Synthesis, Absolute Configuration, Stereoselectivity, and Receptor Selectivity of ($\alpha R,\beta S$)-α,β-Dimethylhistamine,† a Novel Highly Potent Histamine H_3 Receptor Agonist‡

Ralph Lipp,§ Jean-Michel Arrang,‖ Monique Garbarg,‖ Peter Luger,⊥ Jean-Charles Schwartz,‖ and Walter Schunack*,§

Institute of Pharmacy and Institute of Crystallography, Freie Universität Berlin, D-1000 Berlin 33, Germany, and Unité de Neurobiologie, Centre Paul Broca de l'INSERM, F-75014 Paris, France

Received May 18, 1992

Depending on the selected synthetic pathway, structural variations of the neurotransmitter histamine led to mixtures of α,β-dimethylhistamines as well as to the corresponding pure optical isomers. One of these isomers, namely ($\alpha R,\beta S$)-α,β-dimethylhistamine, proved to be a highly potent H_3 receptor agonist with exceptional receptor selectivity. The absolute configuration of the compound was determined by X-ray structure analysis of its dihydrobromide using the anomalous dispersion of bromine. The optical purity of both enantiomers of *erythro*-α,β-dimethylhistamine was checked by ^{1}H NMR investigations after acylation of the amines with (*R*)-2-methoxy-2-phenylacetyl chloride. As expected H_3 receptors distinguish in a very strong way between the title compound and its $\alpha S,\beta R$-configured enantiomer. The agonistic potency of the latter is 2 orders of magnitude lower than the potency of ($\alpha R,\beta S$)-α,β-dimethylhistamine.

The existence of a third histamine receptor was reported for the first time in 1983.[1-4] It proved to be pharmacologically distinct from the H_1 and H_2 receptors previously described.[5] Being presynaptically located on histaminergic neurons it modulates the synthesis of histamine as well as its release into the synaptical cleft. Thus, activation of the H_3 receptor by agonists leads to a decrease of the concentration of the neurotransmitter histamine in the synaptical cleft.[6]

Although the number of H_3 receptors is higher in the central nervous system (CNS),[7] H_3 receptors are located on several peripheral tissues as well.[8-10] Meanwhile the existence of H_3 receptors in the human brain has also been established[11] and with (αR)-α-methylhistamine[7] (Figure 1) the first H_3 agonist has been introduced into clinical trials with human volunteers.[12] The potential therapeutic value of the drug regarding treatment of diseases in the CNS as well as in the respiratory and the gastrointestinal field is currently under investigation within these studies.

Several synthetic attempts have been carried out in search of selective and potent ligands for the H_3 receptor. These trials in the area of H_3 antagonists have led to a number of compounds with good pharmacological in vitro activity,[13-18] but so far only a few selective agonists have been identified.[5] Especially (αR)-α-methylhistamine proved to be highly potent at H_3 receptors while displaying

* Author to whom correspondence should be addressed.

† Nomenclature of substituted histamine derivatives is based on the method of Black and Ganellin.[45]

‡ Presented in part: New Perspectives in Histamine Research, Satellite Symposium of the XIth International Congress of Pharmacology of IUPHAR (Abstract SL07), Noordwijkerhout, July 6-8, 1990. Eur. Pat. Appl. 0 338 939. US Patent 414 923.

§ Institute of Pharmacy, Freie Universität Berlin.

‖ Centre Paul Broca de l'INSERM.

⊥ Institute of Crystallography, Freie Universität Berlin.

(1) Arrang, J.-M.; Garbarg, M.; Schwartz, J.-C. Auto-Inhibition of Brain Histamine Release Mediated by a Novel Class (H3) of Histamine Receptor. *Nature (London)* **1983**, *302*, 832-837.

(2) Arrang, J.-M.; Garbarg, M.; Schwartz, J.-C. Auto-regulation of Histamine Release in Brain by Pre-synaptic H_3-Receptors. *Neuroscience* **1985**, *15*, 553-562.

(3) Arrang, J.-M.; Garbarg, M.; Schwartz, J.-C. *Auto*-inhibition of Histamine Synthesis Mediated by Pre-synaptic H_3-Receptors. *Neuroscience* **1987**, *23*, 149-157.

(4) Ishikawa, S.; Sperelakis, N. A Novel Class (H_3) of Histamine Receptors on Perivascular Nerve Terminals. *Nature (London)* **1987**, *327*, 158-160.

(5) Schwartz, J.-C.; Arrang, J.-M.; Garbarg, M.; Pollard H. A. Third Histamine Receptor Subtype, Localization and Functions of the H_3-Receptor. *Agents Actions* **1990**, *30*, 13-23.

(6) Schwartz, J.-C.; Arrang, J.-M.; Garbarg, M.; Korner, M. Properties and Roles of the Three Subclasses of Histamine Receptors in Brain. *J. Exp. Biol.* **1986**, *124*, 203-224.

(7) Arrang, J.-M.; Garbarg, M.; Lancelot, J.-C.; Lecomte J.-M.; Pollard, H.; Robba, M.; Schunack, W.; Schwartz, J.-C. Highly Potent and Selective Ligands for Histamine H_3-Receptors. *Nature (London)* **1987**, *327*, 117-123.

(8) Ea-Kim, L.; Oudart, N. A. Highly Potent and Selective H_3 Agonist Relaxes Rabbit Middle Cerebral Artery, In Vitro. *Eur. J. Pharmacol.* **1988**, *150*, 393-396.

(9) Ichinose, M.; Stretton, C. D.; Schwartz, J.-C.; Barnes, P. J. Histamine H_3 Receptors Inhibit Cholinergic Neurotransmission in Guinea Pig Airways. *Br. J. Pharmacol.* **1989**, *97*, 13-15.

(10) Trzeciakowski, J. P. Inhibition of Guinea Pig Ileum Contractions Mediated by a Class of Receptor Resembling the H_3 Subtype. *J. Pharmacol. Exp. Ther.* **1987**, *243*, 874-880.

(11) Arrang, J.-M.; Devaux, B.; Chodkiewicz, J.-P.; Schwartz, J.-C. H_3-Receptors Control Histamine Release in Human Brain. *J. Neurochem.* **1988**, *51*, 105-108.

(12) Arrang, J.-M.; Garbarg, M.; Schwartz, J.-C.; Lipp, R.; Stark, H.; Schunack, W.; Lecomte, J. M. The Histamine H_3-Receptor: Roles and Clinical Implications Studied with Agonists. In *New perspectives in histamine research*; Timmerman, H.; van der Goot, H., Eds.; Birkhäuser Verlag: Basel, 1991; pp 55-67.

(13) Arrang, J.-M.; Garbarg, M.; Lancelot, J.-C.; Lecomte, J.-M.; Robba, M.-F.; Schwartz, J.-C. Preparation and Therapeutic Application of (Imidazol-4-yl)piperidines. Eur. Pat. Appl. 0 197 840, 1986 (Institut national de la santé et de la recherche médicinale, Université de Caen, Société Civile Bioprojet).

(14) Van der Werf, J. F.; Bijloo, G. J.; Van der Vliet, A.; Bast, A.; Timmerman, H. H_3 Receptor Assay in Electrically-Stimulated Superfused Slices of Ratbrain Cortex; Effects of N^{α}-Alkylated Histamines and Impromidine Analogues. *Agents Actions* **1987**, *20*, 239-243.

(15) Van der Werf, J. F.; Bijloo, G. J.; Van der Vliet, A.; Timmermann, H. HA Autoreceptor Assay with Superfused Slices of Rat Brain Cortex and Electrical Stimulation. *Eur. J. Pharmacol.* **1987**, *138*, 199-206.

(16) Lipp, R.; Schunack, W.; Arrang, J.-M.; Garbarg, M.; Schwartz, J.-C. Synthesis and H_3-Antagonistic Activity of N^{α}-substituted Histamine Derivatives. Xth International Symposium on Medicinal Chemistry (Abstract P-119) Budapest, August 15-19, 1988.

(17) Stark, H.; Lipp, R.; Schunack, W.; Arrang, J.-M.; Defontaine, N.; Schwartz, J.-C. Structural Variations Outgoing from N^{α}-Acylated Histamine Derivatives and Their Influence on H_3-Antagonistic Activity. In New Perspectives in Histamine Research, Satellite Symposium of the XIth International Congress of Pharmacology of IUPHAR (Abstract P40). Noordwijkerhout, July 6-8, 1990.

(18) Khalaf, Y. S.; Ganellin, C. R.; Hosseini, S. K.; Tertiuk, W.; Arrang, J.-M.; Defontaine, N. Partial Structures of Thioperamide and Related H_3-Receptor Histamine Antagonists. XIX Meeting of the European Histamine Research Society (Abstract, p 38). Kuopio, May 16-20, 1990.

