trap over a 1-hr period. The solution was cooled, extracted three times with 10% aqueous NaOH, dried, filtered, concentrated, and distilled to give 7.0 g (60%) of 2-methoxy-1,3-dioxane: bp 142–144° (745 mm); $n^{20}D$ 1.4250. The material was further purified by gas chromatography: ir (neat), 1240, 1205, 1135 (broad), 1095, 1075, 1035 (broad), 975, and 830 cm^{-1}.

Anal. Calcd for $C_5H_{10}O_3$: C, 50.84; H, 8.53. Found: C, 51.06; H, 8.62.

2-Methoxy-4-methyl-1,3-dioxane was prepared analogously from 1,3-butanediol in 56% yield, bp 130–143° (745 mm). The isomers were separated on a 10 ft × 3/8 in. 5% Carbowax 20M on Chromosorb G column at 120°. The *cis* isomer had the following properties: $n^{20}D$ 1.4250; ir (neat), ten strong peaks in the 8–10 μ region and peaks at 970 (double) and 920 and 895 cm^{-1}; nmr, δ 5.02 ppm for H_2. The *trans* isomer had the following properties: $n^{20}D$ 1.4178; ir (neat), eight peaks in the 8–10 μ region plus peaks at 995, 970, 950, 860, and 790 cm^{-1}; nmr, δ 5.14 ppm for H_2. The configurational assignment must be considered tentative in this case.

Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.43; H, 9.15 (*cis* isomer). Found: C, 54.81; H, 9.00 (*trans* isomer).

2-Ethoxy-4-methyl-1,3-dioxane was prepared similarly but without attempt to remove the benzene–ethanol azeotrope and with only 3 min of reflux time. Under these circumstances the yield was only 14%, bp 51–65.5° (19 mm). Separation on the earlier mentioned 30-ft 6% TCEP column at 125° gave the two isomers in over 95% purity; a second pass produced nearly pure materials. The *cis* isomer had the following properties: $n^{20}D$ 1.4252; ir (neat), 1250, 1200, 1165, 1105, 995, 960, and 875 cm^{-1}; nmr, δ 5.02 ppm for H_2. The *trans* isomer had the following properties: $n^{20}D$ 1.4187; ir (neat), 1260, 1255, 1180, 1165, 1125, 1055 (broad), 1020, 1000, and 980 cm^{-1}; nmr, δ 5.23 ppm for H_2. The configurational assignment must be considered tentative.

Anal. Calcd for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.46; H, 9.65 (*cis* isomer). Found: C, 57.33; H, 9.61 (*trans* isomer).

Equilibrations.—In all cases, equilibrations were initiated with both *cis*-rich and *trans*-rich samples. Solutions in carbon tetrachloride and in acetonitrile were generally 1.4 *M*; those in alcohols were 0.35 *M*. The catalyst in CCl_4 was generated by adding 2 mol % of mutually equivalent amounts of acetyl chloride and the alcohol corresponding to the oxane; in acetonitrile and alcohol solvent the catalyst was 2 mol % *p*-toluenesulfonic acid; in ether the catalyst was 20 mol % boron trifluoride. Equilibrations were carried out in sealed ampoules at 25°; after the requisite time, the ampoules were opened and the acid was neutralized with methanolic sodium methoxide prior to gas chromatography. Response ratios (glpc) were determined for all compounds. Equilibrium was deemed to be reached when *cis*-rich and *trans*-rich starting samples came to the same composition. Each analysis was carried out at least four times (see also ref 1b for details of method).

