallization solvent, methanol-ether, mp 261-163° dec; $[\alpha]_D^{25} + 58.9^\circ$ (c, 1.09 methanol); ir (potassium bromide): 1664 (amide C=O), 1734 cm^{-1} (carboxylic acid C=O); ^1H nmr (dimethyl sulfoxide- d_6): [28] δ 2.16 and 2.19 (s, 3H, COCH₃), 2.90-2.30 (complex, 2H, H-7), 3.92 and 4.48 (d, 1H, H-4), 4.86 and 5.02 (d, 1H, H'-4), 5.27 and 5.71 (d, 1H, H-6), 8.99 and 9.01 (s, 1H, H-2), 14.30 (br s, 1H, NH); ms: (EI) *m/z* 209 (M).

Anal. Calcd. for C₈H₁₁N₃O₃·HCl: C, 44.00; H, 4.93; N, 17.10. Found: C, 44.00; H, 4.94; N, 16.85.

(*S*)-5-Benzoyl-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridine-6-carboxylic Acid (**10h**).

This compound was prepared by Method **D** from spinacine hydrate **1** and benzoyl chloride using dioxane in the reaction medium; yield, 42%, recrystallization solvent, methanol-ether, mp 240-242° dec; $[\alpha]_D^{25} - 36.7^\circ$ (1.06 in 0.1 *N* sodium hydroxide); ir (potassium bromide): 1630, 1640, 1670 cm^{-1} ; ^1H nmr (dimethyl sulfoxide- d_6): [28] δ 2.88-3.00 (complex, 2H, H-7), 4.22 (t, 1H, H-4), 4.48 and 4.96 (d, 1H, H'-4), 4.65 and 5.72 (d, 1H, H-6), 7.45 (m, 5H, Ph), 7.60 and 7.71 (s, 1H, H-2), 10.90 (br s, 2H, NH, OH); ms: (CI) *m/z* 272 (M + 1).

Anal. Calcd. for C₁₄H₁₃N₃O₃: C, 61.99; H, 4.83; N, 15.49. Found: C, 61.83; H, 4.92; N, 15.30.

(*S*)-3,4,6,7-Tetrahydro-5*H*-imidazo[4,5-*c*]pyridine-5,6-dicarboxylic Acid, 5-Phenylmethyl Ester (**10i**) [5-(Benzoyloxycarbonyl)spinacine].

The title compound was prepared by Method **D** from spinacine hydrochloride **1** and benzyl chloroformate, yield 17%, recrystallization solvent, (compound was purified by dissolution in an equivalent amount of 1*N* sodium hydroxide and precipitation with an equivalent amount of glacial acetic acid), mp 251-253° dec; $[\alpha]_D^{25} + 36.2^\circ$ (1.05 glacial acetic acid); ir (potassium bromide): 1700 cm^{-1} (carbamic ester and carboxylic acid C=O); ^1H nmr (dimethyl sulfoxide- d_6): δ 2.95 (dd, 1H, H-7), 3.12 (d, 1H, H'-7), 4.20 and 4.32 (d, 1H, H-4), 4.65 (t, 1H, H'-4), 5.19 (s, 3H, PhCH₂ and H-6), 7.25-7.48 (m, 5H, Ph), 7.62 (s, 1H, H-2), 11.62 (br

s, 2H, NH, OH); ms: (EI) m/z 302 ($M + 1$).

Anal. Calcd. for $C_{15}H_{15}N_3O_4$: C, 59.79; H, 5.02; N, 13.95. Found: C, 59.73; H, 4.98; N, 13.95.

(\pm)-5-Acetyl-4,5,6,7-tetrahydro-1-(phenylmethyl)-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylic Acid (**10j**).

The title compound was prepared by Method **E** starting from racemic **8f**, yield, 58%, recrystallization solvent, 2-propanol, mp 225-227°; ir (potassium bromide): 1652 (amide C=O), 1717 cm^{-1} (carboxylic acid C=O); 1H nmr (dimethyl sulfoxide- d_6): [28] δ 2.10 and 2.13 (s, 3H, COCH₃), 2.60 and 2.75 (dd, 1H, H-7), 3.15 (dd, 1H, H'-7), 3.88 and 4.38 (d, 1H, H-4), 4.58 and 4.80 (d, 1H, H'-4), 5.12 (m, 2H, PhCH₂), 5.27 and 5.60 (d, 1H, H-6), 7.19 (m, 2H, Ph), 7.35 (m, 3H, Ph), 7.72 and 7.75 (s, 1H, H-2); ms: (EI) m/z 299 (M).