0022-2623/92/1835-4434$03.00/0

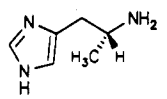
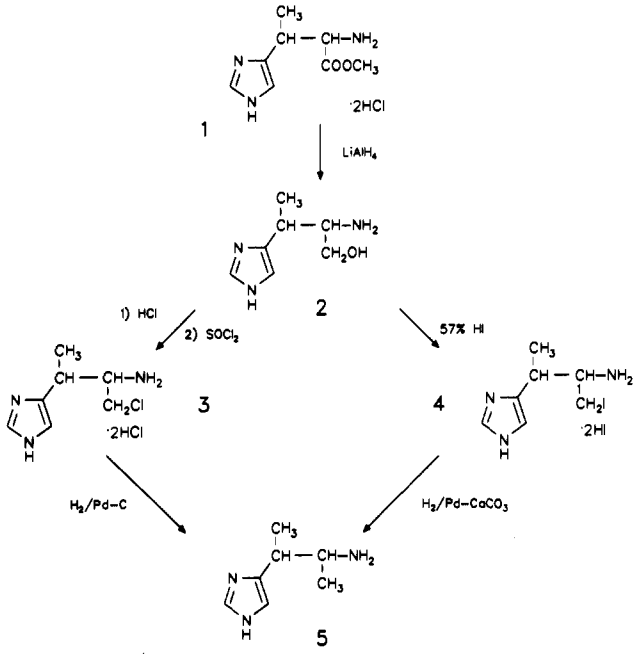


Figure 1. Structure of (αR)-α-methylhistamine.

Scheme I



only inferior activity at other receptors.[5] Taking into account the biological properties of the latter and, at the same time, considering the well-known stereoselectivity of the third histamine receptor,[19] we decided to synthesize several simple side-chain branched derivatives of the natural ligand histamine as potential H_3 agonists.[20] One of these trials resulted in a compound which is slightly more potent than (αR)-α-methylhistamine, being even more selective: ($\alpha R,\beta S$)-α,β-dimethylhistamine (19) (Scheme III).

Chemistry

Synthesis. Lithium aluminum hydride reduction of 1 led to the amino alcohol 2 which was reduced to the corresponding α-methyl derivative via two pathways (Scheme I). Activation to the corresponding chloromethyl derivative 3 and subsequent hydrogenation was more effective than activation to the iodo derivative 4 and its catalytic reduction to 5. ^{1}H NMR investigations of 5 showed that it was a mixture of four stereoisomers consisting of 29% threo and 71% erythro configured material (see Experimental Section).

Since pharmacological tests demonstrated the good H_3 agonistic activity of the isomeric mixture of α,β-dimethylhistamine (5), a second synthetic pathway for selective synthesis of the putative active isomer was designed (Scheme II).

The condensation of 6 with ethyl acetate led to the β-keto ester 7, which was converted to the corresponding ketone 8 by treatment with ethanolic KOH. The condensation of 8 with ethyl 2-(diethylphosphono)propionate was carried out in the presence of sodium amide and led to a mixture of three reaction products. The separation of the products was performed via crystallization and column chromatography on silica gel. Thus, the geometric isomers (*E*)-ethyl 2-methyl-3-[1-(triphenylmethyl)-1*H*-imidazol-4-yl]-2-butenoate (10) and (*Z*)-ethyl 2-methyl-3-[1-(triphenylmethyl)-1*H*-imidazol-4-yl]-2-butenoate (9) as well as their structural isomer (11) were obtained in pure form. Catalytic reduction of *Z*-configured 9 led to the erythro racemate 12. After hydrolysis of 12 the intermediately obtained free carboxylic acid was introduced into a Schmidt reaction. This led to the desired amine in form of its erythro-configured racemate 13.

Starting from the *E*-configured 10 the threo racemate 15 was obtained via analogous reaction steps.

Resolution of the Racemic Mixture (Scheme III). Due to the fact that the erythro racemate 13 showed higher H_3 agonistic activity in pharmacological in vitro tests, we decided to resolve it.

Thus, the racemic amine 13 was dissolved in boiling ethanol (50%) and poured into a hot solution of 2 equiv of (2*S*,3*S*)-*O*,*O*′-*di*toluoyl*t*artaric *a*cid (DTTA). Cooling down to ambient temperature led to the acid salt 16, which was recrystallized from ethanol (50%) several times and subsequently transformed into the dihydrobromide 18. The filtrate of the first crystallization of 16 was used to obtain the acid salt 17. Therefore the included amine base was set free and subsequently treated with (2*R*,3*R*)-*O*,*O*′-ditoluoyltartaric acid. After several recrystallizations the acid salt 17 was transformed into the dihydrobromide 19.

Analysis of Optical Purity (Scheme IV). In order to determine the grade of optical purity of the two enantiomers 18 and 19, the method of Dale et al.[21,22] was applied. Acylation of the chiral amines with (*R*)-2-methoxy-2-phenylacetyl chloride led to diastereomers which were distinguished by different signals in their ^{1}H NMR spectra. To apply this technique for checking the quality of the resolution, the diastereomers 20 and 21 were synthesized starting with small amounts of the acid *O*,*O*′-ditoluoyltartrates 16 and 17. Due to the fact that this purity check was carried out prior to the final conversion of the acid *O*,*O*′-ditoluoyltartrates into the corresponding dihydrobromides, it had basically the function of an in-process control. Application of the latter guaranteed a high level of optical purity for the obtained enantiomers.

Interpreting the ^{1}H NMR spectra of the diastereomers 20 and 21 shows that the most significant differences with regard to their chemical shifts are displayed by the 1′-methyl doublets of 20 (δ = 0.98 ppm) compared to those of 21 (δ = 0.92 ppm, both spectra: 300 MHz, CD_2Cl_2). The total absence of the signal of the opposite diastereomer was required. Meeting this condition, the ^{1}H NMR spectra of 20 as well as 21 offered evidence of optical purity of each one of the two related amines.

Spiking experiments were performed in order to assess the sensitivity of the ^{1}H NMR method. Within these studies optical impurities of 2.5% were clearly detected.

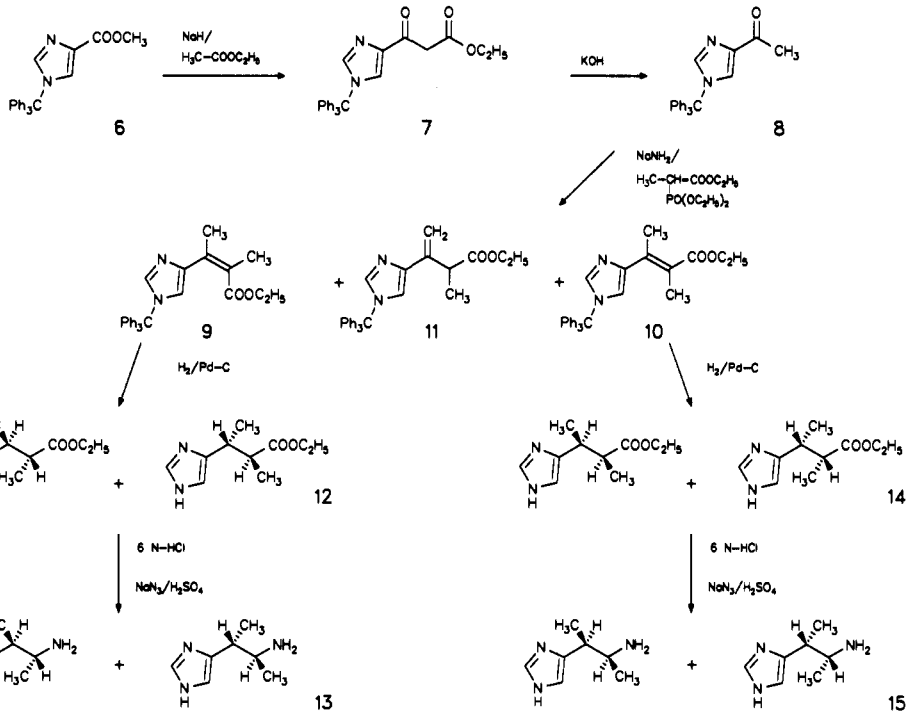
(19) Arrang, J.-M.; Schwartz, J.-C.; Schunack, W. Stereoselectivity of the Histamine H_3-Presynaptic Autoreceptor. *Eur. J. Pharmacol.* **1985**, *117*, 109–114.

(20) Arrang, J.-M.; Garbarg, M.; Lipp, R.; Schunack, W.; Schwartz, J.-C.; Stark, H.; unpublished results.