Registry No.—2-Methoxy-6-methyloxane (*cis*), 17230-07-8; (*trans*), 17230-08-9; 2-ethoxy-6-methyloxane (*cis*), 17230-09-0; (*trans*), 17230-10-3; 2-isopropoxy-6-methyloxane (*cis*), 17230-11-4; (*trans*), 1927-76-0; 2-*t*-butoxy-6-methyloxane (*cis*), 17230-13-6; (*trans*), 17230-14-7; 2-(β,β,β-trifluoroethoxy)-6-methyloxane (*cis*), 17230-15-8; (*trans*), 17230-16-9; 2-(2-methyl-3-butyn-2-oxy)-6-methyloxane (*cis*), 17230-17-0; (*trans*), 17230-18-1; 2-methylthio-6-methyloxane (*cis*), 17230-19-2; (*trans*), 17230-20-5; 2-*t*-butylthio-6-methyloxane (*cis*), 17230-21-6; (*trans*), 17230-22-7; 2-ethoxy-4-methyl-5-oxene (*cis*), 17322-76-8; (*trans*), 17322-77-9; 2-ethoxy-4-methyloxane (*cis*), 17230-25-0; (*trans*), 17322-78-0; 2-methoxy-4-methyloxane (*cis*), 7429-27-8; (*trans*), 7429-28-9; 2,6-diethoxyoxane (*cis*), 17230-29-4; (*trans*), 17230-30-7; 2-methoxy-1,3-dioxane, 17230-31-8; 2-methoxy-4-methyl-1,3-dioxane (*cis*), 17230-32-9; (*trans*), 17230-33-0; 2-ethoxy-4-methyl-1,3-dioxane (*cis*), 17230-34-1; (*trans*), 17230-35-2.

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The Synthesis of 1,4-Substituted Imidazoles[1a]

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A specific and unambiguous synthesis of 1,4-substituted imidazoles is described. α-Amino-β-methylaminopropionic acid was cyclized in triethyl orthoformate with a catalytic amount of hydrochloric acid to 1-methyl-2-imidazoline-4-carboxylic acid, which was esterified and dehydrogenated, using active manganese dioxide, to methyl 1-methyl-4-imidazolecarboxylate. This ester was further converted into several other 1,4-substituted imidazoles. The same procedure has been used to synthesize 1,5-substituted imidazoles; *e.g.*, α-methylamino-β-aminopropionic acid was cyclized, esterified, and dehydrogenated under similar conditions to methyl 1-methyl-5-imidazolecarboxylate.

The wide biological occurrence and physiological importance of compounds incorporating the imidazole nucleus have stimulated considerable synthetic work on this heterocycle.[2] Methods of synthesis or of structural elucidation of unsymmetrical imidazoles are inadequate or ambiguous,[2-4] except for 1,5-substituted imidazoles. In the latter case,[5] only the procedure reported by Jones[5a] is unequivocal, reproducible, and versatile. We now report a general and unambiguous synthesis of 1,4-substituted imidazoles and its application to the synthesis of 1,5-substituted imidazoles as well.

(1) (a) Supported in part by the U. S. Army Research Office, Durham, N. C.; (b) U. S. Public Health Service Postdoctoral Fellow; (c) on leave from the Regional Research Laboratory, Hyderabad, India.

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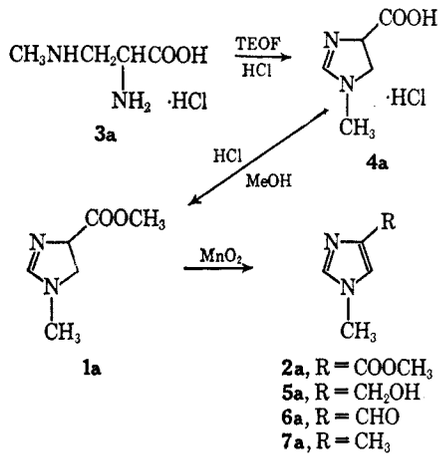
Methyl 1-methyl-4-imidazolecarboxylate (**2a**) was chosen as the primary 1,4-substituted imidazole in order to take advantage of the easy conversion of the carboalkoxy group into a variety of substituents. A preliminary attempt to prepare **2a** was based upon the published procedure[6] for the synthesis of the corresponding 2-amyl compound. However, the reaction of glycine ethyl ester with triethyl orthoformate (TEOF), instead of giving the required intermediate ethyl ethoxymethyleneaminoacetate, yielded N-formylglycine ethyl ester. The yield was 65%, and it is a convenient route to N-formylglycine ethyl ester. Efforts to exclude water did not effect the final result.