Anal. Calcd. for $C_{16}H_{17}N_3O_3$: C, 64.20; H, 5.73; N, 14.04. Found: C, 63.95; H, 5.78; N, 14.17.

(\pm)-5-Benzoyl-4,5,6,7-tetrahydro-1-(phenylmethyl)-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylic Acid (**10k**).

The title compound was prepared by Method **D** starting from racemic **3c** dihydrochloride and benzoyl chloride using dioxane in the reaction medium, yield, 39%, recrystallization solvent, methanol, mp 236-238°; ir (potassium bromide): 1640 (amide C=O), 1725 cm^{-1} (carboxylic acid C=O); 1H nmr (dimethyl sulfoxide- d_6): [28] δ 2.81 (m, 1H, H-7), 3.16 (dd, 1H, H'-7), 4.18 (t, 1H, H-4), 4.43 and 4.92 (d, 1H, H'-4), 4.72 and 5.72 (d, 1H, H-6), 5.18 (t, 2H, PhCH₂), 7.08-7.58 (m, 10 H, Ph), 7.72 and 7.79 (s, 1H, H-2); ms: (EI) m/z 361 (M).

Anal. Calcd. for $C_{21}H_{21}N_3O_3$: C, 69.79; H, 5.30; N, 11.63. Found: C, 69.72; H, 5.29; N, 11.61.

(\pm)-1,4,6,7-Tetrahydro-1-(phenylmethyl)-5*H*-imidazo[4,5-*c*]pyridine-5,6-dicarboxylic Acid, 5-Phenylmethyl Ester, 0.25 Mole Hydrate (**10l**).

The title compound was prepared by Method **D** starting from racemic **3c** and benzyl chloroformate using dioxane in the reaction medium, yield, 56%, recrystallization solvent, methanol-water, mp 123-127°; ir (potassium bromide): 1700 cm^{-1} (carbamic ester and carboxylic acid C=O); 1H nmr (dimethyl sulfoxide- d_6): δ 2.72 (dd, 1H, H-7), 3.12 (d, 1H, H'-7), 4.15 (dd, 1H, H-4), 4.55 (t, 1H, H'-4), 5.16 (m, 5H, PhCH₂N, PhCH₂O, H-6), 7.15 (d, 2H, Ph), 7.20-7.45 (m, 8H, Ph), 7.71 (s, 1H, H-2); ms: (CI) m/z 392 ($M + 1$).

Anal. Calcd. for $C_{22}H_{21}N_3O_4 \cdot 0.25H_2O$: C, 66.74; H, 5.47; N, 10.61. Found: C, 67.03; H, 5.44; N, 10.60.

(\pm)-4,5,6,7-Tetrahydro-5-[(methylphenylamino)carbonyl]-1-(phenylmethyl)-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylic Acid, 0.25 Mole Hydrate (**10m**).

The title compound was prepared by Method **C** and then **E** starting from racemic **4a** base and *N*-methyl-*N*-phenylcarbamoyl chloride, overall yield, 55%, recrystallization solvent, ethyl acetate, mp 192-195° dec; ir (potassium bromide): 1641 (urea C=O), 1725 cm^{-1} (carboxylic acid C=O); 1H nmr (dimethyl sulfoxide- d_6): [28] δ 2.38 (dd, 1H, H-7), 2.97 (d, 1H, H'-7), 3.12 (s, 3H, NCH₃), 3.35 (br s., 1H, OH), 3.78 and 4.02 (d, 2H, H-4), 4.90 (m, 1H, H-6), 5.10 (AB, 2H, PhCH₂), 7.15 (m, 3H, Ph), 7.32 (m, 7H, Ph), 7.63 (s, 1H, H-2); ms: (EI) m/z 390 (M).

Anal. Calcd. for $C_{22}H_{22}N_4O_3 \cdot 0.25H_2O$: C, 66.90; H, 5.74; N, 14.19; H₂O, 1.14. Found: C, 67.08; H, 6.04; N, 14.09; H₂O (KF), 1.53.

(\pm)-5-(Diphenylacetyl)-4,5,6,7-tetrahydro-1-(phenylmethyl)-1*H*-

imidazo[4,5-*c*]pyridine-6-carboxylic Acid (**10n**).