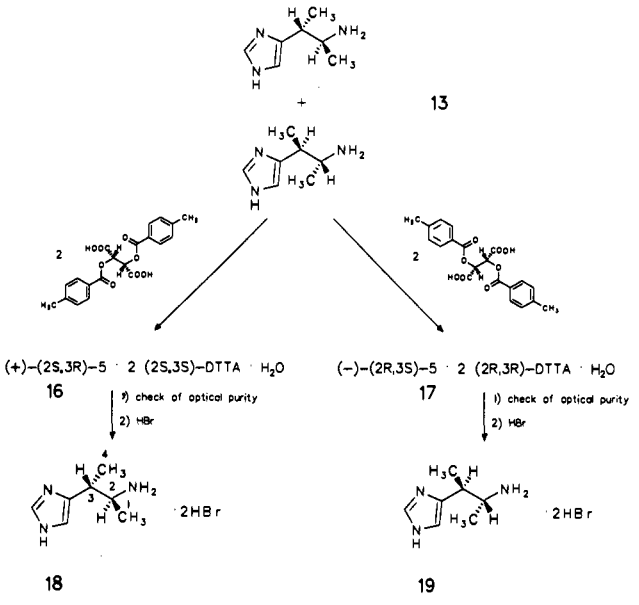
(21) Dale, J. A.; Mosher, H. S. Nuclear Magnetic Resonance Enantiomer Reagents. Configurational Correlations via Nuclear Magnetic Resonance Chemical Shifts of Diastereomeric Mandelate, O-Methylmandelate, and α-Methoxy-α-trifluoromethylphenylacetate (MTPA) Esters. *J. Am. Chem. Soc.* **1973**, *95*, 512–519.

(22) Dale, J. A.; Dull, D. L.; Mosher, H. S. α-Methoxy-α-trifluoromethylphenylacetic Acid, a Versatile Reagent for the Determination of Enantiomeric Composition of Alcohols and Amines. *J. Org. Chem.* **1969**, *34*, 2543.

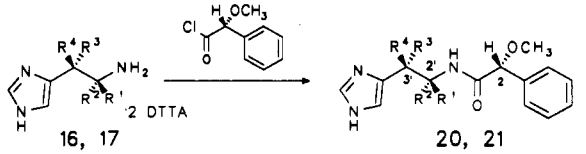
Scheme II



Scheme III



Scheme IV



	R^1	R^2	R^3	R^4	Configuration
20	CH_3	H	CH_3	H	2R, 2'S, 3'R
21	H	CH_3	H	CH_3	2R, 2'R, 3'S

By definition, percent enantiomeric excess equals the percent of the predominant enantiomer in excess of the racemate.[22] Therefore, taking into account the sensitivity of the applied ^1H NMR method, the assigned values of enantiomeric excess are >95% for 18 as well as for 19.

Structural Properties Based on X-ray Analysis and Force Field Calculations. A stereo representation (program SCHAKAL[23]) of one of the two crystallographic independent cations is given in Figure 2. This figure shows the correct enantiomer of 19, which was identified by this X-ray analysis (for details see Experimental Section) to have the $\alpha R,\beta S$-configuration. Bond lengths and angles (see supplementary material) agree within 2-fold (lengths) and 3-fold (angles) standard deviations for the two independent molecules. The values are very close to the corresponding data of the diprotonated histamine fragment in histamine diphosphate monohydrate,[24] except for the bond length C(6)–C(7), which is significantly longer in 19 (1.545 Å compared to 1.491 Å), which is obviously caused by the dimethyl substitution at this site.

The side-chain conformation can be described by the torsion angles τ_1 = 81.8(5)/81.7(4) (mol. 1/mol. 2; for definition of τ_1, τ_2, see Figure 3) and τ_2 = 64.9(4)/64.0(4) in the crystal structure. A similar τ_1 value (84.0) was found in histamine diphosphate monohydrate, but in all X-ray structures of histamine dications previously determined, a trans arrangement was found for τ_2.[25,26] The present gauche conformation, however, was observed for the histidine cation[27] in L-histidine hydrochloride monohydrate. Results of a force field calculation are shown in a two-dimensional Ramachandran plot versus τ_1 and τ_2 in Figure 3. There are relatively sharp energy minima around

(23) Keller, E. *SCHAKAL86, Program for the Graphic Representation of Molecular and Crystallographic Models*; University of Freiburg, Germany, 1986.

(24) Veidis, M. V.; Palenik, G. J.; Schaffrin, R.; Trotter, J. Crystal Structure of Histamine Diphosphate Monohydrate. *J. Chem. Soc. (London) A* **1969**, 2659–2666.

(25) Bonnet, J. J.; Jeannin, Y. Crystallographic Study of the Tetrachlorocobaltate(II) of Diprotonated Histamine. *Acta Crystallogr.* **1973**, *B28*, 1079–1085.

(26) Yamane, T.; Ashida, T.; Kakudo, M. The Crystal Structure of Histamine Sulphate Monohydrate. *Acta Crystallogr.* **1973**, *B29*, 2884–2891.

(27) Donohue, J.; Caron, A. Refinement of the Crystal Structure of Histidine Hydrochloride Monohydrate. *Acta Crystallogr.* **1964**, *17*, 1178–1180.

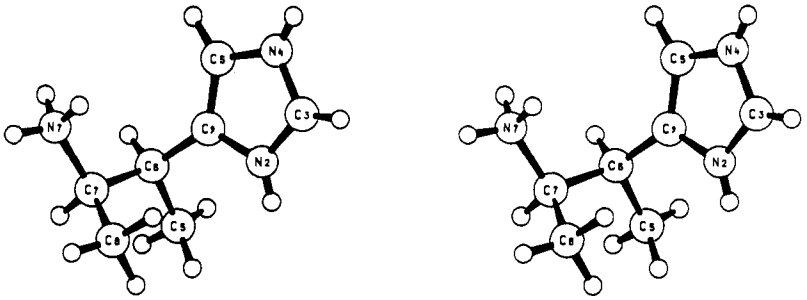


Figure 2. Stereo representation[23] of the correct $\alpha R,\beta S$-enantiomer (19) as derived from the X-ray analysis.

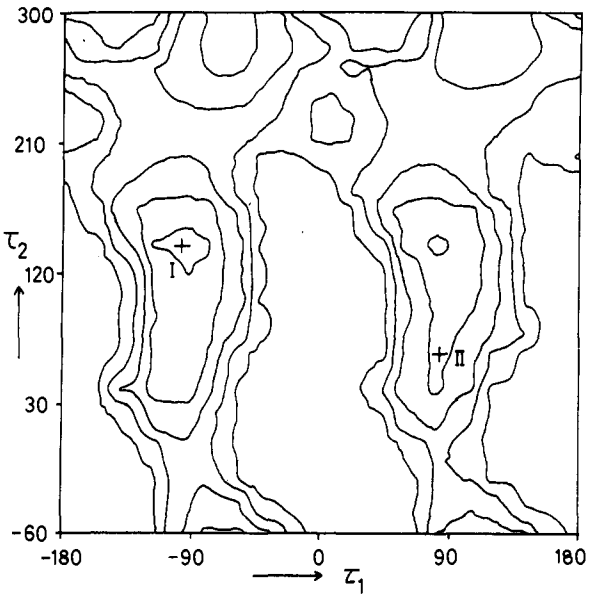


Figure 3. Conformational energy plotted as two-dimensional distribution versus τ_1 = N(2)–C(1)–C(6)–C(7) and τ_2 = C(1)–C(6)–C(7)–N(7). The distribution is obtained from molecular mechanics calculations based on the force field implemented in the CHEMX[46] program package. Contour lines are drawn at 17 kJ/mol intervals. I = absolute minimum. II = conformation of X-ray structure.

$\tau_1 = \pm 90°$; however, a rather broad range of low energy is seen for τ_2 with the absolute minimum at $(\tau_1, \tau_2) = (-100°, 140°)$. The X-ray structure is in a broad hollow next to a second (relative) minimum at (75°, 140°). Obviously there is little energetic constraint in the side-chain conformation, especially along the Cα–Cβ bond, and the actual X-ray conformation may largely be influenced by a total number of 10 hydrogen bonds with which the dication is involved.

All nitrogen-bonded H atoms of the two independent molecules act as donors, while the bromine anions are acceptors in different frequencies: Br(1), five times; Br(2) and Br(3), twice; and Br(4), once. The H···Br$^-$ contacts are in a range of 2.36 (5) to 2.74 (7) Å, the N···Br$^-$ distances vary from 3.275 (4) to 3.541 (4) Å. Since a N···Br$^-$ separation of 3.28–3.44 Å is generally considered for N–H···Br$^-$ hydrogen bonds,[28] one of the contacts found in the crystal structure of 19 must be regarded as a rather weak hydrogen bond.