It has been reported[7] that 2-alkylimidazolines undergo dehydrogenation to 2-alkylimidazoles upon treatment with nickel catalysts at 300° in a liquid phase. Although this reaction has been used[7] to make a variety of 2-alkylimidazoles substituted with long-chain fatty acids, such a drastic method would severely limit the choice of substituents. A much milder oxidation is achieved by the use of manganese dioxide.[8] This reagent, which has been used[9] in the dehydrogenation of indolines to indoles, converts imidazolines into imidazoles in high yield. Thus, methyl 1-methyl-2-imidazoline-4-carboxylate (**1a**) was converted into the imidazole **2a** in 72% yield by stirring a chloroform solution of **1a** with a fourfold excess of finely powdered, activated manganese dioxide. No side products were observed by tlc and nmr.



The required imidazoline **1a** was prepared by the cyclization of α-amino-β-methylaminopropionic acid hydrochloride (**3a**)[10] in triethyl orthoformate with a hydrogen chloride catalyst. The imidazolinecarboxylic acid (**4a**) obtained by this procedure was esterified to increase its solubility in chloroform for the subsequent dehydrogenation step. Cyclization of the diamino acid (**3a**) to the imidazoline ensures that the desired relationship of substituents is obtained. Consequently the imidazole **2a** must be methyl 1-methyl-4-imidazolecarboxylate.

Using the specifically substituted 1,4-imidazole **2a** as a starting point, several other 1,4-substituted imidazoles have been synthesized. Reduction of **2a** with lithium aluminum hydride gave 1-methyl-4-hydroxymethylimidazole (**5a**). Oxidation of **5a** with activated manganese dioxide gave 1-methyl-4-imidazolecarboxaldehyde (**6a**) which was then converted *via* Wolff–Kishner reduction into 1,4-dimethylimidazole (**7a**).

The ready availability of 1,2-diamines and the ease of cyclization and dehydrogenation gives the described procedure broad potential for the synthesis of specifically substituted imidazoles. As an example, we have applied it to the synthesis of DL-3-methylhistidine. A synthesis of 3-methylhistidine has been reported[11] patterned after that reported[12] for the preparation of 1-methylhistidine. Unfortunately, the starting material, 1-methyl-4-hydroxymethylimidazole, used in this case[11] was not shown conclusively to be the required 1,4-substituted compound. The 1,4 orientation was assumed from previous work[13] which had made structural assignments for the hydroxymethylimidazoles based partially upon the melting points of the picrates of the corresponding dimethylimidazoles. The melting points of the two 1,4(5)-dimethylimidazole picrates are, however, identical. Thus, no assignment can be made on this basis.

In extending our work to the synthesis of 3-methylhistidine, we have followed the published procedures, using 1-methyl-4-hydroxymethylimidazole (**5a**) prepared as described in this report and therefore of known orientation. The final product, DL-3-methylhistidine dihydrochloride, mp 242–244° dec (lit.[11] mp 251–253° dec), had an R_F value identical with that of a natural sample in several systems.