The title compound was prepared by Method **E** from racemic **8d**, yield 68%, recrystallization solvent, methanol-ether, mp 167-169°; ir (potassium bromide): 1652 (amide C=O), 1726 cm^{-1} (carboxylic acid C=O); 1H nmr (dimethyl sulfoxide- d_6): [28] δ 2.12 and 2.66 (dd, 1H, H-7), 3.08 (dd, 1H, H'-7), 4.02 and 4.25 (d, 1H, H-4), 4.68 and 4.95 (d, 1H, H'-4), 5.00-5.32 (m, 2H, H-6 and COCHPh₂), 5.72 (t, 2H, PhCH₂), 7.05-7.40 (m, 15H, Ph), 7.70 (s, 1H, H-2); ms: (EI) m/z 451 (M).

Anal. Calcd. for $C_{28}H_{25}N_3O_3$: C, 74.48; H, 5.58; N, 9.31. Found: C, 74.31; H, 5.48; N, 9.17.

(\pm)-4,5,6,7-Tetrahydro-1-(phenylmethyl)-5-[(phenylmethyl)sulfonyl]-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylic Acid (**10o**).

The title compound was prepared by Method **E** from **8h**, yield, 88%, mp 190-192°; ir (potassium bromide): 1620, 1724 cm^{-1} , (carboxylic acid C=O); ms: (CI) m/z 412.2 ($M + 1$).

Anal. Calcd. for $C_{21}H_{21}N_3O_4S$: C, 61.30; H, 5.15; N, 10.21. Found: C, 61.28; H, 5.29; N, 9.97.

(\pm)-4,5,6,7-Tetrahydro-5-(phenylacetyl)-1-(phenylmethyl)-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylic Acid (**10p**).

The title compound was prepared by Method **D** from (\pm)-**3c** and phenylacetyl chloride with dioxane as the organic phase, yield, 5%, mp 221-223°; ir (potassium bromide): 1650, 1740 cm^{-1} ; ms: (EI) m/z 375 (M).

Anal. Calcd. for $C_{22}H_{21}N_3O_3$: C, 70.38; H, 5.64; N, 11.19. Found: C, 70.35; H, 5.66; N, 11.03.

(*S*)-5-Benzoyl-4,5,6,7-tetrahydro-3-(phenylmethyl)-3*H*-imidazo[4,5-*c*]pyridine-6-carboxylic Acid (**10q**).

The title compound was prepared by Method **D** from **3d** and benzoyl chloride, yield, 39%, recrystallization solvent, methanol-water, mp 233-235°; $[\alpha]_D^{25}$ -11.4° (1.12 in 0.1 *N* sodium hydroxide); ir (potassium bromide): 1628 (amide C=O), 1720 cm^{-1} (carboxylic acid C=O); ms: (EI) m/z 361 (M).

Anal. Calcd. for $C_{21}H_{19}N_3O_3$: C, 69.79; H, 5.30; N, 11.63. Found: C, 69.83; H, 5.60; N, 11.67.

(*S*)-8a,9-Dihydro-7-phenyl-3*H*-diimidazo[1,5-*a*:4',5'-*d*]pyridine-6,8-(4*H*,7*H*)-dione, 0.75 Mole Hydrate (**11a**).

Phenyl isocyanate (5.95 g, 0.05 mole) was added to a mixture of **4d** (12.70 g, 0.05 mole), dimethylformamide (150 ml) and triethylamine (15.19 g, 0.05 mole). The mixture was stirred at room temperature for two hours. The triethylamine hydrochloride was filtered and the filtrate was concentrated at reduced pressure. Water (200 ml) was added to give crude **11a** which was recrystallized from methanol-water, yield 69%, mp 133-136°; $[\alpha]_D^{25}$ -201.3° (1.05 methanol); ir (potassium bromide): 1720, 1775 cm^{-1} ; 1H nmr (dimethyl sulfoxide- d_6): δ 2.89-3.15 (complex, 2H, H-9), 4.25 (d, 1H, H-4), 4.59 (m, 1H, H-8a), 4.76 (d, 1H, H'-4), 7.35-7.55 (m, 5H, Ph), 7.66 (s, 1H, H-2); ms: (EI) m/z 268 (M).

Anal. Calcd. for $C_{14}H_{12}N_4O_2 \cdot 0.75H_2O$: C, 59.69; H, 4.80; N, 19.89; H₂O, 4.80. Found: C, 59.45; H, 4.88; N, 19.87; H₂O (KF) 5.17.