Biological Results and Discussion

The α,β-dimethylhistamines and their mixtures were tested for H_3 agonistic activity in the model of Arrang et al.,[1] thereby investigating their influence on K^+-induced histamine release from slices of rat brain cortex. In order to determine the receptor selectivity of the α,β-dimethylhistamines, the mixture of four stereoisomers (5) as well as the pure $\alpha R,\beta S$-configured amine (19) were additionally tested for H_2 agonism on the spontaneously beating guinea pig right atrium and H_1 agonism on guinea pig ileum (see Table I).

All α,β-dimethylhistamines proved to be full agonists at H_3 receptors. Although they did not show any difference in their intrinsic activity, their relative potencies vary greatly compared with the natural ligand histamine. The mixture of 29% of erythro- and 71% of threo-configured α,β-dimethylhistamine (5), as obtained from the first synthetic pathway, shows about 5-fold the activity of histamine at H_3 receptors. The fact that presently only one chiral compound, (αR)-α-methylhistamine, was known to be more active than 5 was the reason to search for the most potent of the four stereoisomers of this mixture. Thus, the threo- and erythro-configured racemates of α,β-dimethylhistamine (15, 13) were synthesized. The erythro racemate proved to be 30-fold as active as the threo racemate, thereby showing 10 times the activity of histamine at H_3 receptors (Figure 4). After resolution of the erythro racemate a very high degree of stereoselectivity of H_3 receptors was found for the resulting enantiomers: the $\alpha R,\beta S$-configured eutomer is 100 times more potent than the $\alpha S,\beta R$-configured distomer.

These data correspond with earlier results indicating a high degree of stereoselectivity of H_3 receptors for α-branched histamine derivatives. In a series of α-branched histamines the enantiomer with a relative configuration equivalent to L-histidine always proved to be more potent than its opposite enantiomer[19,7] (e.g. (αR)-α-methylhistamine). Therefore ($\alpha R,\beta S$)-α,β-dimethylhistamine, being the eutomer, perfectly fits in with these findings.

Furthermore, the high degree of differentiation between the erythro and the threo racemate (13 vs 15), both containing one αR-configured stereocenter, suggests that H_3 receptors have a high degree of stereoselectivity for β-branched histamines, too.

The activity profile of 19 shows that it is 130 000-fold more active at H_3 than at H_1 and H_2 receptors. Therefore 19 is at present not only the most active chiral agonist at H_3 receptors but also the most selective one.

($\alpha R,\beta S$)-α,β-Dimethylhistamine is also found to be a substrate for histamine-*N*-methyltransferase (EC 2.1.1.8), being one of the enzymes responsible for the catabolism of histamine.[29,30] The K_m value of the enzyme for 19 was

(28) Jeffrey, G. A.; Saenger, W. In *Hydrogen Bonding*; Jeffrey, G. A., Saenger, W., Eds.; Springer Verlag: Berlin, 1991; p 29.

(29) Schayer, R. W. Catabolism of Histamine in vivo. In *Handbook of Experimental Pharmacology*; Rocha e Silva, M., Ed.; Springer-Verlag: Berlin, 1966; Vol. 18, pp 672–683.

Table I. Comparison of H_3, H_2, and H_1 Agonistic Activities (EC_{50}, M) of α,β-Dimethylhistamines and Histamine[a]

		Agonism					
		H_3: inhibn of [^{3}H]histamine release		H_2: atrial rate		H_1: Ileum contraction	
compd	configuration	EC_{50}	ia	EC_{50}	ia	EC_{50}	ia
histamine		$6.2 \pm 1.4 \cdot 10^{-8}$	1	$1.0 \pm 0.3 \cdot 10^{-6}$	1	$1.4 \pm 0.9 \cdot 10^{-7}$	1
5	29% $\alpha R,\beta S$; $\alpha S,\beta R$ 71% $\alpha R,\beta R$; $\alpha S,\beta S$	$1.2 \pm 0.3 \cdot 10^{-8}$	1	$9.4 \pm 0.6 \cdot 10^{-4}$	0.66	$1.8 \pm 0.5 \cdot 10^{-4}$	0.94
13 (erythro)	$\alpha R,\beta S$; $\alpha S,\beta R$	$6.2 \pm 1.9 \cdot 10^{-9}$	1	ni		ni	
15 (threo)	$\alpha R,\beta R$; $\alpha S,\beta S$	$1.9 \pm 1.2 \cdot 10^{-7}$	1	ni		ni	
18	$\alpha S,\beta R$	$3.5 \pm 1.7 \cdot 10^{-7}$	1	ni		ni	
19	$\alpha R,\beta S$	$3.4 \pm 2.0 \cdot 10^{-8}$	1	$4.1 \pm 2.8 \cdot 10^{-4}$	0.86	$4.2 \pm 2.5 \cdot 10^{-4}$	0.56

[a] All EC_{50} values are given as $\bar{x} \pm$ sem and were calculated from data of three or four independent pharmacological in vitro experiments. Calculation of EC_{50} values at H_3 receptors was carried out according to the method of Parker and Waud[47] while statistical evaluation of the data for H_1 and H_2 agonism was carried out according to the method of Sachs.[48]

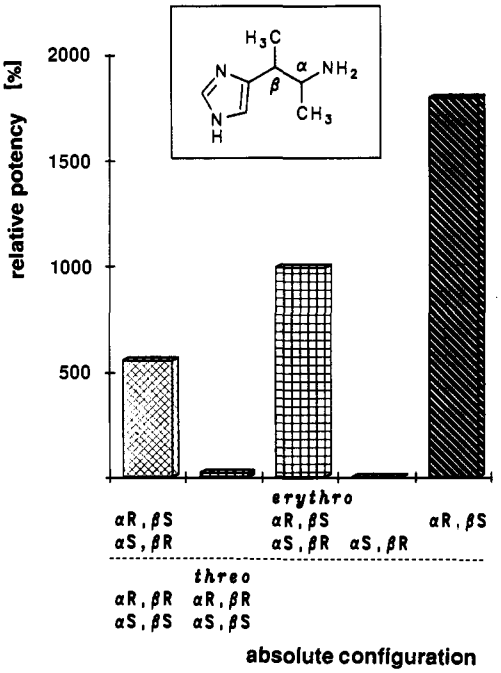


Figure 4. H_3 agonism of α,β-dimethylhistamine, measured as effect on inhibition of K^+-evoked [^{3}H]histamine release from slices of rat brain cortex. Histamine = 100%. The first column represents the activity of a mixture of 29% *erythro*- and 71% *threo*-α,β-dimethylhistamine.

2.8 μM and the V_{max}, 1.7 nmol/mg per h. These kinetic parameters are close to those reported for histamine,[31,32] which suggests that **19** can be methylated as effectively as histamine.

Experimental Section

Chemistry. General Procedures. Melting points are not corrected and were determined by using a Büchi 512 Dr. Tottoli apparatus. ^{1}H NMR spectra were recorded on a Bruker WM 250 or alternatively a Bruker WC 300 spectrometer with TMS as internal standard. A Perkin-Elmer 241 MC polarimeter was used. MS spectra were recorded using Finnigan MAT CH7A (70 eV), Finnigan MAT 711 (80 eV), Kratos MS 25 RF (70 eV) or, in case of $^+$FAB spectra, a Finnigan MAT CH5DF instrument (xenon, DMSO/glycerol). Elemental analyses were performed on Perkin-Elmer 240B and Perkin-Elmer 240C instruments. Thin-layer chromatography (TLC) was performed on silica gel F_{254} plates (Merck). Column chromatography was carried out using silica gel 63–200 μm (Machery & Nagel).

2-Amino-3-(1*H*-imidazol-4-yl)butanol (2). Compound **1** (Methyl 2-amino-3-(1*H*-imidazol-4-yl)butanoate dihydrochloride, prepared according to the method of Kelley et al.[33] (7.7 g, 30 mmol) was added at 0 °C to a stirred suspension of 3.4 g (90 mmol) of lithium aluminum hydride in 125 mL of THF. Subsequently, the mixture was refluxed for 3 h, cooled to 0 °C and hydrolyzed by addition of 6.5 mL of H_2O in 15 mL of THF. Stirring with 20 mL of 5 N NaOH afforded a coarse-grained precipitate which was filtered off and extracted by means of 100 mL of EtOH in 3 portions. The concentration of the fractions afforded an oil which was treated with anhydrous EtOH to separate inorganic material. Filtration and evaporation yielded 4 g (85.9%) of **2**, which was converted into the oily dihydrochloride. An analytical sample was converted into the dipicrate and recrystallized from EtOH–H_2O. Mp: 168 °C. MS (70 eV): *m/z* 155 ($M^{\cdot+}$, <1), 125 (6), 95 (100), 41 (27). ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ 9.12 (1 H, s, imidazole-2-H), 8.63 (4 H, s, 2-pic-3,5-H), 7.87 (3 H, br, exchangeable by D_2O, NH_3^+), 7.56–7.49 (1 H, m, imidazole-5-H), 3.79–3.26 (5 H, m, 1 H exchangeable by D_2O, $CHCHCH_2OH$, 1.32 (3 H, d, J = 6.1 Hz, CH_3). Anal. ($C_7H_{13}N_3O \cdot 2C_6H_3N_3O_7$) C, H, N.