The synthesis and subsequent dehydrogenation of an appropriate imidazoline provides an alternative to the Jones procedure for the preparation of 1,5-substituted imidazoles. The yields are comparable, and this method may be preferable in some cases. To prepare the requisite diamine, N-bromomethylphthalimide[14] (**8**) was condensed with the sodium enolate of diethyl N-methylacetaminomalonate[15] (**9**) to give ethyl α-N-methylacetamino-α-ethoxycarbonyl-β-(N-phthalimido)propionate (**10**). Hydrolysis of **10** gave α-methylamino-β-aminopropionic acid hydrochloride (**3b**) which was subsequently cyclized, esterified, and dehydrogenated to methyl 1-methyl-5-imidazolecarboxylate (**2b**) as described for **2a**. 1-Methyl-5-hydroxymethylimidazole (**5b**), 1-methyl-5-imidazolecarboxaldehyde (**6b**), and 1,5-dimethylimidazole (**7b**) were prepared by methods similar to those used for the 1,4-substituted isomers. In the applicable cases, the compounds which we have prepared are identical with those described by Jones.[5a]

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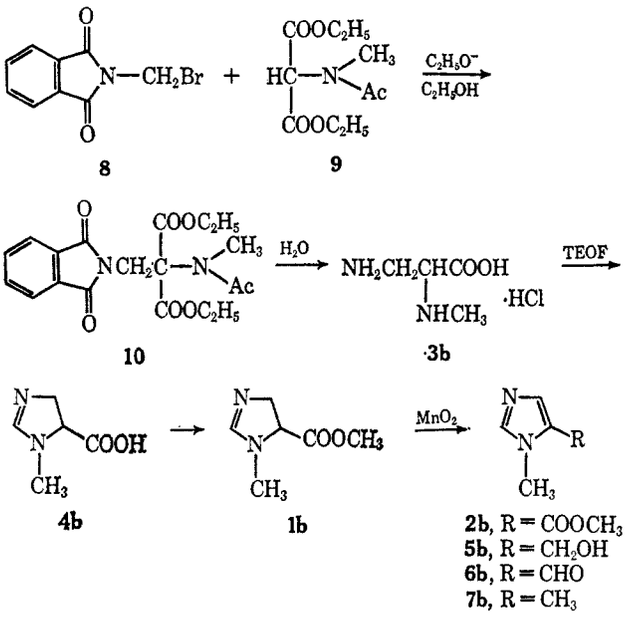

Experimental Section

α-Amino-β-methylaminopropionic acid hydrochloride (3a) was prepared according to the procedure of Vega and Bell.[10] Pyruvic acid (250 g) afforded 140 g of pure **3a**: R_F 0.12 in butanol–acetic acid–water (4:1:5), detected with ninhydrin; $\delta_{DSS}^{D_2O}$ 293 (3 H, s, N—CH_3), 3.60 (2 H, d, -CH_2–), 4.21 (1 H, t, -CHN–).

Anal. Calcd for $C_4H_{10}O_2N_2 \cdot HCl$: C, 31.1; H, 7.2; N, 18.1. Found: C, 31.1; H, 7.6; N, 18.0.

1-Methyl-2-imidazoline-4-carboxylic Acid (4a).—α-Amino-β-methylaminopropionic acid hydrochloride (**3a**) (4.0 g) was stirred in 40 ml of triethyl orthoformate (distilled) and 2.5 ml of HCl (36%) for 12 hr at 90–100°. During the first few hours a low-boiling distillate (56°) was collected and 10 ml of fresh triethyl orthoformate was added at the end of the first hour. The reaction was cooled, and the solid imidazoline was collected by filtration. This light brown product could be washed with a little acetone to give material which after drying was sufficiently pure for further reactions (3.38 g, 79%). Recrystallization from absolute ethanol and drying gave pure material: mp 194–195° dec; $\delta_{DSS}^{D_2O}$ 8.20 (1 H, s, =CH), 5.05 (1 H, t, CHCOOH), 4.31, 4.12 (2 H, d, s, -CH_2–), 3.20 (3 H, s, -CH_3); *m/e* 128 (M^+), 109, 83, 68, 54, 44, 42, 36, 30, 28.

Anal. Calcd for $C_5H_8N_2O_2 \cdot {}^1/_2HCl$: C, 41.0; H, 5.8; N, 19.2; Cl, 12.2. Found: C, 41.1; H, 5.7; N, 19.4; Cl, 12.6.

