crystallized from *n*-hexane to give **25** (1.2 g, 22%).

***N*-Cyano-*N'*-(5,6,7,8-tetrahydro-3-methylquinolin-8-yl)-*N''*-methylguanidine (10).** **25** (2 g, 0.008 mol) was suspended in EtOH (5 mL), a 33% solution of $MeNH_2$ in EtOH (25 mL, 0.27 mol) was added, and the mixture was stirred 1 h at ambient temperature. The solvent was removed by evaporation and the residue was induced to crystallize by trituration with diisopropyl ether and recrystallized from propan-2-ol–diisopropyl ether to give **10** (1.6 g, 85.5%).

***N*-(5,6,7,8-Tetrahydro-3-methylquinolin-8-yl)-*N'*-methyl-*N''*-thiocarbamoylguanidine (12).** A mixture of pyridine (20 mL) and Et_3N (6 mL) was saturated with H_2S at 0 °C. **10** (1.5 g, 0.006 mol) was added and the solution was heated in a bomb at 70 °C for 20 h. The solvent was removed by evaporation and the residue was triturated with Et_2O to give a solid which was recrystallized from propan-2-ol to give **12** (1.1 g, 64%).

***N*-Carbamyl-*N'*-(5,6,7,8-tetrahydro-3-methylquinolin-8-yl)-*N''*-methylguanidine Dihydrobromide (11).** **10** (1.0 g, 0.004 mol) was dissolved in concentrated HBr (50 mL) and evaporated. A 50% EtOH–concentrated HBr solution (50 mL) was added and evaporated and EtOH (50 mL) was added and evaporated. The residue was triturated with propan-2-ol and recrystallized from EtOH to give **11** (0.8 g, 46%).

3,4-Dihydro-1*H*-pyrido[2,3-*d*]pyrimidine-2-thione (7). A solution of 2-aminonicotinonitrile[10] (1.2 g, 0.01 mol) in EtOH (50 mL) previously saturated with NH_3 was hydrogenated at 50 psi and ambient temperature over 5% $Rh–Al_2O_3$ (0.2 g) until uptake ceased. The solution after filtration was evaporated and the residue was dissolved in Et_2O and filtered. The filtrate was acidified with ethereal HCl and the solid removed by filtration and triturated with hot EtOH to give **2-amino-3-aminomethylpyridine dihydrochloride (26)** (0.6 g, 31%), mp 250 °C. Anal. ($C_6H_9N_3 \cdot 2HCl$) C, H, N.

A solution of **26** (3.5 g, 0.028 mol) in 50% EtOH–H_2O (20 mL) at 40 °C was treated with CS_2 (2.1 g, 0.028 mol). The mixture was heated at 60 °C for 1 h and at reflux for 2 h. 12 N HCl (0.5 mL) was then added and reflux was continued for 16 h. After cooling the resulting crystals were removed by filtration and washed with 50% EtOH–H_2O to give **7** (2.5 g, 53%).

Acknowledgment. The authors thank Dr. K. Heatherington for help and advice with spectral and analytical services.

References and Notes

(1) For paper 4, see D. E. Beattie, R. Crossley, A. C. W. Curran, G. T. Dixon, D. G. Hill, A. E. Lawrence, and R. G. Shepherd, *J. Med. Chem.*, preceding paper in this issue.
(2) (a) C. E. Malen, B. H. Danree, and X. B. L. Pascaud, *J. Med. Chem.*, **14**, 244 (1971); (b) T. M. Bustard and Y. C. Martin, *ibid.*, **15**, 1101 (1972).
(3) R. W. Brimblecombe, W. A. M. Duncan, G. J. Durant, J. C. Emmett, C. R. Ganellin, and M. E. Parsons, *J. Int. Med. Res.*, **3**, 86 (1975).
(4) M. M. Robinson, F. P. Butler, and B. L. Robinson, *J. Am. Chem. Soc.*, **79**, 2573 (1957).
(5) E. M. Hawes and H. L. Davis, *J. Heterocycl. Chem.*, **10**, 39 (1973).
(6) H. Rapoport and A. D. Batcho, *J. Org. Chem.*, **28**, 1753 (1963).
(7) A. C. W. Curran, *J. Chem. Soc., Perkin Trans. 1*, 975 (1976).
(8) A. P. Skoldinow, T. V. Protopova, and V. T. Klimko, USSR Patent 136 351 (1961).
(9) A. Hantzsch and M. Wolvekamp, *Justus Liebigs Ann. Chem.*, **331**, 265 (1904).
(10) E. C. Taylor, Jr., and A. J. Crovetti, *J. Org. Chem.*, **19**, 1633 (1954).

