from UDP-GlcUA to phenolphthalein. The GlcUA-phenolphthalein conjugate does not absorb at 540 nm. The assay was a modified version of a procedure obtained from Sigma Chemical Co.

A stock solution of Tris (0.3 M), phenolphthalein (1 mM), MgCl (45 mM), bovine serum albumin (3 mg/mL), and β-mercaptoethanol (3 mM) was prepared in distilled water, and the pH was adjusted to 8.0. A solution of ~0.2 U/mL uridine 5'-diphosphoglucuronyltransferase (EC 2.4.1.17, from bovine liver, Sigma) was prepared in distilled water. A 0.3 mM solution of UDP-GlcUA was also prepared. Two solutions were prepared as follows:

	solution 1	solution 2
stock solution	6.3 mL	6.3 mL
enzyme	0.2 mL	0.0 mL
distilled water	0.0 mL	0.2 mL
UDP-GlcUA	0.5 mL	0.5 mL

Enzymatic transfer of GlcUA from UDP-GlcUA to phenolphthalein was initiated by addition of the enzyme. Aliquots of 0.25 mL were withdrawn at intervals and quenched into 1.5 mL of 95% ethanol. The solutions were centrifuged (13000g, 5 min), 0.5 mL of supernatant was added to 4 mL of glycine buffer (0.2 M, pH 10.4), and the absorbance at 540 nm was recorded. The reaction was allowed to proceed until no further change in A_{540} was observed. The concentration of UDP-GlcUA was calculated from the difference between the final A_{540} from solution 1 and the A_{540} from solution 2, utilizing a molar absorbtivity for phenolphthalein at pH 10.4 of 38 500 L mol^{-1} cm^{-1}.

Acknowledgment. This work was supported by the NIH, grants GM30367 and GM39589.

Registry No. UDP-Glc, 133-89-1; UDP-GlcUA, 2616-64-0; UDP-Glc DH, 9028-26-6; UDP-glucuronyltransferase, 9030-08-4; pyruvate DH, 9014-20-4; lactate DH, 9001-60-9.

Synthesis and X-ray Structure of the Chiral, Polydentate Cation Binder *N*-[*N*-[(5-Methyl-2-thienyl)methylidene]-L-methionyl]histamine

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A synthetic route has been developed to obtain *N*-[*N*-[(5-methyl-2-thienyl)methylidene]-L-methionyl]histamine, optically pure (α^{20} = −8.13°/L mol^{-1} dm^{-1}), from a sequence of reactions involving L-methionine, histamine, and 5-methyl-2-thiophenecarbaldehyde. The described procedure affords gram quantities in an overall yield of 40%, without the need of any chromatographic techniques. Moreover, the removal of the well-known *tert*-butyloxycarbonyl amino-protection group (BOC) with gaseous hydrochloric acid, in the present synthesis, had considerable advantages compared with the commonly applied trifluoroacetic acid method. The structure of *N*-[*N*-[(5-methyl-2-thienyl)methylidene]-L-methionyl]histamine in the solid has been determined by X-ray diffraction techniques. $C_{16}H_{22}N_4OS_2$ crystallizes in the monoclinic space group $P2_1$, with a = 5.233 (1), b = 9.556 (1), and c = 17.919 (1) Å; β = 98.32 (1)°; and Z = 2. Noteworthy aspects of the tertiary structure of the molecule are the fact that it is almost flat, the three arms connected to methionine-C_α, being the (thienylmethylidene)amino moiety, the "imidazole-amide" fragment, and the methionine side chain, spread out. π-Conjugation causes the (thienylmethylidene)amino moiety to have a planar s-cis conformation, and the methionine side chain's all-trans conformation is due to vicinal interactions. The gauche conformation of the "imidazole-amide" does not have a clear origin, but is no artifact of the solid state. Intra- and intermolecular hydrogen bonds are prominently present, the former determining the relative orientations of the aforementioned arms and the latter linking the title molecules into two-dimensional, sheetlike entities.