Methyl 1-Methyl-2-imidazoline-4-carboxylate (1a).—To a suspension of 11.1 g of the acid **4a** in 125 ml of dry methanol (distilled from CaH_2) was added 2 g of molecular sieve. Dry HCl gas was bubbled in rapidly until the solution was saturated and then slowly while the solution was refluxed for 4 hr. The excess HCl was removed by a rapid stream of dry N_2, and the solution was neutralized with solid $NaHCO_3$. Most of the methanol was evaporated; the residue was redissolved in water; and the solution was filtered. After cooling this solution in an ice bath, cold Na_2CO_3 solution was added until pH 9 was exceeded. This solution was extracted with cold chloroform; the chloroform was dried over magnesium sulfate; and the solvent was removed, leaving a pale yellow oil (81% yield). A sample purified by distillation proved to be unstable, bp 77° (0.05 mm), but the nmr spectrum of the crude product showed that it was essentially pure. It was used in this state for further reactions: $\delta_{TMS}^{CHCl_3}$ 6.78 (1 H, d, =CH), 4.52 (1 H, t, -CHCOOCH$_3$), 3.33 (2 H, d, -CH_2–), 2.84 (3 H, s, N—CH_3), 3.68 (3 H, s, -OCH_3).

Methyl 1-Methyl-4-imidazolecarboxylate (2a).—To a solution of 7.5 g of the imidazoline **1a** in 150 ml of chloroform was added 30 g of active manganese dioxide,[8] and the suspension was stirred for 16 hr at room temperature. The manganese dioxide was removed and washed with hot chloroform. The combined chloroform fractions were evaporated to dryness, and 5.32 g of essentially pure product was obtained. Sublimation at 80° (0.05 mm) gave white crystals: mp 97–98°; $\delta_{TMS}^{CHCl_3}$ 7.45 (1 H, d, C-2 H), 7.57 (1 H, d, C-5 H), 3.73 (3 H, s, -OCH_3), 3.85 (3 H, s, N-CH_3); *m/e* 140 (M^+), 110, 109, 82, 42, 28.

Anal. Calcd for $C_6H_8N_2O_2$: C, 51.4; H, 5.8; N, 20.0. Found: C, 51.2; H, 5.8; N, 19.9.

Ethyl α-N-Methylacetamino-α-ethoxycarboxyl-β-(N-phthalimido)propionate (10).—To 1 equiv of sodium ethoxide in ethanol was added 2.30 g of diethyl N-methylacetaminomalonate[15] (**9**) followed by 2.39 g of N-bromomethylphthalimide[14] in ether–ethanol (1:1). The solution was refluxed for 4 hr; water was added; and the aqueous phase was extracted with several portions of methylene chloride. The combined organic phase was dried over magnesium sulfate and evaporated to leave 2.1 g of an oil. This oil was further purified by chromatography on Kiesel gel (Camag) with 10% acetone in chloroform. Three fractions were obtained: N-ethoxymethylphthalimide, the starting malonate **9**, and **10**, in that order. Pure ethyl α-N-methylacetamino-α-ethoxycarbonyl-β-(N-phthalimido)propionate (**10**) is an oil: *m/e* 390 (M^+).

Anal. Calcd for $C_{19}H_{22}O_7N_2$: C, 58.4; H, 5.7; N, 7.2. Found: C, 58.2; H, 5.7; N, 7.3.

Several methods of condensing N-bromomethylphthalimide and diethyl N-methylacetaminomalonate (**9**) were investigated which would be expected to give the final product uncontaminated by solvolysis products. Aprotic solvents (*i.e.*, THF, dioxane, ether) do not provide sufficient solubility to give a good reaction. The *t*-butanol–*t*-butoxide system was also investigated. However, contrary to reports[14] in the literature, N-bromomethylphthalimide undergoes solvolysis in this system to give the *t*-butyl ether, and ether formation is no less significant than in the case of ethanol–ethoxide. Since ethanol is the better solvent, it was chosen for the reaction.