Attempted Inhibition of Histidine Decarboxylase with β-Alkyl Analogues of Histidine

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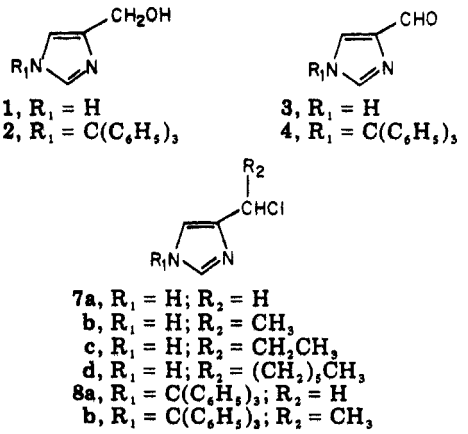
The synthesis of β-methyl- (**10b**), β-ethyl- (**10c**), and β-*n*-hexylhistidine (**10d**) in five steps from 4-(*N*-triphenylmethyl)imidazolecarboxaldehyde (**4**) is described. Neither of the amino acids nor the methyl esters of **10b** or **10c** were inhibitors of the histidine decarboxylase from rat stomach.

As a continuation of our work on inhibition of histidine decarboxylase, we were interested in analogues of histidine containing an alkyl substituent in the β position. We had previously reported that the methyl ester of L-histidine was a potent inhibitor of this enzyme.[1] When an alkyl group was substituted on the α position of the methyl ester, the resultant compound was a very weak enzyme inhibitor. We therefore wanted to test compounds where the alkyl substituent was at the β position since this change might lead to compounds in which the inhibitory potency of the methyl ester of L-histidine was maintained or even increased.

As a synthetic entry to the β-alkylhistidines we chose to modify Albertson's classic synthesis of histidine[2] by use of the appropriate 1-(4-imidazolyl)alkyl chloride (**7**) (Chart I) in reaction with diethyl acetamidomalonate. Use of the *N*-triphenylmethyl blocked aldehyde **4**[3] as a viable intermediate to **7b–d** was attractive in view of the excellent results in protection and subsequent deblocking of an imidazole reported by Burger and co-workers in their synthesis of some β-substituted analogues of histamine.[3,4] Although the blocked aldehyde **4** was available from **3** in reasonable yield by a modification of Burger's[3] method,

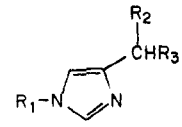
Chart I



1, R_1 = H
2, R_1 = $C(C_6H_5)_3$
3, R_1 = H
4, R_1 = $C(C_6H_5)_3$
7a, R_1 = H; R_2 = H
b, R_1 = H; R_2 = CH_3
c, R_1 = H; R_2 = CH_2CH_3
d, R_1 = H; R_2 = $(CH_2)_5CH_3$
8a, R_1 = $C(C_6H_5)_3$; R_2 = H
b, R_1 = $C(C_6H_5)_3$; R_2 = CH_3

we found that it was more expedient to simply react 4-imidazolylmethanol (**1**)[5] with triphenylmethyl chloride in dimethylformamide to give **2**. Oxidation of **2** with activated manganese dioxide in hot dioxane gave **4** in 80% yield for the two steps. That the triphenylmethyl group in **4** was correctly assigned to the nitrogen atom across the