Introduction

The geometry of the metal site in coordination complexes is determined by an intricate interplay of the ligand molecule and the metal center. Structures of systems with easily adapting ligating functions, like monodentate ligands, are generally dominated by the metal's preferences. However, specific polydentate ligand environments, with built in conformational constraints, can radically alter the characteristics of the metal–ligand interaction. The best examples of the latter principle are metal proteins: coordination compounds, fine-tuned by nature for specific tasks through selected sets of heteroatom donors in organic superstructures.[1]

We have studied the coordination behavior of sets of two nitrogen and two sulfur donor atoms toward silver(I) and copper(I) cations, striving to create M–N_2S_2 chromophores[2] and aiming to develop a better understanding of the structural aspects involved. The polydentate ligands used have been based on (thienylmethylidene)amino fragments, Schiff-bases derived from 2-thiophenecarbaldehyde, and an amine.[3] Thus far, we have reported extensively on complexes in which the metal's N_2S_2 environment is formed by two of these (thienylmethylidene)amines.[4] In order to get a less symmetrical coordination geometry, the

(1) See for example: (a) *Inorganic Biochemistry*; Eichhorn, G. L., Ed.; Elsevier: Amsterdam, 1973; Vols. 1-2. (b) *Metal Ions in Biological Systems*; Sigel, H., Ed.; Marcel Dekker, Inc.: New York, 1974-1981; Vols. 1-13.

(2) Cf. the blue copper protein active site. See for example: (a) Guss, J. M.; Freeman, H. C. *J. Mol. Biol.* **1983**, *169*, 521-563. (b) Guss, J. M.; Harrowell, P. R.; Murata, M.; Norris, V. A.; Freeman, H. C. *J. Mol. Biol.* **1986**, *192*, 361-387. (c) Adman, E. T.; Jensen, L. H. *Isr. J. Chem.* **1981**, *21*, 8-12. (d) Norris, G. E.; Anderson, B. F.; Baker, E. N. *J. Am. Chem. Soc.* **1986**, *108*, 2784-2785.

(3) Cf.: van Koten, G.; Vrieze, K. *Adv. Organomet. Chem.* **1982**, *21*, 151-239.

(4) (a) van Stein, G. C.; van Koten, G.; Vrieze, K.; Spek, A. L.; Klop, E. A.; Brevard, C. *Inorg. Chem.* **1985**, *24*, 1367-1375. (b) van Stein, G. C.; van Koten, G.; Blank, F.; Taylor, L. C.; Vrieze, K.; Spek, A. L.; Duisenberg, A. J. M.; Schreurs, A. M. M.; Kojić-Prodić, B.; Brevard, C. *Inorg. Chim. Acta* **1985**, *98*, 107-120. (c) Spek, A. L.; Duisenberg, A. J. M.; van Stein, G. C.; van Koten, G. *Acta Crystallogr.* **1985**, *C41*, 374-377. (d) Modder, J. F.; Ernsting, J.-M.; Vrieze, K.; De Wit, M.; Stam, C. H.; van Koten, G. *Inorg. Chem.* **1991**, *30*, 1208-1214.

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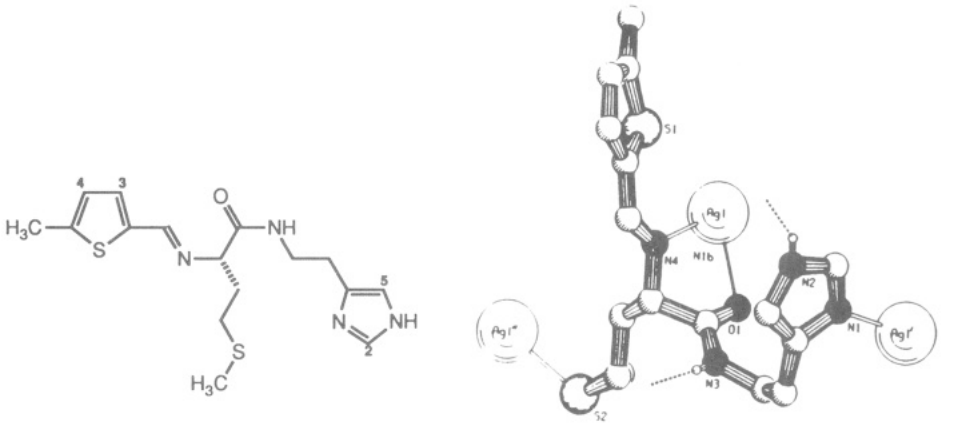


Figure 1. Schematic structure of (5Me)Th-Met-Histam (left) and part of the structure of the $[Ag\{(5Me)Th\text{-}Met\text{-}Histam\}]^+$ polymer showing the conformation of the complexed ligand.

cation-binding molecule *N*-[*N*-(5-methyl-2-thienylmethylidene)-L-methionyl]histamine (abbreviated as (5Me)Th-Met-Histam,[5] Figure 1), was recently designed.