1-Chloro-3-(1*H*-imidazol-4-yl)-2-butanamine Dihydrochloride (3). Compound **2**·2HCl (3 g, 13.2 mmol) was dissolved in a mixture of 25 mL of tetramethylene sulfone and 10 mL of $SOCl_2$ and stirred for 12 h at ambient temperature. Dropwise addition of 200 mL of $CHCl_3$ afforded 2.87 g (88.2%) of **3** as a hygroscopic precipitate. MS (70 eV): *m/z* 173 ($M^{\cdot+}$, <1), 137 (7), 96 (98), 95 (100). ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ 14.7 (2 H, br, exchangeable by D_2O, 2 imidazole-NH), 9.15 (1 H, s, imidazole-2-H), 8.75 (3 H, br, exchangeable by D_2O, NH_3^+), 7.56–7.49 (1 H, m, imidazole-5-H), 4.03 (2 H, d, J = 7 Hz, CH_2Cl), 3.86–3.77 (1 H, m, C*H*NH_3^+), 3.55–3.42 (1 H, m, C*H*-imidazole), 1.37 (3 H, d, J = 7 Hz, CH_3). An analytical sample was converted into the dipicrate and recrystallized from EtOH–H_2O. Mp: 196–198 °C. Anal. ($C_7H_{12}ClN_3 \cdot 2C_6H_3N_3O_7$) C, H, N.

3-(1*H*-Imidazol-4-yl)-1-iodo-2-butanamine Dihydriodide (4). Compound **2** (12.7 g) was refluxed for 3 d in 250 mL of 57% HI. After evaporation, the resulting oil was crystallized by means of dimethoxyethane, yielding 17.88 g (41.9%) of **4** in the form of white crystals. Mp: 204 °C. $^+$FAB–MS: 267/266 ([M + H]$^+$, 9/100), 133 (33), 123 (46), 99 (44). ^{1}H NMR (300 MHz, [D$_6$]-DMSO): δ 9.21 (1 H, s, imidazole-2-H), 8.12 (3 H, br, exchangeable by D_2O, NH_3^+), 7.57 (1 H, s, imidazole-5-H), 3.51 (2 H, J = 3.7 Hz, CH_2), 3.44–3.35 (1 H, m, CHN), 3.27–3.13 (1 H, m, imidazole-C*H*), 1.27 (3 H, d, J = 7 Hz, CH_3). Anal. ($C_7H_{12}IN_3 \cdot 2HI$) C, H, N.

3-(1*H*)-Imidazol-4-yl)-2-butanamine (5). Method A. Compound **4** (3.11 g, 6.0 mmol) was dissolved in 250 mL of 25% acetic acid. Pd–Ca_2CO_3 (1.5 g, 5%) was added and the mixture was hydrogenated for 48 h at 10 bar and ambient temperature. After evaporation, the residue was alkalized by addition of sufficient 6 N Na_2CO_3. Evaporation, extraction of the semisolid residue by means of EtOH, and column chromatography using silica gel

(30) Brown, D.; Tomshick, R.; Axelrod, J. The Distribution and Properties of a Histamine-methylating Enzyme. *J. Biol. Chem.* **1959**, *224*, 2948–2950.

(31) Baudry, M.; Chast, F.; Schwartz, J. C. Studies on S-Adenosylhomocysteine Inhibition of Histamine Transmethylation in Brain. *J. Neurochem.* **1973**, *20*, 13–21.

(32) Matuszewska, B.; Borchardt, R. T. Guinea Pig Brain Histamine N-Methyltransferase: Purification and Partial Characterization. *J. Neurochem.* **1983**, *41*, 113–118.

(33) Kelley, J. L.; Miller, C. A.; McLean, E. W. Attempted Inhibition of Histidine Decarboxylase with β-Alkyl Analogues of Histidine. *J. Med. Chem.* **1977**, *20*, 721–723.

(62–200 μm; eluent, $CHCl_3$–MeOH saturated by NH_3 (9 + 1)) led to 0.42 g of **5** as a colorless oil.

Method B: A mixture of 2 g (8.1 mmol) of **3**, 1.3 g (16.2 mmol) of NaOAc and 100 mL of 10% AcOH, was hydrogenated over 0.5 g Pd–C (10%) for 10 d at 10 bar and ambient temperature. The catalyst was removed by filtration and the filtrate brought to pH 1 by addition of concentrated HCl. After evaporation the oily residue was dissolved in dry EtOH and inorganic material was removed by filtration. By addition of petroleum ether, **5** crystallized as the dihydrochloride. Recrystallization from MeOH–MeCN yielded 0.72 g (40.4%) of **5**·2HCl·0.25MeOH as colorless crystals. Mp: 249–254 °C dec. MS (70 eV): *m/z* 140 (11), 139 ($M^{\cdot+}$, 1), 124 (14), 96 (95), 81 (35), 44 (100). ^1H NMR (250 MHz, [D_6]DMSO): δ 14.76 (2 H, br, exchangeable by D_2O, 2 imidazole-NH), 9.12 (1 H, s, imidazole-2-H) 8.36 (3 H, br, exchangeable by D_2O, NH_3^+), 7.58 (0.71 H, s *erythro*-imidazole-5-H), 7.51 (0.29 H, s, *threo*-imidazole-5-H), 3.40 (1 H, m, C*H*NH_3^+), 3.28 (1 H, m, C*H*-imidazole), 1.30 (3 H, m, imidazole-CHC*H*$_3$), 1.19 (0.71·3 H, d, *J* = 6.5 Hz, *threo*-NCHC*H*$_3$), 1.12 (0.29·3 H, d, *J* = 6.5 Hz, *erythro*-NCHC*H*$_3$). Anal. ($C_7H_{13}N_3$·2HCl·0.25CH_4O) C, H, N.

Ethyl 3-Oxo-3-[1-(triphenylmethyl)-1*H*-imidazol-4-yl]-propanoate (7). Methyl 1-(triphenylmethyl)-1*H*-imidazole-4-carboxylate (**6**, prepared according to the method of Belgadere et al.[34]) (202.7 g, 0.55 mol) was dissolved in 0.8 L of dry toluene at 85 °C. NaH (44 g, 1.1 mol, 60% dispersion in mineral oil) was added. To the stirred solution were added dropwise 96.9 g (1.1 mol) of AcOEt within 2 h. The mixture was allowed to react overnight at 70 °C. Subsequently the toluene was removed under reduced pressure. The resulting mixture was introduced into the following step without purification. For analytical purposes a small amount of the brown oily residue was dissolved in CH_2Cl_2. Washing with 2 M NH_4Cl and H_2O, drying over Na_2SO_4, and evaporation led to an oil. Crystallization with Et_2O and recrystallization from EtOH–Et_2O afforded **7** as white crystals. Mp: 136–139 °C. MS (80 eV): *m/z* ($M^{\cdot+}$, <1), 344 (19), 243 (100). ^1H NMR (60 MHz, $CDCl_3$): δ 7.62 (1 H, d, *J* = 1.4 Hz, imidazole-2-H), 7.55–6.99 (16 H, m, aryl), 4.61 (2 H, q, *J* = 6.1 Hz, CH_2O), 3.99 (2 H, s, CH_2CO), 1.24 (3 H, t, *J* = 6.1 Hz, CH_2CH_3). Anal. ($C_{27}H_{24}N_2O_3$) C, H, N.

1-[1-(Triphenylmethyl)-1*H*-imidazol-4-yl]ethanone (8). The residue as described above was dissolved in a mixture of 75 g of KOH, 140 mL of H_2O and 1.3 L of EtOH. The solution was heated under reflux for 10 h. Solid material was removed by filtration. After evaporation and dissolving in CH_2Cl_2, it was washed three times with 400 mL of H_2O, dried over Na_2SO_4, and evaporated. Stirring and addition of Et_2O afforded 115.3 g of **8** (59.5% based on **6**). An analytical sample was recrystallized from EtOH. Mp: 164–165 °C. MS (80 eV): *m/z* 352 ($M^{\cdot+}$, <1), 244 (22), 243 (100), 183 (85). ^1H NMR (300 MHz, $CDCl_3$): δ 7.45–7.20 (17 H, m, aryl-H), 3.06 (3 H, s, CH_3). Anal. ($C_{24}H_{20}N_2O$) C, H, N.