Table I. Imidazole Derivatives



No.	R_1	R_2	R_3	Method	% yield	Mp, °C	Formula[a]
5b	$C(C_6H_5)_3$	CH_3	OH	A	87	160-161[b]	$C_{24}H_{22}N_2O$
5c	$C(C_6H_5)_3$	CH_2CH_3	OH	A	77[b]	133-134	$C_{25}H_{24}N_2O$
5d	$C(C_6H_5)_3$	n-C_6H_{13}	OH	A	43	82-83[c]	$C_{29}H_{32}N_2O$
6b	H	CH_3	OH	B	82	123-124[d]	$C_5H_8N_2O$·HCl
6c	H	CH_2CH_3	OH	B	83	118-120[d]	$C_6H_{10}N_2O$·HCl·0.25H_2O
6d	H	n-C_6H_{13}	OH	B	99	111-113[d]	$C_{10}H_{18}N_2O$·HCl
9b	H	CH_3	$C(NHCOCH_3)(COOCH_2CH_3)_2$	C	56	66-71[e]	$C_{14}H_{21}N_3O_5$·H_2O
9c	H	CH_2CH_3	$C(NHCOCH_3)(COOCH_2CH_3)_2$	C	55[e]	98-101	$C_{15}H_{23}N_3O_5$·0.5H_2O
9d	H	n-C_6H_{13}	$C(NHCOCH_3)(COOCH_2CH_3)_2$	C		Oil	
10b	H	CH_3	$CH(NH_2)COOH$	D	58[f]	231-233 dec	$C_7H_{11}N_3O_2$
10c	H	CH_2CH_3	$CH(NH_2)COOH$	D	65	239-241 dec[f]	$C_8H_{13}N_3O_2$
10d	H	n-C_6H_{13}	$CH(NH_2)COOH$	D	70	~238 dec[e]	$C_{12}H_{21}N_3O_2$·H_2O
11b	H	CH_3	$CH(NH_2)COOCH_3$	E	24[g]	188-189 eff	$C_8H_{13}N_3O_2$·2HCl
11c	H	CH_2CH_3	$CH(NH_2)COOCH_3$	E	47	198-200 eff[g]	$C_9H_{15}N_3O_2$·2HCl

[a] All compounds were analyzed for C, H, and N. [b] Recrystallized from $CHCl_3$-hexanes. [c] Recrystallized from EtOAc-hexanes. [d] Recrystallized from EtOH-Et_2O. [e] Recrystallized from H_2O. [f] Recrystallized from EtOH-H_2O. [g] Recrystallized from MeOH-Et_2O.

ring from the carbonyl group was supported by the 100-MHz NMR after the method of Matthews and Rapoport.[6] That **4** was a 1,4-disubstituted imidazole was evident from the NMR signals at δ 7.52 (doublet) and 7.60 (doublet) with J = 1.2–1.3 Hz.

The blocked aldehyde **4** reacted smoothly with the appropriate commercial Grignard reagent to give the secondary alcohols **5b–d** (Table I) in 43–87% yield. Several attempts to chlorinate **5b** gave only a mixture of **8b** and the deblocked imidazole **7b**. This contrasted with the reactivity of **2** toward thionyl chloride which readily formed the crystalline chloride **8a**.[7] Consequently, we chose to remove the triphenylmethyl blocking group prior to chlorination since its purpose had been served in the synthetic sequence. Treatment of **5b–d** with 2 N hydrochloric acid at 60–70 °C readily afforded the deblocked imidazoles **6b–d** in high yield. Chlorination of the secondary alcohols with thionyl chloride gave **7b–d**, which were not purified because of their hygroscopic nature, but were carried on in reaction with diethyl acetamidomalonate to give **9b–d**. Hydrolysis of **9b–d** with 12 N hydrochloric acid readily gave the desired β-alkylhistidines **10b–d** as the free bases following neutralization from an ion-exchange resin [Rexyn 101(H)]. The methyl esters **11b** and **11c** were made in methanol containing thionyl chloride.[8] Both **10b–d** and **11b,c** were diastereoisomeric mixtures which were not separable by TLC. No attempt was made to separate the diastereomers since the compounds were not inhibitors.