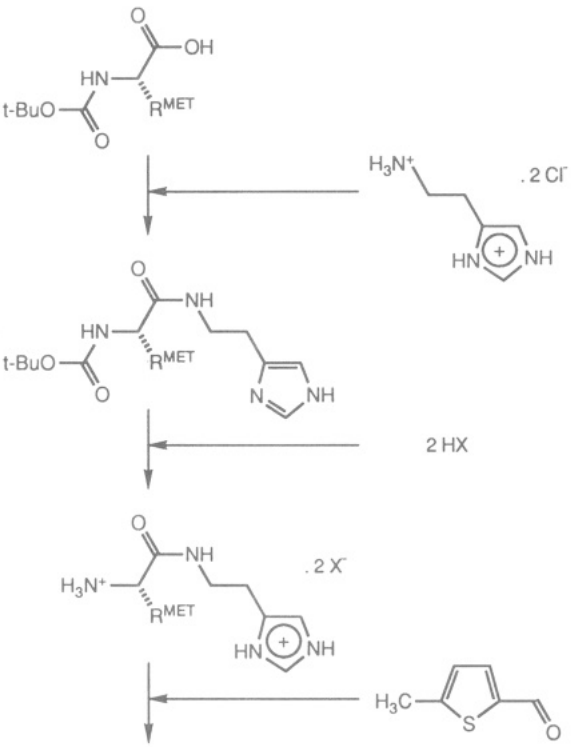
(5Me)Th-Met-Histam incorporates an N,N′,S,S′ heteroatom set, suitable for coordination and specially arranged to accommodate a single metal center. CPK molecular model studies confirmed that a folded molecule conformation, bringing together the potentially bidentate coordinating, N,S donating (thienylmethylidene)amino moiety and the two monodentate donor functions, i.e. the thioether S and imidazole N atoms, is possible. It was therefore surprising to observe that reacting equimolar amounts of (5Me)Th-Met-Histam and $Ag(I)O_3SCF_3$ in methanol did not yield a mononuclear complex. Instead, as evidenced by the crystal structure,[6] a fascinating helical coordination polymer is stereoregularly formed, due to the fact that each molecule of (5Me)Th-Met-Histam is stretched out, with the intended donor functions coordinating to three separate Ag(I) cations, see Figure 1. The completely stereoselective self-assembly process has to be induced by the ligand's single stereogenic center, i.e. methionine-C_α.

Apparently, the "coordinating power" of the Ag(I) cations is not enough to afford mononuclear complexes of (5Me)Th-Met-Histam. Therefore, the organic ligand might possess some interesting steric constraints. This prompted us to investigate the solid-state structure of uncomplexed (5Me)Th-Met-Histam, which we will present and discuss in this paper. Moreover, the synthetic route developed is of interest because it produces gram quantities of the product in reasonable yields (overall 40%) and without the use of chromatographic techniques.

Results and Discussion

Synthesis of *N*-[*N*-[(5-Methyl-2-thienyl)-methylidene]-L-methionyl]histamine [(5Me)Th-Met-Histam]. The first step of the synthesis (depicted in Scheme I) involves condensation of BOC-Met-OH with histamine. In order to minimize racemization at methionine-C_α during amide bond formation, preactivation of the acid function through conversion in its succinimide ester

Scheme I



by means of dicyclohexylcarbodiimide (DCC) seemed a promising procedure.[7] According to a procedure published by Hiskey and co-workers,[8] BOC-Met-OH was reacted with *N*-hydroxysuccinimide and DCC, followed by addition of the amine under alkaline conditions. Upon completion of the reaction, the mixture was poured into dilute acid to convert the excess DCC into its practically insoluble urea derivative. An extractive workup was than used to purify BOC-Met-Histam.

Removal of the amino protection function BOC can be achieved by a number of strong acids.[9] Initially, we applied the commonly used method of dissolution in tri-

(5) The nomenclature and abbreviations used in this paper are derived from peptide chemistry conventions. To avoid confusion with histidine, Histam is chosen as abbreviation of histamine. (5Me)Th symbolizes the (5-methyl-2-thienyl)methylidene function.

(6) The Ag(I) complex structure was described in a preliminary communication;[a] a detailed comparison of the structural features of the free and complexed ligand will be published elsewhere.[b] (a) Modder, J. F.; van Koten, G.; Vrieze, K.; Spek, A. L. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1698–1700. (b) Modder, J. F.; Vrieze, K.; Spek, A. L.; Challa, G.; van Koten, G. *J. Am. Chem. Soc.*, submitted.

(7) See for example: Wünsch, E.; et al. *Methoden der Organischen Chemie (Houben-Weyl), Vol. XV/2*; Müller, E., Wünsch, E., Eds.; Georg Thieme Verlag: Stuttgart, 1974; pp 111–113 and references cited.

