sodium 2-ethylhexanoate (ca. 0.2 g). The mixture was then evaporated and 2-propanol was added to the residue giving a white solid which was collected by filtration, washed twice with 2-propanol, and dried under vacuum to give the sodium salt 11 (0.12 g, 79%) as a white powder which decomposed on attempted melting point determination: UV ($H_2O$) 292 nm ($\epsilon$ 20100); IR (KBr) 1765, 1740, 1663, 1620 $cm^{-1}$; NMR ($Me_2SO$-$d_6$) 1.97 (s, 3 H, OAc), 3.44 (s, 2 H, 2-$CH_2$), 3.73 (s, 2 H, thiophene methylene), 4.53 (d, $J$ = 6 Hz, 2 H, 3'-$CH_2$), 4.98 (d, $J$ = 4.5 Hz, 1 H, 6-H), 5.48 (dd, $J$ = 4.5, 9 Hz, 1 H, 7-H), 5.65 (dt, $J$ = 16, 6 Hz, 1 H, 2'-H), 6.8–7.0 (m, 2 H, thiophene), 7.06 (d, $J$ = 16 Hz, 1 H, 1'-H), 7.2–7.5 (m, 1 H, thiophene), 9.06 (d, $J$ = 9 Hz, 1 H, NH).

**Sodium 3-[3-(1-Methyltetrazol-5-ylthio)prop-1-*trans*-enyl]-7$\beta$-[2-(2-thienyl)acetamido]-3-cephem-4-carboxylate (12). Method A.** The ester **10** (0.2 g) was deprotected, and the sodium salt of the resulting acid was prepared as described above for the ester **9**. Obtained was 0.11 g (71%) of the sodium salt **12** as a white powder which decomposed on attempted melting point determination: UV ($H_2O$) 296 nm ($\epsilon$ 20100); IR (KBr) 1760, 1660, 1600 $cm^{-1}$; NMR ($Me_2SO$-$d_6$) 3.4 (br s, 2 H, 2-$CH_2$), 3.75 (s, 2 H, thiophene methylene), 3.92 (s, 3 H, NMe), 4.00 (d, $J$ = 7.5 Hz, 2 H, 3'-$CH_2$), 4.97 (d, $J$ = 5 Hz, 1 H, 6-H), 5.47 (dd, $J$ = 5, 9 Hz, 1 H, 7-H), 5.71 (dt, $J$ = 15, 7.5 Hz, 1 H, 2'-H), 6.8–7.0 (m, 2 H, thiophene), 7.10 (d, $J$ = 15 Hz, 1 H, 1'-H), 7.25–7.4 (m, 1 H, thiophene), 9.06 (d, $J$ = 9 Hz, 1 H, NH).

**Method B.** A solution of the acetate **11** (0.1 g, 0.22 mmol), 5-mercapto-1-methyltetrazole (30 mg, 0.26 mmol), and sodium bicarbonate (25 mg, 0.3 mmol) in water (10 mL) was stirred at 50 °C for 8 h. The pH of the cooled mixture was adjusted to 2 with dilute HCl, and the mixture was extracted twice with EtOAc. The combined extracts were washed with brine, dried ($Na_2SO_4$), and evaporated, giving the crude acid as an amorphous solid. This was dissolved in EtOAc (4 mL) and an excess of sodium 2-ethylhexanoate (ca. 0.1 g) was added. The mixture was stirred for 15 min and the white solid which separated was collected by filtration, washed twice with 2-propanol, and dried under vacuum, giving 75 mg (67%) of the sodium salt **12** as a white powder, identical with the material obtained using method A.