Inhibition of histidine decarboxylase from rat stomach by the β-alkylamino acids and esters **10b–d** and **11b,c** was measured as previously described.[1] None of these compounds showed significant inhibition of the enzyme at 1×10^{-4} M. This loss of inhibitory potency by the methyl ester of L-histidine (50% inhibition at 4×10^{-6} M) on substitution at its β position, as is evident with **11b** and **11c**, is the same sort of effect that was observed on substitution in the α position of the methyl ester of L-histidine with a methyl or n-butyl group.[1] There is clearly a lack of bulk tolerance[9] for hydrophobic substituents at these positions on the methyl ester of histidine.

Experimental Section

Melting points were taken in capillary tubes on a Mel-Temp block and are uncorrected. NMR data were recorded on Varian XL-100-15-FT and T-60 spectrometers using Me_4Si as an internal standard. Each analytical sample had spectral data compatible with its assigned structure and moved as a single spot on TLC. The analytical samples gave combustion values for C, H, and N within 0.4% of the theoretical value.

4-(*N*-Triphenylmethyl)imidazolylmethanol (2). To a stirred mixture of 3.99 g (29.6 mmol) of dry **1** hydrochloride,[5] 30 mL of DMF, and 10 mL (71.5 mmol) of Et_3N under N_2 and protected from moisture with a $CaCl_2$ tube was added a solution of 8.50 g (30.5 mmol) of Ph_3CCl in 110 mL of DMF. After 0.5 h an additional portion of Et_3N (1 mL) and Ph_3CCl (0.85 g, 3.0 mmol) in 25 mL of DMF was added since TLC indicated that the reaction was incomplete. After an additional 0.5 h the reaction mixture was poured over 500 g of crushed ice; the solids were collected and washed with H_2O. The crude product was digested with 100 mL of dioxane, cooled, collected by filtration, and washed with Et_2O: yield, 8.87 g (88%); mp 219–221 °C. Several recrystallizations of a portion from dioxane gave the analytical sample: mp 228–230 °C (lit.[3] mp 234–236 °C). Anal. ($C_{23}H_{20}N_2O$) C, H, N.

4-(*N*-Triphenylmethyl)imidazolecarboxaldehyde (4). Alkylation. To a stirred, ice-bath-cooled solution of 2.14 g (22.3 mmol) of **3**[10,11] and 2.26 g (22.3 mmol) of Et_3N in 100 mL of DMF was added 6.22 g (22.3 mmol) of Ph_3CCl in 50 mL of DMF over 45 min. After 18 h at ambient temperature the reaction was poured over 500 g of crushed ice, and the solid was collected and recrystallized from $CHCl_3$–hexanes: yield, 5.62 g (74%); mp 194–195 °C. An additional recrystallization gave the analytical sample: mp 196–197 °C (lit.[3] mp 197–199 °C); NMR ($CDCl_3$) δ 7.00–7.42 (m, 15 H, ArH), 7.52 (d, 1 H, J = 1.2 Hz, ImH), 7.60 (d, 1 H, J = 1.2 Hz, ImH), 9.87 (s, 1 H, HC=O). Anal. ($C_{23}H_{18}N_2O$) C, H, N.

Oxidation. A mixture of 45.52 g (0.133 mol) of **2**, 114.0 g (1.33 mol) of activated MnO_2, and 1.25 L of dioxane was refluxed with mechanical stirring for 4 h. The hot reaction mixture was filtered through a Celite pad and the solids were washed with three 400-mL portions of hot dioxane. The combined filtrate and washings were spin evaporated in vacuo, and the white solid was dried in vacuo at ~110 °C to remove residual dioxane: yield, 41.2 g (91%); mp 189–192 °C. This was free of starting material as determined by NMR and was sufficiently pure for subsequent transformations.