(8) Hiskey, R. G.; Beacham, L. M.; Matl, V. G. *J. Org. Chem.* **1972**, *37*, 2472–4278.

(9) Wünsch, E.; et al. *Methoden der Organischen Chemie (Houben-Weyl), Vol. XV/1*; Müller, E., Wünsch, E., Eds.; Georg Thieme Verlag: Stuttgart, 1974; pp 117–129.

Table I. Crystal Data and Details of the Structure Determination of (5Me)Th-Met-Histam

crystal data		data collection	
formula, mol wt	$C_{16}H_{22}N_4OS_2$	radiation	Mo Kα(Zr), 0.71073
mol wt	350.50	θ_{max}, deg	27.5
crystal system	monoclinic	$\omega/2\theta$ scan, °$\Delta\omega$	0.65 + 0.35 tan(θ)
space group	$P2_1$	dataset	h −6:0; k −12:12; l −23:23
Z	2	reference reflections	−104; 020
F(000), electrons	372	tot data, uniq data	9049, 4075
a, Å	5.233 (1)	observed data	2847
b, Å	9.556 (1)	refinement	
c, Å	17.919 (1)	R, R_w, S	0.050, 0.044, 0.58
β, deg	98.32 (1)	weighting scheme	$w^{-1} = \sigma^2(F)$
V, Å^3	886.6 (2)	n_{ref}, n_{par}	2846, 219
μ, cm^{-1}	3.0	max. and av shift/error	0.5, 0.1
d_{calc}, g cm^{-3}	1.313	min and max. resd dens, eA^{-3}	−0.40, 0.71

fluoroacetic acid (TFA). Apart from taking a relatively long time (>24 h), purification of the resulting bis(trifluoroacetic acid salt) proved to be difficult because the gel-like substance, remaining after removal of excess TFA by distillation, could not be handled conveniently. This particular problem was overcome by washing the gel, through stirring with ether, followed by decantation. After executing this procedure a few times, drying in vacuo afforded H-Met-Histam·2TFA as a hygroscopic but manageable solid.

As the use of the bis(trifluoroacetic acid salt) proved to be disadvantageous during purification of the final product (vide infra), the deprotection procedure was adapted to afford the bis(hydrochloride salt). This was achieved by bubbling HCl gas through a solution of BOC-Met-Histam in ethyl acetate, an adaptation of a method described by Schwyer et al.,[10] which removed the BOC group in a clean and very rapid way (≈25 min). After decantation of the solvent, washing with diethyl ether, and drying in vacuo, H-Met-Histam·2HCl could be isolated.

To complete the synthesis of the target molecule, the thienylmethylidene function was introduced through an imine bond by refluxing equimolar amounts of the salt of H-Met-Histam and 5-methyl-2-thiophenecarbaldehyde in ethyl acetate over a large excess of Na_2CO_3. In the case of the bistrifluoroacetic acid salt derivative, it proved impossible to remove all of the sodium trifluoroacetate formed, by extraction of the ethyl acetate layer with water. Therefore, the final version of the synthesis was based on the bishydrochloride salt, allowing complete removal of sodium chloride by water extraction. The remaining gel, after drying and evaporation of ethyl acetate, afforded (5Me)Th-Met-Histam as a white solid upon stirring with diethyl ether.

Structure of (5Me)Th-Met-Histam. The molecular geometry of (5Me)Th-Met-Histam and the adopted numbering scheme are shown in Figure 2. Selected bond distances and angles are listed in Table III; those not mentioned are well within the accepted ranges.

(5Me)Th-Met-Histam can be viewed as a set of three different (multi)functionalized arms, being an "imidazole-amide" unit, a (thienylmethylidene)amino moiety, and a methionine side chain, connected to a single stereogenic carbon center, in casu methionine-C_α (C7). The most notable feature of the solid-state structure is the fact that these arms are almost maximally spread out, creating

(10) Schwyer, R.; Kappeler, H.; Iselin, B.; Rittel, W.; Zuber, H. *Helv. Chim. Acta* **1959**, *42*, 1702–1708.

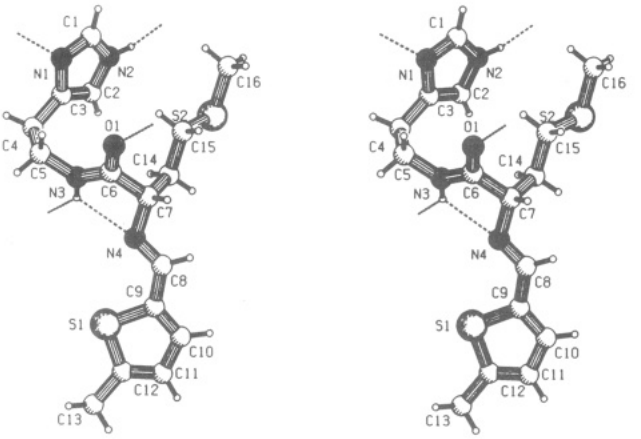


Figure 2. Stereoview of (5Me)Th-Met-Histam with labeling.