(*S*)-8a,9-Dihydro-1*H*-diimidazo[1,5-*a*:4',5'-*d*]pyridine-6,8-(4*H*,7*H*)-dione, Monohydrochloride (**11b**).

A solution of **10c** (4.00 g, 0.019 mole) in concentrated hydrochloric acid (20 ml) was heated at reflux for fifteen minutes and concentrated to dryness at reduced pressure. The residue

was heated with methanol (100 ml) to the boiling point, ether (20 ml) was added to give 4.00 g of pure **11b**, yield 92%, mp 315-325°; $[\alpha]_D^{25}$ -138.1° (c, 1.08 water); ir (potassium bromide): 1640, 1690, 1725, 1745 cm^{-1} ; ^1H nmr (deuterium oxide): δ 3.05 (m, 1H, H-9), 3.35 (dd, 1H, H'-9), 4.42 (d, 1H, H-4), 4.62 (q, 1H, H-8a), 4.88 (br s, 3H, H₂O), 5.02 (d, 1H, H'-4), 8.70 (s, 1H, H-2); ms: (EI) m/z 192 (M).

Anal. Calcd. for $\text{C}_8\text{H}_8\text{N}_4\text{O}_2 \cdot \text{HCl}$: C, 42.02; H, 3.97; N, 24.51. Found: C, 41.80; H, 3.98; N, 24.51.

8a,9-Dihydro-7-phenyl-1-(phenylmethyl)-1*H*-diimidazo[1,5-*a*:4',5'-*d*]pyridine-6,8(4*H*,7*H*)-dione (**12a**) and 8a,9-Dihydro-7-phenyl-3-(phenylmethyl)-1*H*-diimidazo[1,5-*a*:4',5'-*d*]pyridine-6,8(4*H*,7*H*)-dione (**12b**).

Benzyl bromide (17.40 g, 0.10 mole) was added to a solution of **11a** (27.30 g, 0.10 mole) in dimethylformamide (60 ml) containing 20% tetramethylammonium hydroxide-in-methanol (46.50 g, 0.102 moles). After one-half hour the separated solids were filtered, washed with dimethylformamide (50 ml) and then water (200 ml) to give 13.70 g of **12a** as the least soluble isomer. Pure **12a**, 9.20 g, was obtained by recrystallization from dimethylformamide, yield, 25%, mp 277-279°; ir (potassium bromide): 1720, 1775 cm^{-1} ; ^1H nmr (trifluoroacetic acid): δ 3.05 (dd, 1H, H-9), 3.55 (dd, 1H, H'-9), 4.61 (d, 1H, H-4), 4.82 (q, 1H, H-8a), 5.35 (d, 1H, H'-4), 5.47 (AB, 2H, PhCH_2), 7.32 (m, 4H, Ph), 7.52 (m, 6H, Ph), 7.68 (s, 1H, H-2); ms: (EI) m/z 358 (M).

Anal. Calcd. for $\text{C}_{21}\text{H}_{18}\text{N}_4\text{O}_2$: C, 70.38; H, 5.06; N, 15.63. Found: C, 70.14; H, 5.19; N, 15.56.

Isolation of Regioisomer **12b**.

Water (200 ml) was added to the above dimethylformamide reaction filtrate to precipitate a crude solid. The dried solid was triturated with acetone (ca. 200 ml) and the mixture was filtered. The filtrate was concentrated and the residue was recrystallized from dimethylformamide to give pure **12b**, mp 227-229°; $[\alpha]_D^{25}$ 0.00° (c, 1.00 *N* hydrochloric acid); ir (potassium bromide): 1716, 1775 cm^{-1} ; ^1H nmr (trifluoroacetic acid): δ 3.15 (dd, 1H, H-9), 3.55 (dd, 1H, H'-9), 4.20 (d, 1H, H-4), 4.70 (m, 1H, H-8a), 5.05 (d, 1H, H'-4), 5.35 (AB, 2H, PhCH_2), 7.25 (m, 4H, Ph), 7.42 (m, 6H, Ph), 8.56 (s, 1H, H-2); ms: (EI) m/z 358 (M).

Anal. Calcd. for $\text{C}_{21}\text{H}_{18}\text{N}_4\text{O}_2$: C, 70.38; H, 5.06; N, 15.63. Found: C, 70.41; H, 5.07; N, 15.73.

(*S*)-8a,9-Dihydro-7-(1-methylethyl)-3-phenylmethyl-3*H*-diimidazo[1,5-*a*:4',5'-*d*]pyridine-6,8(4*H*,7*H*)-dione, Hydrochloride (**12c**).