1-[4-(*N*-Triphenylmethyl)imidazolyl]ethanol (5b). Method A. To an ice-bath-cooled solution of 6.7 mL (20.0 mmol) of 3 M CH_3MgBr in 75 mL of dry Et_2O in a flame-dried, 250-mL three-neck round-bottom flask equipped with a $CaCl_2$ drying tube, pressure equalizing addition funnel, and N_2 inlet tube was added a solution of 3.38 g (10.0 mmol) of **4** in 50 mL of freshly distilled THF. After 1.5 h at ambient temperature a concentrated solution

of 1.34 g (25.0 mmol) of NH_4Cl in H_2O was added to the reaction mixture. The mixture was stirred for 1 h and filtered and the solids were washed with THF. The combined filtrate and washes were washed with H_2O and brine, dried (Na_2SO_4), and spin evaporated in vacuo to afford a white powder which was recrystallized from $CHCl_3$–hexanes: yield, 3.10 g (87%); mp 156–157 °C. An additional recrystallization afforded the analytical sample: mp 160–161 °C.

1-(4-Imidazolyl)ethanol Hydrochloride (6b). Method B. A solution of 19.5 g (55.0 mmol) of **5b** in 200 mL of 2 N HCl was heated on a steam bath for 40 min during which time a voluminous precipitation of Ph_3COH occurred. The reaction mixture was cooled and filtered, and the solids were washed with H_2O. The combined filtrate and washes were evaporated to two-thirds the original volume when additional precipitation occurred. This mixture was again cooled and filtered, and the filtrates were spin evaporated in vacuo. EtOH was added to the residual syrup and evaporated to remove the last traces of H_2O. This syrup was digested with Et_2O to give a solid which was recrystallized from EtOH–Et_2O: yield, 6.71 g (82%); mp 121–124 °C. The analytical sample had mp 123–124 °C.

Ethyl α-Acetamido-α-carbethoxy-β-(4-imidazolyl)butyrate Hydrate (9b). Method C. To 6.65 g (44.7 mmol) of **6b** hydrochloride in a 100-mL round-bottomed flask topped with a condenser and cooled on an ice bath was added 20 mL of thionyl chloride. Vigorous effervescence ensued and after a few seconds subsided. The resultant solution was heated at reflux for 20 min, cooled, diluted with benzene, and spin evaporated in vacuo. The residue was covered with benzene and reevaporated several times to remove the last traces of $SOCl_2$, then dissolved in ethanol–benzene (1:1), and spin evaporated in vacuo to give **1-(4-imidazolyl)ethyl chloride hydrochloride (7b)** as a hygroscopic solid: yield, 7.20 g (96%); mp 92–96 °C which was used without further purification.

To a solution of 2.68 g (49.6 mmol) of NaOMe and 50 mL of anhydrous EtOH in a 200-mL round-bottom flask equipped with a magnetic stirrer, $CaCl_2$ drying tube, and N_2 inlet tube was added 5.36 g (24.6 mmol) of diethyl acetamidomalonate. After 0.5 h the solution was cooled on an ice bath and 3.74 g (22.4 mmol) of crude **7b** hydrochloride in 20 mL of EtOH was added. After 18 h at ambient temperature the reaction mixture was filtered, and the solids were washed with EtOH. The combined filtrate and wash was spin evaporated in vacuo and the residue was dissolved in 100 mL of $CHCl_3$ which was washed with four 10-mL portions of H_2O and 10 mL of brine, dried ($MgSO_4$), and spin evaporated in vacuo. The residual syrup was crystallized by trituration with wet ether: yield, 4.40 g (59%); mp 63–66 °C. Recrystallization of a portion from water gave the analytical sample: mp 66–71 °C.