α-Methylamino-β-aminopropionic Acid (3b).—The crude condensation product (**10**) was dissolved in 10 ml of 4 *N* HCl and refluxed for 8 hr. Upon cooling, crystals formed which were removed, and the solution was evaporated. The residue was dissolved in absolute ethanol; the solution was evaporated; and the residue was crystallized from ethanol–acetone–water to yield 0.6 g, 30% based on N-bromomethylphthalimide, mp 172–174° dec.

Anal. Calcd for $C_4H_{10}N_2O_2 \cdot 2HCl$: N, 14.7. Found: N, 15.1.

1-Methyl-2-imidazoline-5-carboxylic Acid (4b).—The diamino acid **3b** (2.5 g) was stirred in 40 ml of TEOF and 2.5 ml of concentrated HCl at 65° for 48 hr. The product was collected by filtration, after cooling, and washed with a little acetone. At this point **4b** was pure enough for further synthesis. It could be recrystallized from absolute ethanol to give colorless crystals: 1.6 g, 74% yield; mp 178–179°; $\delta_{DSS}^{D_2O}$ 8.28 (1 H, s, =CH), 4.18 [2 H, d (d), -CH_2–], 3.27 (3 H, s, N—CH_3), 4.85 (1 H, t, -CHCOOH).

Anal. Calcd for $C_5H_8O_2N_2 \cdot HCl$: C, 36.5; H, 5.5; N, 17.0. Found: C, 36.8; H, 5.6; N, 17.1.

Methyl 1-methyl-2-imidazoline-5-carboxylate (1b) was prepared in the same manner described above for the 1,4 isomer **1a**. Again the nmr spectrum indicated the product was sufficiently pure to be immediately subjected to oxidation: $\delta_{TMS}^{CHCl_3}$ 6.77 (1 H, s, =CH), 4.00 (2 H, m, -CH_2–), 2.90 (3 H, s, N—CH_3), 3.74 (3 H, s, -OCH_3), 4.00 (1 H, m, -CHCOOH); *m/e* 142 (M^+), 115, 102, 83, 56, 42.

Methyl 1-methyl-5-imidazolecarboxylate (2b) was prepared in the same manner as described for the 1,4 isomer **2a** in 87% yield. Sublimation at 25° (0.01 mm) gave crystals of mp 56–57° (lit.[6a] mp 56–57°): $\delta_{TMS}^{CHCl_3}$ 7.53 (1 H, s, C-2 H), 7.70 (1 H, d, C-4 H), 3.82 (3 H, s, -OCH_3), 3.91 (3 H, s, N—CH_3); *m/e* 140 (M^+), 109, 81, 54, 42, 28, 15.

1-Methyl-4-hydroxymethylimidazole (5a).—To a solution of 1.5 g of lithium aluminum hydride in 40 ml of tetrahydrofuran at 0° was added 2.23 g of imidazole ester **2a** in 90 ml of THF over a 30-min period. Stirring was continued for 20 min, followed by removal of the ice bath and addition of wet ether to decompose excess hydride. The mixture was filtered; the insoluble material was washed with 200 ml of hot chloroform; and the filtrate was evaporated to dryness. The residue, a brown oil, was fractionally sublimed at 0.1–0.2 mm. After removing the oil which distilled at room temperature, heating was continued at 60° overnight, and the crystalline sublimate melted at 61–62°.

Anal. Calcd for $C_5H_8N_2O$: C, 53.6; H, 7.2; N, 25.0. Found: C, 53.5; H, 7.0; N, 25.1.