Table II. Fractional Atomic Coordinates and Equivalent Isotropic Thermal Parameters of the Non-hydrogen Atoms of (5Me)Th-Met-Histam

atom	x/a	y/b	z/c	U^{eq},[a]
S1	0.3800 (2)	0.2710[b]	0.00017 (5)	0.0421 (3)
S2	−0.4956 (2)	0.7080 (1)	−0.31291 (6)	0.0606 (4)
O1	−0.5833 (5)	0.2073 (3)	−0.2490 (1)	0.0554 (9)
N1	−0.4711 (6)	0.1931 (3)	−0.4625 (2)	0.045 (1)
N2	−0.4128 (7)	0.4194 (3)	−0.4740 (2)	0.048 (1)
N3	−0.1530 (6)	0.1870 (3)	−0.2498 (2)	0.040 (1)
N4	−0.0737 (6)	0.3480 (3)	−0.1208 (2)	0.040 (1)
C1	−0.5674 (7)	0.3096 (4)	−0.4928 (2)	0.046 (1)
C2	−0.2046 (8)	0.3685 (4)	−0.4280 (2)	0.050 (1)
C3	−0.2381 (7)	0.2282 (4)	−0.4208 (2)	0.037 (1)
C4	−0.0710 (7)	0.1227 (4)	−0.3763 (2)	0.045 (1)
C5	−0.1643 (8)	0.0757 (4)	−0.3049 (2)	0.045 (1)
C6	−0.3605 (7)	0.2451 (4)	−0.2273 (2)	0.037 (1)
C7	−0.3124 (7)	0.3688 (4)	−0.1744 (2)	0.038 (1)
C8	−0.0524 (7)	0.4184 (4)	−0.0607 (2)	0.039 (1)
C9	0.1624 (7)	0.4071 (3)	−0.0009 (2)	0.038 (1)
C10	0.2193 (8)	0.4860 (4)	0.0619 (2)	0.051 (1)
C11	0.4358 (8)	0.4383 (4)	0.1109 (2)	0.055 (2)
C12	0.5434 (7)	0.3236 (4)	0.0861 (2)	0.042 (1)
C13	0.7707 (8)	0.2413 (5)	0.1238 (2)	0.058 (2)
C14	−0.2908 (7)	0.5039 (4)	−0.2192 (2)	0.042 (1)
C15	−0.5245 (7)	0.5332 (4)	−0.2772 (2)	0.041 (1)
C16	−0.7974 (8)	0.7226 (5)	−0.3732 (3)	0.071 (2)

[a] U^{eq} = 1/3 of the trace of the orthogonalized U tensor. [b] Fixed parameter.

Table III. Selected Distances (Å) and (Dihedral) Angles (deg) of (5Me)Th-Met-Histam

H[N3]···N4	2.37 (3)
H[N3]···O1′	2.30 (4)
H[N2]···N1″	1.90 (4)
N3–H[N3]···N4	108 (3)
N3–H[N3]···O1′	137 (3)
N4···H[N3]···O1′	114 (2)
N4–C8–C9–S1	−12.2 (5)
O1–C6–N3–H[N3]	−170 (3)
N4–C7–C14–C15	178.8 (3)
C7–C14–C15–S2	170.0 (2)
C14–C15–S2–C16	−175.8 (3)

a rather flat molecule. The thienylmethylidene moiety is close to planar due to π-conjugation between the imine function (which has the E configuration as found in all aldimines of this type)[4,11] and the thiophene ring system.

(11) Due to the low activation energy of the imine E/Z isomerization, aldimines exclusively adopt the sterically less hindered E configuration.[a] In a forthcoming study we will demonstrate that in the case of thiophene ketimines, both the E and Z configurations can be isolated.[b] (a) Patai, S. *The Chemistry of the Carbonyl Group*; Interscience Publishers: New York, 1966; p 610. (b) Modder, J. F.; Leijen, R. J.; Vrieze, K.; van Koten, G.; Smeets, W. J. J.; Spek, A. L. *J. Chem. Soc. Dalton Trans.*, submitted.