(*Z*)-Ethyl 2-Methyl-3-[1-(triphenylmethyl)-1*H*-imidazol-4-yl]-2-butenoate (9). $NaNH_2$ (11.7 g, 0.3 mol) was suspended in 300 mL of THF under nitrogen. Ethyl 2-(diethylphosphono)propionate (71.5 g, 0.3 mol) was added dropwise to the mixture, which was kept at ambient temperature for 2 h subsequently. **8** (30.5 g, 86.5 mol) was added and the mixture was held under reflux for 16 h. Evaporation and dissolving in 1 L of $CHCl_3$–iPrOH (3 + 1) was followed by washing three times with H_2O. Drying over Na_2SO_4 and evaporation resulted in an oil which mainly consisted of (*E*)-ethyl 2-methyl-3-[1-(triphenylmethyl)-1*H*-imidazol-4-yl]-2-butenoate (**10**). Treating this residue with Et_2O afforded 10.9 g of a solid material mainly bearing the *Z*-isomer. Purification via column chromatography (silica gel 63–200 μm, petroleum ether–Et_2O (2 + 3)) led to 5.6 g (14.8%) of **9** as a white solid. An analytical amount was recrystallized from Et_2O–EtOH, resulting in colorless crystals. Mp: 166–168 °C. MS (80 eV): *m/z* 436 ($M^{\cdot+}$, 2), 244 (20), 243 (100), 165 (23). ^1H NMR (300 MHz, $CDCl_3$): δ 7.58–7.11 (16 H, m, aryl-H), 6.76 (1 H, d, *J* = 1 Hz, imidazole-5-H), 4.07 (2 H, q, *J* = 7.1 Hz, CH_2O), 1.98 (6 H, s, $H_3CC{=}CCH_3$), 1.17 (3 H, t, *J* = 7.1 Hz, CH_2CH_3). Anal. ($C_{29}H_{28}N_2O_2$) C, H, N.

(*E*)-Ethyl 2-Methyl-3-[1-(triphenylmethyl)-1*H*-imidazol-4-yl]-2-butenoate (10). The above mentioned solution of the *E*-isomer was evaporated. The residue was purified using column chromatography (silica gel 63–200 μm, petroleum ether–Et_2O (1 + 1)). The resulting oil, **10** (15.5 g, 41.8%), crystallized while standing at ambient temperature. An analytical sample was recrystallized from cyclohexane. Mp: 103–104 °C. MS (80 eV): *m/z* 436 ($M^{\cdot+}$, <1), 391 (<1), 243 (100), 165 (23). ^1H NMR (300 MHz, $CDCl_3$): δ 7.48 (1 H, d, *J* = 1.3 Hz, imidazole-2-H), 7.35–7.15 (15 H, m, 3 phenyl), 6.82 (1 H, d, *J* = 1.3 Hz, imidazole-5-H), 4.22 (2 H, q, *J* = 7.1 Hz, CH_2), 2.28 (3 H, d, *J* = 1.3 Hz, α-CH_3), 2.02 (3 H, d, *J* = 1.3 Hz, β-CH_3), 1.31 (3 H, t, *J* = 7.1 Hz, CH_2CH_3). Anal. ($C_{29}H_{28}N_2O_2$) C, H, N.

Ethyl 2-Methyl-3-[1-(triphenylmethyl)-1*H*-imidazol-4-yl]-3-butenoate (11). The last fractions obtained from column chromatography described above afforded 1.23 g (3.3%) **11** which was recrystallized from EtOH. Mp: 152 °C. MS (80 eV): *m/z* 436 ($M^{\cdot+}$, 4), 361 (1), 243 (100), 165 (99). ^1H NMR (300 MHz, $CDCl_3$): δ 7.41 (1 H, d, *J* = 1.2 Hz, imidazole-2-H), 7.34–7.11 (15 H, m, 3 phenyl), 6.88 (1 H, imidazole-5-H), 5.83 (1 H, s, $=CH_2$ (Z)), 5.11 (1 H, s, $=CH_2$ (E)), 4.01 (2 H, m, OCH_2), 3.53 (1 H, q, *J* = 7.1 Hz, CH), 1.38 (3 H, d, *J* = 7.1 Hz, $CHCH_3$), 1.11 (3 H, t, *J* = 7.1 Hz, CH_2CH_3). Anal. ($C_{29}H_{28}N_2O_2$) C, H, N.

(2*R,3*S**)-(±)-Ethyl 3-(1*H*-Imidazol-4-yl)-2-methylbutanoate (12).** Compound **9** (10.2 g, 23.4 mol) was dissolved in 350 mL of THF; 1.5 g of Pd–C (10%) was added. The mixture was hydrogenated for 3 d at ambient temperature and 10 bar. After removal of the catalyst by filtration the solution was evaporated to dryness. The residue was purified by column chromatography (silica gel 63–200 μm; eluent 1, Et_2O; eluent 2, $CHCl_3$–MeOH saturated with NH_3 (1 + 1)), leading to 3.9 g (84.9%) of **12** as a colorless oil. A small amount was converted into the hydrogen maleate, which was recrystallized from EtOH–Et_2O. Mp: 91–94 °C. MS (80 eV): *m/z* 196 ($M^{\cdot+}$, 11), 123 (30), 95 (100). ^1H NMR (300 MHz, [D_6]DMSO): δ 8.88 (1 H, s, imidazole-2-H), 7.46 (1 H, s, imidazole-5-H), 6.05 (2 H, s, CH=CH), 4.08 (2 H, q, *J* = 6.7 Hz, CH_2O), 3.10 (1 H, dq, $J_1 = J_2 = 7$ Hz, CHC=O), 2.70 (1 H, dq, $J_1 = J_2 = 7$ Hz, C*H*-imidazole), 1.22–1.13 (6 H, m, CH_2CH_3), β-CH_3), 0.95 (3 H, d, *J* = 7 Hz, α-CH_3). Anal. ($C_{10}H_{16}N_2O_2$·$C_4H_4O_4$) C, H, N.

(2*R,3*S**)-(±)-3-(1*H*-Imidazol-4-yl)-2-butanamine (13).** Compound **12** (3.8 g, 19.4 mol) was dissolved in 60 mL of 6 M HCl and heated under reflux for 5 h. Evaporation afforded *erythro*-3-(1*H*-imidazol-4-yl)-2-methylbutanoic acid hydrochloride as a hygroscopic oil which was dissolved in 20 mL of concentrated H_2SO_4. Subsequently 125 mL of $CHCl_3$ was added. The mixture was stirred and 5.85 g (90 mmol) of NaN_3 was added over 1 h at 0 °C. The reaction mixture was held at 45 °C for 14 h. After addition of some ice the organic layer was removed. The aqueous phase was brought to pH 8.5 and evaporated to dryness. Soxhleting the resulting solid material for 3 h by means of iBuOH afforded the title compound as a crude oil, which was purified via column chromatography (silica gel 63–200 μm; eluent, $CHCl_3$–MeOH saturated with NH_3 (85 + 15)) affording 2.32 g (85.9%) of **13** as a colorless oil. $^+$FAB-MS (**13**·2HCl) *m/z* 140 ($[M + H]^+$, 14), 123 (5), 93 (100), 74 (28). ^1H NMR (**13**·2HCl, 300 MHz, [D_6]DMSO): δ 9.10 (1 H, s, imidazole-2-H), 8.32 (3 H, br, exchangeable by D_2O, NH_3^+), 7.55 (1 H, s, imidazole-5-H), 3.42–3.37 (1 H, m, C*H*NH_3^+), 3.17–3.12 (1 H, m, C*H*-imidazole), 1.33 (3 H, *J* = 7.2 Hz, β-CH_3), 1.12 (3 H, d, *J* = 6.6 Hz, α-CH_3). An analytical sample was converted into the dipicrate and recrystallized from EtOH. Mp: 228–232 °C. Anal. ($C_7H_{13}N_3$·2$C_6H_3N_3O_7$) C, H, N.

(2*R,3*R**)-(±)-Ethyl 3-(1*H*-Imidazol-4-yl)-2-methylbutanoate (14).** Compound **14** was synthesized similarly to **12**. Starting from **10**, compound **14**·2HCl was obtained in 87.2% yield. An analytical sample was converted into the dihydrogen maleate. Mp: 79–81 °C (EtOH–Et_2O). MS (80 eV): *m/z* 196 ($M^{\cdot+}$, 10), 181 (4), 135 (5), 123 (30), 95 (100), 68 (27). ^1H NMR (300 MHz, [D_6]DMSO): δ 8.87 (1 H, s, imidazole-2-H), 7.41 (1 H, s, imidazole-5-H), 6.06 (2 H, s, CH=CH), 4.01 (2 H, q, *J* = 7 Hz, CH_2O), 3.22 (1 H, dq, $J_1 = J_2 = 7$ Hz, CHC=O), 2.81 (1 H, dq, $J_1 = J_2 = 7$ Hz, C*H*-imidazole), 1.21 (3 H, d, *J* = 7 Hz, β-CH_3), 1.10 (3 H, t,

(34) Belgadere, E.; Bossio, R.; Parrini, V.; Pepino, R. Imidazole Derivatives with Potential Biological Activity. *Arzneim.-Forsch.* **1980**, *30*, 1051–1056.