α-Amino-β-(4-imidazolyl)butyric Acid (10b). Method D. A solution of 3.36 g (10.2 mmol) of **9b** hydrate and 50 mL of 12 N HCl was heated on a steam bath for 19 h. The reaction mixture was cooled, filtered to remove some tar, and spin evaporated in vacuo to afford the amino acid hydrochloride as a syrup. An aqueous solution of this material was applied to a column of 70 g of ion-exchange resin [Rexyn 101(H)] and washed with H_2O, and the free amino acid was eluted with dilute NH_4OH. The eluate was spin evaporated in vacuo to afford a hard foam: yield, 1.67 g (91%); mp 218–224 °C dec. Recrystallization of 0.540 g from EtOH–H_2O afforded the analytical sample: yield, 0.344 g (59%); mp 231–233 °C dec.

Methyl α-Amino-β-(4-imidazolyl)butyrate Dihydrochloride (11b). Method E. To a stirred, ice-bath-cooled mixture of 0.50 g (2.95 mmol) of **10b** and 5 mL of MeOH was cautiously added 2 mL of $SOCl_2$. The resultant solution was stirred at ambient temperature with protection from moisture for 24 h and then heated at reflux for 6 h. The solution was spin evaporated in vacuo to give a foam which was crystallized from Et_2O–MeOH: yield, 0.180 g (24%); mp 188–189 °C eff.

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References and Notes

(1) J. L. Kelley, C. A. Miller, and H. L. White, *J. Med. Chem.*, **20**, 506 (1977).
(2) N. F. Albertson and S. Archer, *J. Am. Chem. Soc.*, **67**, 308 (1945).
(3) M. Bernabé and A. Burger, *J. Med. Chem.*, **14**, 883 (1971).
(4) A. Burger, M. Bernabé, and P. W. Collins, *J. Med. Chem.*, **13**, 33 (1970).
(5) J. R. Totter and W. J. Darby in "Organic Syntheses", Collect. Vol. III, E. C. Horning, Ed., Wiley, New York, N.Y., 1955, p 460.
(6) H. R. Matthews and H. Rapoport, *J. Am. Chem. Soc.*, **95**, 2297 (1973).
(7) Unpublished results from this laboratory.
(8) M. Brenner and W. Huber, *Helv. Chim. Acta*, **36**, 1109 (1953).
(9) B. R. Baker, "Design of Active-Site-Directed Irreversible Enzyme Inhibitors; the Organic Chemistry of the Enzymic Active-Site", Wiley, New York, N.Y., 1967, p 116.
(10) F. L. Pyman, *J. Chem. Soc.*, **109**, 186 (1916).
(11) E. P. Popadopoulos, A. Janar, and C. H. Issidorides, *J. Org. Chem.*, **31**, 615 (1966).

3-Aryl-*as*-triazines as Potential Antiinflammatory Agents

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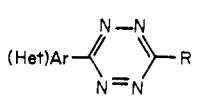
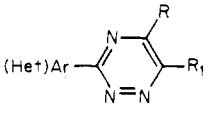
A number of 3-aryl-*as*-triazines were synthesized as analogues of 3-aryl-*s*-tetrazines which have extensive antiinflammatory activity. The 3-aryl-*as*-triazines displayed activity when tested against carrageenan-induced edema in the rat but were inactive in further evaluation.

Aryl-*s*-tetrazines (1)[1] displayed antiinflammatory activity when tested against carrageenan-induced edema in the rat, UV-induced erythema in the guinea pig, and adjuvant-induced arthritis in rats. These agents were also active analgesics but caused a lowering of the red blood cell count in normal healthy rats. As an extension of these studies, a number of structurally related aryl-*as*-triazines (**2**) were prepared and their antiinflammatory effects were examined.



1, R = H, CH_3, C_2H_5



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Chemistry. *as*-Triazines were prepared by the condensation of α,β-dicarbonyl compounds and amidrazones[2] as described in Scheme I. The reaction of aryl amidrazones, generated in situ,[3] and α,β-dicarbonyl compounds gave varying results with substantial amounts of polymeric materials and/or self-condensation products also being produced. Reaction of free amidrazones with bisulfite