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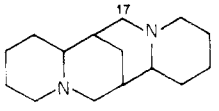
# Analogues of Sparteine. 5. Antiarrhythmic Activity of Selected N,N'-Disubstituted Bispidines

Peter C. Ruenitz* and Corwin M. Mokler

*Departments of Medicinal Chemistry and Pharmacology, School of Pharmacy, The University of Georgia, Athens, Georgia 30602.* *Received June 20, 1977*

A series of seven N,N'-disubstituted bispidines, structurally analogous to the inner (B and C) rings of sparteine (1) and encompassing a range of lipophilicity in which 1 was centered, has been compared to 1 in regard to antiarrhythmic potency and acute toxicity. Several of the bispidines were of comparable potency, and all but one were somewhat less toxic than 1. The ability of the mononitrate salts of 1 and bispidines **6** and **7** to bind calcium and magnesium cations in $Me_2SO$-$d_6$ solvent has been evaluated by proton magnetic resonance analysis. No binding could be demonstrated under these conditions, which suggested that pharmacologic effects of these compounds may be due to properties other than direct binding of these cations.

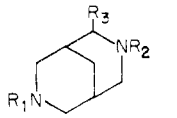
Sparteine (**1**), one of the more common quinolizidine alkaloids, has been used in the management of cardiac arrhythmias.[1] Its antiarrhythmic activity as well as its



**1**

effects on uterine and skeletal muscle appears to be due to a "stabilizing" effect on muscle cell membrane function.[2]

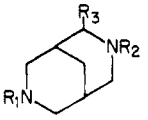
The two inner rings of sparteine constitute the 3,7-diazabicyclo[3.3.1]nonane (bispidine[3]) moiety. We have prepared several N,N'-disubstituted bispidines **2–8**, whose chemical and physical similarity to **1** warranted their evaluation as antiarrhythmics. Compounds were chosen for this study which appeared to encompass a significant range of lipophilicity in which **1** would be approximately centered. We took this approach since a study of the comparative antiarrhythmic effects of **1** and a series of 17-alkyl analogues had indicated that activity was dependent not only on the presence of a protonated amino group but also on lipophilicity.[4] Other reports have also emphasized the influence of this property in determining potency.[5]



| | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| 2 | $CH_3$ | $n$-$C_4H_9$ | H |
| 3 | $CH_3$ | $CH_3$ | $i$-$C_3H_7$ |
| 4 | $CH_3$ | $CH_2Ph$ | H |
| 5 | $n$-$C_4H_9$ | $n$-$C_4H_9$ | H |
| 6 | $n$-$C_4H_9$ | $CH_2Ph$ | H |
| 7 | $CH_2Ph$ | $CH_2Ph$ | H |
| 8 | $CH_3$ | $CHPh_2$ | H |

Lipophilicity (hydrophobicity) has been measured in series of compounds such as this by determination or calculation[6] of apparent or intrinsic octanol–water partition coefficients.[7] In this paper, we report the results of an-

Table I. Antiarrhythmic Potencies and Toxicities of N,N'-Disubstituted Bispidines




| Compd | $R_1$ | $R_2$ | $R_3$ | Log $D_{7.4}$ | Potency, μmol/kg ip | | Toxicity, μmol/kg ip | | Therapeutic index[h] |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | $N$[g] | $ED_{50}$ | $N$[g] | $LD_{50}$ | |
| 2[a] | $CH_3$ | $n$-$C_4H_9$ | H | −3.39 | 18 | 192 (182-202)[f] | 6 | 207 (193-222)[f] | 1.08 |
| 3[b] | $CH_3$ | $CH_3$ | $i$-$C_3H_7$ | −3.40 | 14 | 191 (182-200) | 10 | 279 (267-293) | 1.46 |
| 4[c] | $CH_3$ | $CH_2Ph$ | H | −2.57 | 15 | 154 (146-162) | 11 | 189 (181-198) | 1.23 |
| 5[d] | $n$-$C_4H_9$ | $n$-$C_4H_9$ | H | −2.07 | 14 | 170 (164-176) | 7 | 196 (180-212) | 1.23 |
| 1[e] | (sparteine) | | | −1.57 ± 0.20[f] | 17 | 150 (141-159) | 16 | 134 (133-136) | 0.89 |
| 6[d] | $n$-$C_4H_9$ | $CH_2Ph$ | H | −1.22 ± 0.05 | 8 | 159 (150-170) | 7 | 198 (182-217) | 1.25 |
| 7[d] | $CH_2Ph$ | $CH_2Ph$ | H | −0.43 | 19 | 160 (154-166) | 15 | 199 (188-210) | 1.24 |
| 8[d] | $CH_3$ | $CHPh_2$ | H | −0.43 ± 0.13 | 10 | 259 (241-277) | 5 | 225 (216-234) | 0.87 |
| Disopyramide | | | | | 13 | 60 (54-66) | 16 | 504 (497-511) | 8.40 |
| Propranolol[d] | | | | | 9 | 100 (87-114) | 12 | 406 (393-419) | 4.06 |