The title compound was prepared by cyclization of **10e** with concentrated hydrochloric acid at 100° for fifteen minutes, yield, 94%, mp 246-248°; $[\alpha]_D^{25}$ -151.6° (c, 1.05 methanol); ^1H nmr (dimethyl sulfoxide-*d*₆): δ 1.31 (t, 6H, *i*-Pr CH₃), 2.87 (dd, 1H, H-9), 3.15 (dd, 1H, H'-9), 4.07 (d, 1H, H-4), 4.15 (m, 1H, *i*-Pr CH), 4.35 (m, 1H, H-8a), 4.75 (d, 1H, H'-4), 5.54 (s, 2H, PhCH_2), 7.43 (s, 5H, Ph), 9.39 (s, 1H, H-2); ms: (EI) m/z 324 (M).

Anal. Calcd. for $\text{C}_{18}\text{H}_{20}\text{N}_4\text{O}_2 \cdot \text{HCl}$: C, 59.91; H, 5.87; N, 15.53. Found: C, 60.29; H, 5.76; N, 15.33.

(*S*)-4,5,6,7-Tetrahydro-3*H*-imidazo[4,5-*c*]pyridine-6-carboxamide, Hydrochloride (**13a**) (Spinacine Amide).

A solution of **4d** (18.00 g, 0.10 mole) and concentrated ammonium hydroxide (120 ml) was heated on the steam bath for ten minutes. Additional ammonium hydroxide (20 ml) was added and heating was continued for ten more minutes. A third portion of

ammonium hydroxide was added and after another fifteen minutes the excess ammonia and water were distilled at reduced pressure. The residue was triturated with methanol and filtered to give 13.00 g of crude **13a**. Recrystallization from water-2-propanol gave 8.40 g (41%) of pure **13a** as the hydrochloride, mp 259-261°; $[\alpha]_D^{25}$ -127.9° (c, 1.03 water); ir (potassium bromide): 1613, 1629, 1685, 3370 cm^{-1} ; ^1H nmr (deuterium oxide): δ 3.05 (dd, 1H, H-7), 3.28 (dd, 1H, H'-7), 4.13-4.38 (complex, 3H, H-6, H-4), 4.90 (s, H₂O), 8.17 (s, 1H, H-2); ms: (EI) m/z 166 (M).

Anal. Calcd. for $\text{C}_7\text{H}_{10}\text{N}_4\text{O} \cdot \text{HCl}$: C, 41.49; H, 5.47; N, 27.65; Cl, 17.50. Found: C, 41.60; H, 5.50; N, 27.83; Cl, 17.35.

(±)-4,5,6,7-Tetrahydro-1-(phenylmethyl)-1*H*-imidazo[4,5-*c*]pyridine-6-carboxamide (**13b**).

A solution of **4a** base (5.00 g, 0.018 mole), methanol (20 ml) and concentrated ammonium hydroxide (40 ml) was allowed to stand at room temperature for two hours. The separated crystals were filtered and recrystallized from methanol-ether to give 2.80 g of pure **13b**, yield 61%, mp 212-214°; ir (potassium bromide): 1681 cm^{-1} (amide C=O); ^1H nmr (dimethyl sulfoxide-*d*₆ + deuterium oxide): 2.38 (dd, 1H, H-7), 2.63 (dd, 1H, H'-7), 3.32 (q, 1H, H-6), 3.57 (s, H₂O), 3.65 (m, 2H, H-4), 5.10 (s, 2H, PhCH_2), 7.18 (d, 2H, Ph), 7.35 (m, 3H, Ph), 7.63 (s, 1H, H-2); ms: (EI) m/z 256 (M).

Anal. Calcd. for $\text{C}_{14}\text{H}_{16}\text{N}_4\text{O}$: C, 65.60; H, 6.29; N, 21.86. Found: C, 65.32; H, 6.02; N, 21.65.

(*S*)-4,5,6,7-Tetrahydro-5-methyl-3-(phenylmethyl)-3*H*-imidazo[4,5-*c*]pyridine-6-carboxylic Acid (**14**).