As predicted by MNDO and AM1 calculations,[12] the s-cis configuration of the S1–C9–C8–N4 moiety is energetically favored over the s-trans form. The all-trans conformation of the N4–C7–C14–C15–S2–C16 fragment clearly suggests that the stereochemistry of the methionine side chain is governed by the demands of its vicinal interactions. The overall structure of the "imidazole-amide" branch cannot easily be explained. The amide group (O1–C6–N3–H) does possess the commonly found trans configuration.[13] However, the gauche conformation of the remaining part (N3–C5–C4–imidazole) is certainly not the stereochemistry expected on basis of the vicinal interactions. Whatever the driving force, it is not attributable to an artifact of this particular crystal, since in the Ag(I) complex of (5Me)-Th-Met-Histam, the torsion angles of the "imidazole-amide" fragment are very similar (compare the conformations of the free and complexed ligand in Figures 1 and 2).[6] This indicates that the solid-state structure of the 1:1 Ag(I)OTF coordination polymer seems to be mainly ligand controlled.

Hydrogen bonding interactions in the structure of (5Me)Th-Met-Histam are prominently present. An intramolecular hydrogen bond of the amide hydrogen H[N3] with the imine nitrogen N4, determines the relative orientations of the "imidazole-amide" and (thienylmethylidene)amino arms. The hydrogen bonding of H[N3] is bifurcated,[14] since it also partakes in an intermolecular hydrogen interaction with amide O1 of a translated molecule, as usually found,[15] linking all amide functions. The imidazole ring systems are connected in a similar way, as a result of an intermolecular hydrogen bond of H[N2] with N1 of a translated molecule.[16] Both intermolecular interactions are independent, in the *a*- and *b*-axis directions, respectively. Therefore, a two-dimensional network of sheetlike entities is formed, which are stacked in the *c*-axis direction to construct the three-dimensional crystal.

Experimental Section

Physical Measurements. All NMR data were obtained in CD_3OD at room temperature. For ^{19}F spectra $CFCl_3$ was used as an external reference. Optical rotations were measured in methanol of p.a. grade at 293 K, λ = 589 nm, 1 = 2 dm.

Preparation of *N*-[*N*-[(5-Methyl-2-thienyl)-methylidene]-L-methionyl]histamine [(5Me)Th-Met-Histam]. Diethyl ether and hexane were freshly distilled and stored under nitrogen. Other solvents used in the preparation were of p.a. grade and used as such unless denoted otherwise. All organic chemicals used were purchased from Janssen Chimica and were used without further purification. *N*-(*tert*-Butyloxycarbonyl)-L-methionine (BOC-Met-OH) is commercially available, but the compound used was synthesized according to ref 17 (^1H NMR spectrum submitted as supplementary material). HCl gas was purchased from Hoekloos.

***N*-[*N*-(*tert*-Butyloxycarbonyl)-L-methionyl]histamine (BOC-Met-Histam).** In a typical experiment a solution of 17.36 g (83.8 mmol) of dicyclohexylcarbodiimide in 100 mL of ethyl acetate was added to a mixture of 18.90 g (76 mmol) of BOC-Met-OH and 9.65 g (83.8 mmol) of *N*-hydroxysuccinimide in 100 mL of ethyl acetate cooled to 0 °C. The resulting off-white suspension was stirred for 2 h at 0 °C and another 18 h at room temperature. Subsequently the reaction mixture was filtered and the residual dicyclohexylurea was washed with ethyl acetate (3 × 50 mL). The volume of the combined ethyl acetate fractions was reduced to 100 mL by evaporation, after which a suspension of 13.54 g (73.6 mmol) of histamine dihydrochloride and 23.40 g (220.1 mmol) of Na_2CO_3 in 100 mL of water was added. The resulting binary system was stirred for at least 24 h at room temperature. With cold, concentrated hydrochloric acid the water layer was brought to a pH of 1. After 1 h the layers were separated and the ethyl acetate layer was extracted with acidic water (2 × 50 mL). By adding KOH to the combined water layers cooled to 0 °C, the pH was brought to 12. After saturation with NaCl, the water layer was extracted with ethyl acetate (4 × 50 mL). Filtration and evaporation of the combined ethyl acetate layers afforded a light-yellow solid. Yield: 65%. Mp: 82–83 °C. ^1H NMR data (ppm): δ 1.9 (m, Met: H_2C_β), 2.06 (s, Met: H_3C_ϵ), 2.47 (t, Met: H_2C_γ), 2.84 (t, Histam: H_2C_β), 3.44 (t, Histam: H_2C_α), 4.07 (dd, Met: HC_α), 6.85 (s, Histam: H^5), 7.58 (d, Histam: H^2).