[a] Monohydrobromide salt. [b] Dihydrochloride salt. [c] Monomesylate salt. [d] Monohydrochloride salt. [e] Sulfate salt. [f] 95% confidence limits. [g] Number of mice used. [h] $LD_{50}/ED_{50}$.

tiarrhythmic activity and acute toxicity evaluation of 1 and 2–8 and a comparison of these with their apparent partition (distribution) coefficients between octanol and pH 7.4 buffer.

A study of the proton magnetic resonance ($^1H$ NMR) spectra of mononitrate salts of 1 and two of the bispidines (6 and 7) in the presence of varying concentrations of magnesium or calcium ions in dimethyl sulfoxide solution is also reported. This has been shown to be a convenient sensitive method for studying ligand–metal binding.[8] It has been suggested that 1 may owe its biologic effects in part to a direct interference with the dynamic behavior of membrane-associated cations such as magnesium.[9]

## Results and Discussion

Antiarrhythmic potencies and toxicities of compounds 1–8 are listed in Table I, in order of increasing lipophilicity as measured by distribution coefficients (log $D_{7.4}$). Also listed are the potencies and toxicities of two standard antiarrhythmics.

In general, although the bispidines were reasonably potent, they were also quite toxic as indicated by the $LD_{50}$ values. The $LD_{50}/ED_{50}$ values remained approximately constant over the entire lipophilicity range of compounds in this series, which suggests that potency and toxicity are correlated equally with this property. Optimal potency was seen in compounds which had log $D_{7.4}$ values between −2.57 and −0.43. Compounds 2 and 3, which were each an order of magnitude less lipophilic, were significantly less potent than compounds within these limits of lipophilicity. Surprisingly, compound 8 was less potent than any of the other bispidines but retained comparable toxicity, while structural isomer 7 was considerably more potent.

**Metal Binding Studies.** We were interested in determining whether the monoprotonated forms of 1 and the analogues described here would interact with magnesium or calcium ions, since their antiarrhythmic activity could conceivably be due in part to such an interaction. Accordingly, the $^1H$ NMR spectra of the mononitrate salts of 1, 6, and 7, using dimethyl-$d_6$ sulfoxide as solvent, were recorded in the absence and in the presence of varying concentrations of calcium or magnesium nitrate (see Experimental Section). In all cases, addition of metal ions caused no shifting or broadening of the spectral peaks. In contrast, ethereal solutions of 1 as the free base have been demonstrated to interact with magnesium salts and organomagnesium reagents.[9,10] Also, we have observed shifting and broadening of the ring $N$-methylene proton signals in spectra of the free base of 4 in methanol-$d_4$ on addition of solutions of either calcium or magnesium salts in this solvent. These results indicate that while the *free bases* of 1 and 4 (and presumably the rest of the bispidines) bind the magnesium and calcium, at least in relatively nonpolar solvents, the monoprotonated forms of these compounds do not. Under physiologic conditions all of these compounds would exist almost exclusively in the monoprotonated form, since their $pK_{a_1}$ and $pK_{a_2}$ values are ≤3.3 and ≥11.8, respectively.[11] Thus, although the pharmacologic activity of 1 and analogues 2–8 may be the result of an effect on the dynamic behavior of metal cations in nerve or muscle cell membranes,[2] our results suggest that this effect is not due to a *direct binding* of the cations by these compounds. Additional evidence in support of this statement was provided by a comparison of the $ED_{50}$ values of compounds 2 and 3 (Table I). Compound 2 has been found to prefer the double-chair conformation while 3 was found to adopt a chair–boat conformation.[12c] The double-chair conformation of the inner rings of 1 has been shown to result in optimum binding of magnesium.[9] Therefore, 2 would be expected to be more active than 3 if activity was primarily a result of magnesium binding; however, the two compounds have been about the same antiarrhythmic potency.