A mixture of the free amino acid **3d** (2.00 g, 7.80 mmoles) and 37% aqueous formaldehyde (5.40 g, 60 mmoles) was warmed on the steam bath to dissolved solids. A quantity of 95-97% formic acid (60 ml) was added. The solution was heated on the steam bath for three hours and concentrated to near dryness at reduced pressure. The dihydrochloride was prepared by dissolving the residue in warm 2-propanol (100 ml), treating with excess hydrogen chloride gas and adding ethyl acetate. The precipitated hygroscopic salt was filtered and dissolved in 50 ml of methanol. Ethyl acetate was added to turbidity. The crystals that separated were filtered and washed with ether acetate, wt 1.59 g, yield, 59%, mp 234-236° dec; $[\alpha]_D^{25}$ -2.1° (c, 1.05 water) (possible racemization); ir (potassium bromide): 1741 cm^{-1} (carboxylic acid C=O); ^1H nmr (dimethyl sulfoxide-*d*₆): δ 2.60 and 2.69 (s, 3H, NCH_3), 3.08 (dd, 1H, H-7), 3.19 (dd, 1H, H'-7), 3.99-4.10 (m, 2H, H-4), 4.30 (m, 1H, H-6), 5.45 and 5.52 (s, 2H, PhCH_2), 7.25-7.45 (s, 1H, H-2); ms: (EI) m/z 271 (M).

Anal. Calcd. for $\text{C}_{13}\text{H}_{17}\text{N}_3\text{O}_2 \cdot 2\text{HCl}$: C, 52.33; H, 5.56; N, 12.21. Found: C, 52.16; H, 5.68; N, 11.98.

(±)-4,5,6,7-Tetrahydro-1,5-bis(phenylmethyl)-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylic Acid, Methyl Ester (**15**).

A solution of racemic **4a** base (2.00 g, 0.0076 mole), acetonitrile (20 ml), triethylamine (0.84 g, 0.008 mole) and benzyl bromide (1.28 g, 0.0076 mole) was allowed to stand at room temperature for four days. The solvent was removed, water (10 ml) was added and the product was extracted with ethyl acetate. Recrystallization from ethyl acetate-petroleum ether gave 0.82 g of **15**, yield 30%, mp 91-93°; ir (liquid film): 1728 cm^{-1} (ester C=O); ^1H nmr (deuteriochloroform): δ 2.71 (dd, 1H, H-7), 2.88 (dd, 1H, H'-7), 3.63 (s, 3H, OCH_3), 3.70-4.05 (m, 5H, H-4, H-6, PhCH_2N), 5.02 (s, 2H, $\text{PhCH}_2\text{N}'$), 7.08 (d, 2H, Ph), 7.15-7.40 (m, 8H, Ph), 7.42 (s, 1H, H-2); ms: (EI) m/z 361 (M).

Anal. Calcd. for $C_{22}H_{23}N_3O_2$: C, 73.11; H, 6.41; N, 11.63. Found: C, 73.19; H, 6.17; N, 11.59.

(±)-4,5,6,7-Tetrahydro-5-[(methylphenylamino)carbonyl]-1-(phenylmethyl)-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylic Acid (**16**).

A solution of **15** (1.00 g, 0.0028 mole), methanol (10 ml) and 1 *N* sodium hydroxide (4.0 ml) was heated at reflux for fifteen minutes. The methanol was removed and 2 *N* hydrochloric acid (2.0 ml) was added to precipitate crude **16**. Recrystallization from methanol gave 0.26 g of pure **16**, yield 27%, mp 220-222°; ir (potassium bromide): 1633, 1708 cm^{-1} (carboxylic acid C=O); 1H nmr (dimethyl sulfoxide- d_6): 2.68 (dd, 1H, H-7), 2.87 (d, 1H, H'-7), 3.48 (d, 1H, H-4), 3.73 (d, 1H, H'-4), 3.76 (m, 1H, H-6), 3.92 (AB, 2H, $PhCH_2N$), 5.14 (AB, 2H, $PhCH_2N^{im}$), 7.20-7.41 (m, 10H, Ph), 7.65 (s, 1H, H-2); ms: (CI) m/z 348 ($M + 1$).

Anal. Calcd. for $C_{21}H_{21}N_3O_2$: C, 72.60; H, 6.09; N, 12.01. Found: C, 72.32; H, 6.35; N, 11.95.

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- [27] See Scheme I for numbering system of histidine derivatives.
- [28] The nmr spectra of compounds with an acyl group in the 5-position often show a doubling-up of peaks due to *E* and *Z* conformers. Spectra run at 70-100° in DMSO- d_6 show a coalescence of the double peaks.
- [29] 1-Substituted histidines afford 3-substituted spinacines on treatment with formaldehyde. Similarly, 3-substituted histidines give 1-substituted spinacines.