***N*-(L-Methionyl)histamine Bis(trifluoroacetic acid salt) (H-Met-Histam·2TFA).** BOC-Met-Histam was dissolved in an appropriate amount (about 3 mL/g) of trifluoroacetic acid and stirred at room temperature for at least 24 h. Subsequently the excess trifluoroacetic acid was removed by distillation. The residue, a brown gel-like substance, was washed by stirring with distilled diethyl ether followed by decantation, a procedure that was repeated until the ether remained colorless. Finally the gel was dried in vacuo, yielding almost quantitatively a white foamy material. The product was very hygroscopic and remained rather sticky; therefore no reproducible melting point could be obtained. ^1H NMR data (ppm): δ 2.0 (m, Met: H_2C_β), 2.09 (s, Met: H_3C_ϵ), 2.49 (t, Met: H_2C_γ), 2.97 (t, Histam: H_2C_β), 3.58 (t, Histam: H_2C_α), 3.93 (t, Met: HC_α), 7.38 (s, Histam: H^5), 8.83 (d, Histam: H^2). ^{19}F NMR (ppm): δ −75.32.

***N*-(L-Methionyl)histamine Bis(hydrochloride salt) (H-Met-Histam·2HCl).** BOC-Met-Histam was dissolved in ethyl acetate (10 mL/g), and HCl gas was bubbled through the solution for 25 min, resulting in an immediate formation of a yellow sticky solid. Subsequently the ethyl acetate was decanted and the solid was washed with diethyl ether (2 × 50 mL). To allow the evolution of excess HCl gas the solid was left open to the air (~3 h) prior to drying in vacuo. This procedure afforded H-Met-Histam·2HCl, a dry but very hygroscopic off-white solid, in almost quantitative yield. Due to the hygroscopicity no constant melting point was measured.

The ^1H NMR data of the bis(hydrochloride salt) and the bis(trifluoroacetic acid salt) (vide supra) are identical.

(5Me)Th-Met-Histam. Derived from the Trifluoroacetic Acid Salt. A mixture of 8.25 g (17.6 mmol) of H-Met-Histam·2TFA, 2.18 g (17.6 mmol) of 5-methyl-2-thiophenecarbaldehyde, and 5.90 g (55.7 mmol) of Na_2CO_3 in ethyl acetate (75 mL) was heated at reflux for 1 h. After cooling to room temperature water (100 mL) was added, and the binary system was stirred for 15 min. Subsequently the layers were separated and the water layer was extracted with ethyl acetate (2 × 50 mL). Filtration and evaporation of the combined ethyl acetate fractions resulted in a brown gel, which was washed with dry diethyl ether in the previously described way (vide supra). Drying the residue in vacuo afforded 4.0 g of an ivory-colored foam. Elemental analysis of this product revealed the presence of fluorine, most probably due to contamination with sodium trifluoroacetate (about 14 mass % on basis of % C).

^1H NMR data: equal to those obtained for (5Me)Th-Met-Histam derived from the bis(hydrochloride salt) (vide infra). ^{19}F NMR data (ppm): δ −75.21.

Derived from the Hydrochloride Salt. A mixture of 5.02 g (16 mmol) of H-Met-Histam·2HCl, 2.04 g (16 mmol) of 5-methyl-2-thiophenecarbaldehyde, and 5.20 g (49 mmol) of Na_2CO_3 in ethyl acetate (30 mL) was processed as described for the bis(trifluoroacetic acid salt) derivative. However in this case the gel, remaining after evaporation of the ethyl acetate, turned into white solids upon stirring with diethyl ether. These solids were collected by filtration and washed with cold diethyl ether. Drying in vacuo yielded 3.30 g (59%) of a white powder, which, according to elemental analyses, was (5Me)Th-Met-Histam of sufficient purity: found (calcd for $C_{16}H_{22}N_4OS_2$): C, 54.81 (54.83); H, 6.52 (6.33); N, 15.83 (15.99); O, 5.25 (4.56); S, 17.70 (18.29). Mp: 91–92 °C. ^1H NMR data (ppm): δ 2.0 (m, Met: H_2C_β), 2.01 (s, Met:

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H_3C_ϵ), 2.4 (m, Met: H_2C_γ), 2.48 (s, (5Me)Th: H_3C), 2.78 (t, Histam: H_2C_β), 3.49 (t, Histam: H_2C_α), 3.90 (dd, Met: HC_α), 6.78 (dd, (5Me)Th: H^4), 6.83 (s, Histam: H^5), 7.23 (d, (5Me)Th: H^3), 7.55 (d, Histam: H^2), 8.26 (s, (5Me)Th: H^{im}).