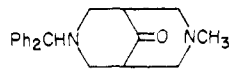
## Experimental Section

**Materials.** Sparteine sulfate was obtained from Delta Chemical Works, Inc., New York, N.Y. $N$-Benzhydryl-$N'$-methylbispidine (8) was prepared as described below. The remaining compounds in Table I were prepared as described previously.[12] Anhydrous nitrate salts of magnesium and calcium were prepared by published methods.[13]

**Methods.** Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Ga. Infrared (IR) spectra were recorded on a Perkin-Elmer 467 spectrophotometer and $^1H$ NMR spectra on a Hitachi R 20A spectrometer using 1% tetramethylsilane as internal standard. Analytical gas–liquid chromatography (GLC) was carried out using a Perkin-Elmer 881 gas chromatograph with single-column flame ionization detection: carrier gas, helium (30 mL/min); detector gases, hydrogen (50 mL/min) and compressed air (200 mL/min); instrument temperatures, injection port (260 °C), detector (250 °C), oven (170–230 °C); column, 6 ft × 0.125 in. stainless steel containing 80–100 mesh Gas Chrom Q which had been coated with ca. 3% OV-17 by the filtration method.[14] The column was conditioned at 300 °C (helium flow, 50 mL/min) for 48 h prior to use. Measurement of pH was made using a Corning Model 10 pH meter equipped with a Fisher microcombination electrode.

Compounds 4–8 were purified as their monoperchlorate salts. Conversion to their water-soluble monohydrochlorides was effected by dissolution of each in methanol or acetone–methanol, followed by passage through a column of BioRad AG2-X8 (50–100 mesh, chloride form) containing approximately 50 mmol of chloride per millimole of compound applied. Methanol was used as solvent. Mononitrates of 1, 6, and 7 were prepared in a similar manner using nitrate as the exchanging anion. Eluates were concentrated in vacuo at 40 °C. Residual solvent was removed azeotropically with benzene in vacuo.

**Synthesis. *N*-Benzhydryl-*N'*-methylbispidinone (9).** A mixture of 16.0 g (0.14 mol) of *N*-methyl-4-piperidone, 26.0 g (0.14




9

mol) of benzhydrylamine, 17.4 g (0.29 mol) of acetic acid, and 32.0 g (1.07 equiv) of paraformaldehyde in 500 mL of methanol was stirred for 40 days. The solution was concentrated in vacuo. The residue was dissolved in 200 mL of water and the mixture extracted with two 300-mL portions of chloroform. These extracts were discarded. Addition of 20 g of sodium hydroxide pellets to the ice-cold aqueous phase was followed by extraction of the resulting suspension with two 400-mL portions of methylene chloride. The combined, dried (sodium sulfate) extracts were filtered and concentrated in vacuo to give 14.95 g of an orange crystalline solid. This was digested with methanol and filtered to afford 8.8 g (20%) of **9**: mp 151–152.5 °C; IR ($CCl_4$) 3.28, 3.37, 3.56, 5.70, 6.83 $\mu$; $^1$H NMR ($CDCl_3$) $\delta$ 2.30 (s, 3, $NCH_3$), 4.33 (s, 1, $NCHPh_2$), 7.06–7.60 (m, 10, $C_6H_5$). A sample of **9** was dissolved in acetone–ether and precipitated by addition of excess ethereal hydrogen chloride. The precipitated hydrochloride was filtered and washed with ether: mp 159–161 °C (darkening). Anal. ($C_{21}H_{26}Cl_2N_2O\cdot1.5H_2O$) C, H, N.