1-Methyl-4-imidazolecarboxaldehyde (6a).—To a solution of 1.06 g (9.47 mmol) of the hydroxymethylimidazole **5a** in 20 ml of chloroform was added 4 g of MnO_2 (predried in an oven at 110° for 30 min). The resulting slurry was stirred at room

temperature for 16 hr; the mixture was filtered; the insoluble material was washed with hot chloroform; and the filtrate was evaporated to dryness, giving a liquid which slowly crystallized. Sublimation at 60° (0.1 mm) gave 860 mg: 83% yield; mp 65–66.5°; $\delta_{TMS}^{CDCl_3}$ 7.77 (1 H, s, C-5 H), 7.84 (1 H, d, C-2 H), 10.0 (1 H, s, -CHO), 3.98 (3 H, s, $-CH_3$); *m/e* 110 (M^+), 109, 108, 81, 67, 53, 42, 28, 15.

Anal. Calcd for $C_5H_6N_2O$: C, 54.5; H, 5.5; N, 25.4. Found: C, 54.6; H, 5.5; N, 25.4.

1,4-Dimethylimidazole (7a).—Into a small distillation apparatus were placed 550 mg (5 mmol) of imidazolealdehyde **6a**, 1.5 g of 85% hydrazine hydrate, and 6 ml of diethylene glycol. The temperature was raised slowly to 150°; the heat was removed; 1.4 g (25 mmol) of potassium hydroxide was added; and heat was reapplied at 150° for 1.5 hr, followed by 1 hr at 200°. After cooling, the solution was diluted with 100 ml of water and extracted with five 30-ml portions of chloroform, and the combined chloroform extracts were washed with water, dried over sodium sulfate, and evaporated to yield 140 mg (29%) of liquid. Repetition of the extraction of the aqueous phase gave an additional 145 mg (30%). After short-path distillation at 40° (50 μ) the product was obtained: $\delta_{TMS}^{CDCl_3}$ 2.2 (3 H, d, C–CH_3), 3.58 (3 H, s, –NCH_3), 6.68 (1 H, s, C-5 H), 7.28 (1 H, s, C-2 H); *m/e* 97, 96 (M^+), 95, 81, 68, 54, 42, 28, 15.

Anal. Calcd for $C_5H_8N_2$: C, 62.5; H, 8.4; N, 29.1. Found: C, 61.9; H, 8.5; N, 29.2.

1-Methyl-4-chloromethylimidazole hydrochloride was prepared from the hydroxymethylimidazole **5a** in 88% yield as described for the analogous 1,5 compound by Jones and McLaughlin:[12] mp 153–155° (lit.[11] mp 153–154°); $\delta_{DSS}^{D_2O}$ 3.98 (3 H, s, –NCH_3), 4.82 (2 H, s, –CH_2Cl), (1 H, s, C-5 H), 8.7 (1 H, s, C-2 H).

Anal. Calcd for $C_5H_7N_2Cl \cdot HCl$: C, 36.0; H, 4.8; N, 16.8. Found: C, 36.2; H, 5.0; N, 17.0.

Ethyl α-acetamino-α-ethoxycarbonyl-β-(1-methyl-4-imidazolyl)-propionate was prepared from the chloromethylimidazole as described for the analogous 1,5 compound.[12] A 1.6-g (10 mmol) sample of starting material gave 1.1 g: mp 119–120°; $\delta_{TMS}^{CDCl_3}$ 7.48 (1 H, s, C-2 H), 6.81 (1 H, s, C-5 H), 3.81 (3 H, s, N–CH_3), 3.73 (2 H, s, Im–CH_2–), 2.2 (3 H, s, -Ac), 4.46 (4 H, q, –OCH_2–), 1.47 (6 H, t, CH_2CH_3).

Anal. Calcd for $C_{14}H_{21}N_3O_5$: C, 54.0; H, 6.8; N, 13.5. Found: C, 54.3; H, 7.0; N, 13.7.