J = 7 Hz, CH_2CH_3), 0.95 (3 H, d, J = 7 Hz, α-CH_3). Anal. ($C_{10}H_{16}N_2O_2 \cdot C_4H_4O_4$) C, H, N.

(2R*,3R*)-(±)-3-(1H-Imidazol-4-yl)-2-butanamine (15). The preparation of 15 was carried out analogously to the synthesis of 13. Starting with 14, 15·2HCl was obtained in 39.5% yield. Mp: 266–269 °C (EtOH). $^+$FAB-MS: m/z 140 ([M + H]$^+$, 40), 123 (8), 93 (100), 74 (31). ^{1}H NMR (13·2HCl, 300 MHz, [D$_6$]-DMSO): δ 14.78 (2 H, br, exchangeable by D_2O, 2 imidazole-NH), 9.12 (1 H, d, J = 1 Hz, imidazole-2-H), 8.37 (3 H, br, exchangeable by D_2O, NH_3^+), 7.51 (1 H, d, J = 1 Hz, imidazole-5-H), 3.57 (1 H, br, C*H*NH$_3^+$), 3.33 (1 H, dq, $J_1 = J_2$ = 7 Hz, C*H*-imidazole), 1.32 (3 H, J = 7.2 Hz, β-CH_3), 1.19 (3 H, d, J = 6.5 Hz, α-CH_3). Anal. ($C_7H_{13}N_3 \cdot 2HCl$) C, H, N.

(+)-(2S,3R)-3-(1H-Imidazol-4-yl)-2-butanamine Bis[hydrogen (2S,3S)-O,O'-ditoluoyltartrate] Monohydrate (16). Compound 13 (0.56 g, 4 mmol) was dissolved in 30 mL of hot EtOH–H_2O (1 + 1) and added to a hot solution of 3.13 g (8.1 mmol) of (2S,3S)-O,O'-ditoluoyltartaric acid in 80 mL of hot EtOH–H_2O (1 + 1). After being left at ambient temperature for 3 d, the resulting white crystals were recrystallized several times from EtOH–H_2O (1 + 1) until the ^{1}H NMR test (see Analysis of Optical Purity and the method for 20) gave evidence of ee >95%. Yield: 0.79 g (42.5%) of 16. Mp: 181 °C. ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ 7.87–7.84 (9 H, m, 4 phenyl-2,6-H, imidazole-2-H), 7.34 (8 H, d, J = 8 Hz, 4 phenyl-3,5-H), 6.99 (1 H, s, imidazole-5-H), 5.69 (4 H, s, 2 OCHCHO), 3.38–3.31 (1 H, m, C*H*NH$_3^+$), 3.08–2.97 (1 H, m, C*H*-imidazole), 2.37 (12 H, s, 4 phenyl-C*H*$_3$), 1.14 (3 H, d, J = 7.1 Hz, β-CH_3), 0.95 (3 H, d, J = 6.5 Hz, α-CH_3). $[\alpha]^{20}_D$ = +110.6 (2)° (c = 0.1, MeOH). Anal. ($C_7H_{13}N_3 \cdot 2C_{20}H_{18}O_8 \cdot H_2O$) C, H, N.

(2S,3R)-(−)-3-(1H-Imidazol-4-yl)-2-butanamine Dihydrobromide (18). Compound 16 (0.77 g, 0.83 mmol) was dissolved in 60 mL of EtOH–H_2O (2 + 1), and 0.5 mL of 47% HBr was added. Evaporation and redissolving in 20 mL of H_2O plus 20 mL of CH_2Cl_2 were followed by extraction (4×) with 20 mL of CH_2Cl_2. The aqueous solution was evaporated and delivered from excess HBr. Adding Et_2O and iPrOH followed by stirring afforded 0.18 g (72%) of 18. Mp: 226–227 °C (EtOH–Et_2O). The ^{1}H NMR spectrum of 18 was entirely the same as that of 13. $[\alpha]^{20}_D$: −6.3° (c = 0.5, H_2O). Anal. ($C_7H_{13}N_3 \cdot 2HBr$) C, H, N.

(−)-(2R,3S)-3-(1H-Imidazol-4-yl)-2-butanamine Bis[hydrogen (2R,3R)-O,O'-ditoluoyltartrate] Monohydrate (17). The filtrate of the first crystallization of 18 was evaporated to dryness and converted into the dihydrobromide. Dissolving in dry EtOH and adding an equivalent amount of $KOCMe_3$ resulted, after filtration and evaporation, in 0.17 g (1.2 mmol) of the free base. The latter was dissolved in 10 mL of hot EtOH–H_2O (1 + 1) and given to a solution of 1.07 g (2.5 mmol) of (2R,3R)-O,O'-ditoluoyltartaric acid in 30 mL of hot EtOH–H_2O (1 + 1). After 3 d at ambient temperature the obtained white crystals were recrystallized from EtOH–H_2O (1 + 1), until the ^{1}H NMR test (see Analysis of Optical Purity and the method for 21) gave evidence of ee >95%, affording 0.21 g of 17 (11.3% based on the educt in 16). Mp: 181 °C. ^{1}H NMR of 17 proved to be the same as that of 16. $[\alpha]^{20}_D$: −109.4° (c = 0.1, MeOH). Anal. ($C_7H_{13}N_3 \cdot 2C_{20}H_{18}O_8 \cdot H_2O$) C, H, N.

(2R,3S)-(+)-3-(1H-Imidazol-4-yl)-2-butanamine Dihydrobromide (19). Compound 17 (0.2 g, 0.22 mmol) was converted into the dihydrobromide in the way described for 18, affording 60 mg (86.7%) of 19. Mp: 226–227 °C. The ^{1}H NMR of 19 was the same as that of 18. $[\alpha]^{20}_D$: 6.2° (c = 0.4, H_2O). Anal. ($C_7H_{13}N_3 \cdot 2HBr$) C, H, N.

(2R,2'S,3'R)-N-[3-(1H-Imidazol-4-yl)-2-butyl]-2-methoxy-2-phenylacetamide (20). Dissolution of 0.1 mmol of 16 in 10 mL of EtOH, addition of 0.1 mL of 47% HBr, and evaporation to dryness were followed by dissolution in H_2O and washing with H_2O four times. Addition of 0.5 mL of 1 M NaOH, 1 mL of CH_2Cl_2 and 0.25 mmol of (R)-2-methoxy-2-phenylacetyl chloride as well as shaking for 5 min afforded 20 as a solution in CH_2Cl_2. This solution was purified using TLC (one 20 cm × 20 cm sheet of silica gel 60 F_{254}, Merck) and $CHCl_3$–MeOH (19 + 1) in ammonia atmosphere as eluent. The zone which contained the product (R_f = 0.66) was scraped off and eluted by 3 × 3 mL of EtOH. Evaporation to dryness was followed by redissolving in CH_2Cl_2, filtration, and final evaporation. The resulting oily 20 was directly used for ^{1}H NMR purposes. ^{1}H NMR (300 MHz, CD_2Cl_2): δ 7.82 (1 H, exchangeable by D_2O, d, J = 8.4 Hz, NH-CO), 7.63 (1 H, s, imidazole-2-H), 7.35–7.31 (5 H, m, phenyl), 6.72 (1 H, s, imidazole-5-H), 4.57 (1 H, s, CHO), 4.14 (1 H, s, C*H*NHCO), 3.33 (3 H, s, OCH_3), 2.97 (1 H, t, J = 5.9 Hz, C*H*-imidazole), 1.19 (3 H, d, J = 7 Hz, 2'-CH_3), 0.98 (3 H, d, J = 6.5 Hz, 1'-CH_3).

(2R,2'R,3'S)-N-[3-(1H-Imidazol-4-yl)-2-butyl]-2-methoxy-2-phenylacetamide (21). Compound 21 was analogously prepared as described for 20 but starting from 17. ^{1}H NMR (300 MHz, CD_2Cl_2): δ 7.81 (1 H, exchangeable by D_2O, d, J = 8.4 Hz, NHCO), 7.59 (1 H, s, imidazole-2-H), 7.35 (5 H, s, phenyl), 6.82 (1 H, s, imidazole-5-H), 4.57 (1 H, s, CHO), 4.14 (1 H, s, C*H*NHCO), 3.36 (3 H, s, OCH_3), 3.03 (1 H, t, J = 5.9 Hz, C*H*-imidazole), 1.27 (3 H, d, J = 6.9 Hz, 2'-CH_3), 0.92 (3 H, d, J = 6.5 Hz, 1'-CH_3).