***N*-Benzhydryl-*N'*-methylbispidine (8).** To a stirred solution of 2.2 g (6.9 mmol) of **9** and 2.6 g of 85% hydrazine hydrate in 40 mL of triethylene glycol, heated at ca. 50 °C under nitrogen, was added in portions 4.0 g of 85% potassium hydroxide pellets. The resulting solution was then stirred and refluxed for 3 h. The cooled suspension was poured into 50 mL of water and the mixture was extracted with three 100-mL portions of ether. The combined ethereal extracts were washed with two 25-mL portions of 1% aqueous sodium hydroxide, dried (anhydrous sodium sulfate), filtered, and concentrated in vacuo affording a colorless oil: IR (neat) 3.28, 3.44, 3.62, 6.90, 7.87, 13.6, 14.4, 15.0 $\mu$; $^1$H NMR ($CCl_4$) $\delta$ 1.43 (m, 2, $CH_2$ bridge), 1.81 (m, 2, bridgehead CH), 2.30 (s, 3, $NCH_3$), 2.76 (dd, $J_1$ = 11 Hz, $J_2$ = 1.5 Hz, 4, *endo*-NCH), 4.28 (s, 1, $NCHPh_2$), 7.00–7.55 (m, 10, $C_6H_5$). This oil was dissolved in 50 mL of ether, cooled in ice, and treated with excess 40% aqueous ethanolic perchloric acid. The precipitated perchlorate salt was filtered and crystallized from methanol–water (90:10) as white needles: 2.64 g (94%); mp 208–209.5 °C dec. Anal. ($C_{21}H_{27}ClN_2O_4$) C, H, N.

**Determination of Partition Coefficients.** The method used for determination of the partition coefficient of 8 is representative of the procedure used for all compounds in the series. To each of four 5-mL volumetric flasks was added 0.5 mL of a methanolic solution of 8 (5.57 mg/mL). Solvent was evaporated under a stream of nitrogen. To each flask was added 0.5 mL of octanol (octan-1-ol) saturated with 0.2 M phosphate buffer, pH 7.4. A 10-$\mu$L aliquot of each solution was withdrawn with a Hamilton syringe and diluted with 25 $\mu$L of internal standard solution (sparteine, 1.39 mg/mL in methanol). Each solution was analyzed in triplicate by GLC, using 1–2-$\mu$L samples. The oven temperature was held at 170 °C until elution of sparteine was maximal and then allowed to increase linearly at 10 °C/min until 8 eluted at 225–230 °C. The amount of 8 was estimated using a standard curve of peak height ratio (8/sparteine) vs. milligrams of 8, prepared previously.

To each of the octanol solutions prepared above was added 0.5 mL of octanol-saturated 0.2 M phosphate buffer, pH 7.4. Each mixture was shaken vigorously for 1 min, poured into a 15-mL centrifuge tube, and centrifuged. To 0.1 mL of each of the upper layers was added 0.25 mL of the internal standard solution. The resulting solutions were analyzed as before.

The apparent partition coefficient (log $D_{7.4}$) was calculated as follows

$$\log [C/(C_0 - C)] = \log D_{7.4}$$

where $C$ = milligrams of 8 after extraction and $C_0$ = milligrams of 8 before extraction.

The pH of each aqueous phase was found to be increased over pH 7.4 by 0.08–0.15 unit after shaking with solutions of 8 in octanol. This increase was subtracted from the appropriate calculated log $D$ value in order to normalize all values.

In a similar manner, the apparent partition coefficient of **6** was determined using 5 mL of buffer-saturated octanol (3.4 mg/mL of **6**) per milliliter of octanol-saturated buffer. Samples were analyzed at a GLC oven temperature of 180 °C (isothermal). Calculations were made using the equation above, with the $C_0 - C$ term multiplied by five to make up for the phase volume difference. These modifications of the originally described procedure were also used in determining log $D_{7.4}$ of 1, using 2-nitronaphthalene (0.75 mg/mL) as internal standard.