Optical rotation: $\alpha^{20} = -8.13°$ L mol^{-1} dm^{-1} (concentration independent).

Data Collection and Structure Determination of (5Me)-Th-Met-Histam. Crystallization of (5Me)Th-Met-Histam was achieved from a solution of about 2 g in a mixture of methanol (5 mL), diethyl ether (10 mL), and hexane (5 mL) placed at 4 °C.

X-ray data were collected for a transparent plate-shaped [0.1 × 0.2 × 0.5 mm] crystal, glued on top of a glass fiber. Crystal data and numerical results of the structure determination have been collected in Table I. Cell parameters were derived from the SET4 setting angles of 25 reflections [6° < θ < 12°]. Data were corrected for L_p and averaged [$R_{av} = 0.04$]. The structure was solved by direct methods [SHELXS-86][18] and refined by full-matrix least-squares [SHELX-76].[19] All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms (except for H[N3] that was located from a difference map and its position refined) were introduced on calculated positions and refined with fixed geometry, C–H = 0.98 Å, with two common isotropic thermal parameters. Reflection 001 was omitted from the final refinement cycles. Final coordinates are listed in Table II. Neutral scattering factors were obtained from ref 20 and corrected for anomalous dispersion.[21] The programs PLUTON and PLATON[22] were used for geometrical calculations and illustrations.

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Registry No. BOC-Met-OH, 2488-15-5; H-Histam·2HCl, 56-92-8; BOC-Met-Histam, 124780-96-7; H-Met-Histam·2TFA, 124780-95-6; H-Met-Histam·2HCl, 134781-03-6; (5Me)Th-Met-Histam, 134757-70-3; (5Me)Th-Met-Histam·TFA, 134929-64-9; 5-methyl-2-thiophenecarbaldehyde, 13679-70-4.

Supplementary Material Available: An ORTEP figure (50% probability), H bond network plot, H atom coordinates, anisotropic thermal parameters, bond distances and angles, and NMR spectra of BOC-Met-OH (^{1}H), BOC-Met-Histam (^{1}H), H-Met-Histam·2TFA (^{1}H, ^{19}F), H-Met-Histam·2HCl (^{1}H), and TFA-salt derived (5Me)Th-Met-Histam (^{1}H, ^{19}F) (14 pages); tables of structure factors (25 pages). Ordering information is given on any current masthead page.

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Highly Regioselective Bromination Reactions of Polymethylpyrimidines

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4,5-Dimethyl- and 4,5,6-trimethyl-substituted pyrimidines are brominated at C5-Me with NBS in CCl_4 and at C4(6)-Me with bromine in acetic acid to give the corresponding bromomethyl derivatives in a high yield. The remaining methyl group(s) can also be brominated with high regioselectivity. The 2-methylthio substituent is not oxidized under these conditions.

Introduction

Direct bromination of polymethylbenzenes has been widely used in the synthesis of bromomethyl derivatives.[1] By contrast, a few efficient preparations of bromomethyl-substituted azaaromatic compounds via direct bromination have been reported because overbromination is a major problem. In fact, many successful preparations of tribromomethyl-substituted pyridines,[2] pyrimidines,[3] quinolines,[4] quinoxalines,[4] phenanthridines,[4] and phenanthrolines[5] from the corresponding methyl derivatives are known. Bromination of *o*-dimethyl-substituted pyridines, pyrazine, pyrimidine, and 1,2,4-triazine is of synthetic value for the preparation of the corresponding bis(dibromomethyl) derivatives.[6] These results are in contrast to numerous unsuccessful attempts to improve the low-yield synthesis of 2,6-bis(bromomethyl)pyridine by bromination of 2,6-dimethylpyridine under a variety of experimental conditions.[1,7] The direct bromination of only one methyl group of the latter pyridine[7a] or its 3,5-isomer[8] was also inefficient. Interestingly, however, regioselective brominations of 2,3-dimethylpyridine[9] and 3,4-dimethylpyridine[8] with 1 equiv of NBS have been reported to give mainly a 3-(bromomethyl)-substituted product in both cases, albeit in a low overall yield. A similar regioselectivity was observed in the reaction of 4,6-dichloro-2,5-dimethylpyrimidine with NBS,[10] which gave a 5-(bromomethyl)-pyrimidine. Of related interest is opposite regioselectivity of the bromination reaction of ethyl 6-hydroxy-2,5-dimethyl-4-pyrimidinecarboxylate with bromine in acetic

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