3-Methylhistidine Dihydrochloride.—The acetaminomalonate was hydrolyzed in 6 *N* hydrochloric acid for 20 hr at reflux. Most of the water was evaporated, and the sample was completely dried by adding and evaporating absolute ethanol. The residue was dissolved in 1 ml of ethanol, and the addition of acetone caused crystals to form rapidly. A 600-mg sample gave 447 mg (97% yield) of 3-methylhistidine dihydrochloride: mp 242–244°; $\delta_{DSS}^{D_2O}$ 8.72 (1 H, d, C-2 H), 7.47 (1 H, d, C-5 H) 3.90 (3 H, s, –NCH_3), 3.46 (2 H, d, Im–CH_2–), 4.42 (1 H, t, –$CHNH_2$). On paper in *t*-butanol–acetic acid–water (2:1:1), L-histidine had R_F 0.43; L-1-methylhistidine had R_F 0.46; and both synthetic (DL) and commercial (natural, L) 3-methylhistidine had R_F 0.50.

Anal. Calcd for $C_7H_{11}N_3O_2 \cdot 2HCl$: C, 34.7; H, 5.4; N, 17.4. Found: C, 35.2; H, 5.2; N, 17.1.

1-Methyl-5-hydroxymethylimidazole (5b), mp 113–114° (lit.[12] mp 113–114°), and **1-methyl-5-imidazolecarboxaldehyde (6b)**, mp 53–54° (lit.[12] mp 53–54°), were prepared as described[12] from the corresponding methyl 1-methyl-5-imidazolecarboxylate (**2b**).

1,5-Dimethylimidazole (7b) was prepared as described for the 1,4 isomer **7a**. It is a liquid: $\delta_{TMS}^{CDCl_3}$ 7.25 (1 H, s, C-2 H), 6.66 (1 H, s, C-4 H), 3.40 (3 H, s, N–CH_3), 2.06 (3 H, s, C–CH_3); *m/e* 97, 96 (M^+), 95, 81, 68, 54, 42, 28, 15.

Anal. Calcd for $C_5H_8N_2$: C, 62.5; H, 8.4; N, 29.1. Found: C, 62.3; H, 8.2; N, 29.1.

N-Formylglycine Ethyl Ester.—Glycine ethyl ester hydrochloride (14.0 g, 0.1 mol) was stirred with triethyl orthoformate (15 g, 0.1 mol, distilled) while the temperature was gradually raised to 100°. At this point a vigorous reaction commenced. Material distilled from the reaction at bp 60° (6 ml of ethyl formate) and 76–78° (9.5 ml of ethanol). The residue was taken up in chloroform, stirred with potassium carbonate, filtered, and concentrated. The crude product was distilled *in vacuo* to give pure material: 9.0 g, 65% yield; bp 92–94° (0.1 mm); $\delta_{TMS}^{CDCl_3}$ 1.08 (3 H, t, CH_3), 4.00 (2 H, q, CH_2CH_3), 4.00 (2 H, s, N–CH_2–), 7.8 (1 H, broad s, NH), 8.0 (1 H, s, CHO). The preparation of this compound has been reported,[5a] but no characterization or analytical data were given.

Anal. Calcd for $C_5H_9O_3N$: C, 45.8; H, 6.9; N, 10.7. Found: C, 46.0; H, 6.7; N, 10.9.

Registry No.—**1a**, 17289-17-7; **1b**, 17289-18-8; **2a**, 17289-19-9; **2b**, 17289-20-2; **3a**, 17289-21-3; **3b**, 17289-22-4; **4a**, 17289-23-5; **4b**, 17289-24-6; **5a**, 17289-25-7; **6a**, 17289-26-8; **7a**, 6338-45-0; **7b**, 10447-93-5; **10**, 17289-29-1; 1-methyl-4-chloromethylimidazole hydrochloride, 17289-30-4; ethyl α-acetamino-α-ethoxycarbonyl-β-(1-methyl-4-imidazolyl)propionate, 17289-31-5; 3-methylhistidine dihydrochloride, 17289-32-6; N-formylglycine ethyl ester, 3154-51-6.