The partition coefficients determined in this way are listed in Table I, with 95% confidence limits in parentheses. The remaining log $D_{7.4}$ values listed were calculated using appropriate substituent $\pi$ values.[6]

**$^1$H NMR Experiments.** Stock solutions (1 M) of calcium and magnesium nitrate in anhydrous dimethyl-$d_6$ sulfoxide containing 1% tetramethylsilane were prepared. Then stock solutions of the mononitrate salts of 1, **6**, and **7** were prepared similarily, and the $^1$H NMR spectra of each of these last solutions (0.5 mL) were recorded. The spectra were rerecorded after addition of 0.1-mL aliquots of the metal cation solution to each by pipet. Four successive 0.1-mL aliquots of the metal cation solution were added.

**Pharmacologic Evaluation.** To evaluate the antiarrhythmic potency of the compounds, the mouse–chloroform fibrillation assay of Lawson[15] as modified by Berger[16] was used. Briefly, adult $CF_1$ mice were injected ip with the test compound dissolved in distilled water in a volume of less than 0.25 mL. After exactly 10 min, each mouse was placed in a 400-mL covered beaker containing 20 mL of chloroform on gauze sponges. When all visible signs of respiration had ceased (60–90 s) the mouse was removed and needle electrodes were inserted in all four paws for ECG recording. The Lead II or III ECG was recorded with Grass Model 79 polygraph through Model 7P4 EKG–Tachograph preamplifier at a paper speed of 25 mm/s. The R waves were counted for 6 s to obtain the rate. The drug response was considered positive if the rate was regular and less than 200/min. Control mice were injected at regular intervals with distilled water and subjected to the test; invariably tachycardia or ventricular fibrillation was observed.

The $ED_{50}$ values were estimated by the "up-and-down" method of Dixon[17] for small samples of quantal data. Using this method, the $ED_{50}$ values for the standard antiarrhythmic drugs propranolol and disopyramide were also determined.

The acute $LD_{50}$ values ip in mice of compounds 1–8, propranolol, and disopyramide were obtained in order to calculate therapeutic indices. Adult $CF_1$ mice were dosed and placed alone in a holding cage for a 2-h observation period. Survivors at the end of this period were considered not to have received a lethal dose. The $LD_{50}$ values were estimated as before.[17]

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# Potential Histidine Decarboxylase Inhibitors. 1. α- and β-Substituted Histidine Analogues

J. I. DeGraw,* J. Engstrom, M. Ellis, and H. L. Johnson

*Department of Pharmaceutical Chemistry, Stanford Research Institute, Menlo Park, California 94025.*
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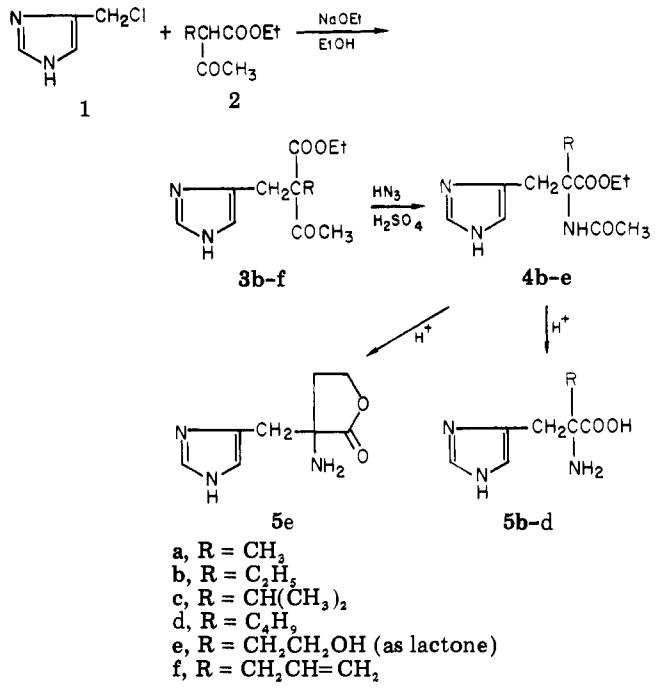
Histidine analogues with alkyl substitution at $C_\alpha$ and $C_\beta$ were prepared as potential inhibitors of specific histidine decarboxylase. Activity was assessed in vitro using extracts of rat pyloric stomach and a radioisotopic assay of $^{14}CO_2$ evolved from carboxyl-$^{14}$C-labeled histidine. α-Substituted analogues ($C_2$–$C_4$) including 2-hydroxyethyl were less potent than α-methylhistidine; the α-*n*-butyl analogue was completely inactive at $10^{-3}$ M. Similarly, β,β-dimethylhistidine and homohistidine failed to exhibit activity at $10^{-3}$ M.

A major source of the histamine contained in most mammalial tissues is presumably the decarboxylation of histidine by a specific decarboxylase.[1] Inhibitors of this enzyme are of interest both as research tools and as potentially useful therapeutic agents for minimizing effects mediated at both $H_1$- and $H_2$-histamine receptors.[2] Although potent inhibitors of the specific decarboxylase are available, none are unequivocally adequate in terms of both specificity and in vivo effectiveness; in particular, those whose activity is based on reaction with pyridoxal phosphate cofactor lack specificity[1] even in terms of other enzyme reactions involved in histamine metabolism.[3]

A logical approach to the design of potent, specific inhibitors would be based on close structural similarity to the natural substrate, histidine. Such reasoning is supported by indications of specificity in the case of α-methylhistidine.[1] The present investigation was designed to assess the degree of steric tolerance toward substitution at the α and β positions of histidine with respect to retention of affinity for the enzyme active site and enhancement of inhibitor properties. Accordingly, a series of α-alkylhistidines **5a–e**, β,β-dimethylhistidine (**13**), and homohistidine was prepared and evaluated as inhibitors of specific histidine decarboxylase obtained from rat pyloric stomach (Table I). α-Methylhistidine (**5a**), a relatively weak inhibitor, was the best in this series, showing 40% inhibition at $10^{-3}$ M and 30% at $10^{-4}$ M. An increase in the size of the substituent caused a substantial decline in inhibitory potency, such that the *n*-butyl analogue **5d** was totally inactive at $10^{-3}$ M. β,β-Dimethylhistidine (**13**) and homohistidine (**14**) were also inactive at $10^{-3}$ M. Synthetic difficulties prevented evaluation of the α-allyl or β-methyl analogues. The results do not allow a definite conclusion regarding β-substitution but indicate rather poor steric tolerance at the α position. The stringent requirements for acceptance at the enzyme binding site are further borne out by the complete lack of activity by the homohistidine.

**Scheme I**




**a**, R = $CH_3$
**b**, R = $C_2H_5$
**c**, R = $CH(CH_3)_2$
**d**, R = $C_4H_9$
**e**, R = $CH_2CH_2OH$ (as lactone)
**f**, R = $CH_2CH{=}CH_2$

The route utilized for synthesis of the α-substituted histidines is outlined in Scheme I. 4-Chloromethylimidazole hydrochloride[4] (**1**) was added to a solution of an appropriate 2-alkyl acetoacetate (**2b–d,f**) or 2-acetylbutyrolactone (**2e**) in ethanol solution containing 2 equiv of sodium ethoxide to afford the 2-alkyl 2-(4-imidazolylmethyl)acetoacetate (**3**). When the keto ester **3** was allowed to react with a slight excess of hydrazoic acid in sulfuric acid solution, the *N*-acetylhistidine esters **4b–e** were obtained in 50–70% yields. Under the acidic conditions employed, the α-allyl analogue **3f** was apparently subjected to additional attack on the vinyl moiety, leading