Single Crystal X-ray Analysis. Crystals of $C_7H_{13}N_3 \cdot 2HBr$ (19·2HBr) were grown from EtOH–Et_2O. Precise lattice parameters (from 120 high-order reflections with 20° ≤ 2θ ≤ 50°) and three-dimensional intensity data were measured on a Stoe diffractometer using Ni-filtered CuKα-radiation (λ = 1.5418 Å). A single crystal with approximate dimensions 0.35 × 0.08 × 0.07 mm was used to collect the intensity data of 4180 reflections of one hemisphere ($\theta \leq 64°$; $\pm h$; $\pm k$; l) by using the ω–2θ scan technique. No significant intensity variations monitored via two check reflections were observed. The intensity data set was corrected for Lorentz and polarization effects. Merging after analytical absorption correction gave 3685 unique reflections (R_{int} = 0.78%, R_σ = 0.84%), of which 57 reflections with $I < 2\sigma(I)$ were considered unobserved. Friedel-related reflections were *not* merged.

Crystal Data. Molecular formula, $C_7H_{13}N_3 \cdot 2HBr$ (M_r = 301.0); space group, monoclinic $P2_1$; unit cell, a = 11.352 (2) Å, b = 11.881 (2) Å, c = 8.992 (2) Å, β = 113.16 (2)°, V = 1115.0 Å^3, Z = 4, ρ_x = 1.793 g cm^{-3}, ρ_{exp} = 1.81 g cm^{-3}, μ(CuKα) = 98.84 cm^{-1}. Phase determination was made with direct methods (program SHELXS86[35]); refinement was done with the corresponding least-squares programs of the XTAL program system (version 2.2, 1987[36]). All hydrogens were located from difference syntheses. A $1/\sigma^2(F_o)$ weighting scheme was used; $\sigma(F_o)$ was from counting statistics. No significant peaks or holes were seen in a final difference Fourier map. After convergence, R values of R = 1.91% and R_w = 1.9% were obtained for the $\alpha R,\beta S$-enantiomer, when anomalous dispersion corrections were considered for all non-hydrogen atoms with the corresponding values for $\Delta f'$ and $\Delta f''$ from the *International Tables for X-ray Crystallography*, Vol. IV.[37] For the structure of the opposite enantiomer R = 2.62% and R_w = 2.9% were found.[38] The R value ratios $R = R(-)/R(+)$ of 1.372 for the nonweighted and 1.532 for the weighted R values are extremely high. Hence, from extrapolation of the corresponding significance tables given by Hamilton,[39] a confidence level of more than 99.9% can be estimated, so that the absolute configuration of 19 as the $\alpha R,\beta S$ enantiomer is safe at least within 99.9%.

Pharmacology. Experiments with Slices of Rat Brain Cortex.[1] Male Wistar rats (170–190 g) were killed by decapitation and the brains were immediately removed. Slices (0.3 mm thick) from cerebral cortex were preincubated for 30 min with [^{3}H]-L-histidine (0.3 μM). After extensive washings, aliquots of the slice suspension (2–3 mg of protein) were incubated at 37 °C for 2 min in the presence of 2 or 30 mM KCl (final concentration). When required, slices were preincubated for 5 min before the depolarizing stimulus in the presence of the various drugs tested as agonists. Incubations were stopped by rapid centrifugation, and [^{3}H]histamine levels present in tissue and medium were quantified as described.[1]

(35) Sheldrick, G. M. In *Crystallographic Computing 3*; Sheldrick, G. M., Krüger, C., Goddard, R., Eds.; Oxford University Press: Oxford 1985; pp 175–198.

(36) Stewart, J. M.; Hall, S. R., Eds.; XTAL Program System 2.2, User's Manual; Universities of Western Australia and Maryland, 1987.

(37) Ibers, J. A.; Hamilton, W. C., Eds.; International Tables for X-ray Crystallography; Kynoch Press: Birmingham, England, 1974; Vol. IV, p 148.

(38) Rogers, G. On the Application of Hamilton's Ratio Test to the Assignment of Absolute Configuration and an Alternative Test. *Acta Crystallogr.* 1981, *A37*, 734–741.

(39) Hamilton, W. C. Significance Test on the Crystallographic R Factor. *Acta Crystallogr.* 1965, *18*, 502–510.

Experiments with the Isolated Spontaneously Beating Guinea Pig Right Atrium.[40] Male guinea pigs (350–500 g) were killed by a blow to the head. The heart was removed and incubated in McEvan's solution[41] at 32.5 °C which was gassed with oxygen containing 5% CO_2. The right atrium was separated, placed in a 20-mL organ bath containing McEvan's solution as described above. The latter was continuously substituted during the equilibration time of 1 h. The obtained isometric impulses were recorded by a heart frequency meter. Each preparation was used only for one single test. Three or four experiments were conducted with each compound. To test the H_2 agonistic activity, histamine standard curves (10^{-7}–10^{-5} M concentration in the bath) were recorded using a cumulative technique. After thoroughly washing the preparation from histamine the potential H_2 agonist was tested by recording an entire concentration–response curve.

Experiments with the Isolated Guinea Pig Ileum. Male guinea pigs (350–500 g) were killed by a blow to the head. Pieces of the ileum 3 cm in length were incubated in a 20-mL organ bath containing Tyrode solution at 37 °C. Oxygen containing 5% CO_2 was bubbled through the solution. Contraction effects were isotonically recorded. To determine the H_1 agonistic activity of a compound, a histamine standard curve was recorded first. Therefore histamine concentration was geometrically increased in the bath until maximal contraction of the ileum was reached.[42] Following thorough washing of the preparation, a concentration–response curve of the potential agonist was recorded in the same manner.

Experiments with Histamine *N*-Methyltransferase. Histamine *N*-methyltransferase activity was quantified by measuring the conversion of histamine into [^{3}H]-τ-methylhistamine using [^{3}H]-*S*-adenosylmethionine as a [^{3}H]methyl donor. The enzyme was purified from rat kidney according to the method of Bowsher et al.,[43] slightly modified as by Garbarg et al..[44] ($\alpha R,\beta S$)-α,β-Dimethylhistamine in increasing concentrations was incubated with the enzyme and a mixture of unlabeled and tritiated *S*-adenosylmethionine (5 μM final concentration) for 1 h at 25 °C. The reaction was stopped by addition of perchloric acid (0.4 N final concentration) followed by NaOH (1 N final concentration). [^{3}H]-τ-Methylhistamine was extracted into toluene–isoamyl alcohol (3 + 2) and quantified by liquid scintillation spectrometry.

Acknowledgment. We are grateful to Agnés Rouleau for technical assistance. Support of this work by the Verband der Chemischen Industrie is greatly acknowledged.

Supplementary Material Available: X-ray data including atomic coordinates, anisotropic displacement parameters, distances and angles, hydrogen bond distances for compound 19·2HBr (7 pages); observed and calculated structure factors (33 pages). Ordering information is given on any current masthead page.

(40) Lennartz, H. G.; Hepp, M.; Schunack, W. Histamine Analogues. XVI. Synthesis and Action of 5-Alkyl substituted Histamines and N^{α}-Methylhistamines. *Eur. J. Med. Chem. Chim. Ther.* **1978**, *13*, 229–234.

(41) Black, J. W.; Duncan, W. A. M.; Durant, G. J.; Ganellin, C. R.; Parsons, M. E. Definition and Antagonism of Histamine H_2-Receptors. *Nature (London)* **1972**, *236*, 385–390.

(42) van Rossum, J. M. Cumulative Dose Response Curves. *Arch. Int. Pharmacodyn. Ther.* **1963**, *143*, 299–330.

(43) Bowsher, R. B.; Verburg, K. M.; Henry, D. P. Rat Histamine N-Methyltransferase. Quantification, Tissue Distribution, Purification and Immunologic Properties. *J. Biol. Chem.* **1983**, *258*, 12215–12251.

(44) Garbarg, M.; Dam Trung Tuong, M.; Gros, C.; Schwartz, J. C. Effects of Histamine H_3-Receptor Ligands on Various Biochemical Indices of Histaminergic Neuron Activity in Rat Brain. *Eur. J. Pharmacol.* **1989**, *164*, 1–11.

(45) Black, J. W.; Ganellin, C. R. Naming Substituted Histamines. *Experientia* **1974**, *30*, 111–113.

(46) Davies, E. K. CHEMX1990; developed and distributed by Chemical Design Ltd., Oxford, England.

(47) Parker, R. B.; Waud, D. R. Pharmacological Estimation of Drug-Receptor Dissociation Constants. Statistical Evaluation. II Competitive Antagonists. *J. Pharmacol. Exp. Ther.* **1971**, *177*, 13–24.

(48) Sachs, L. *Angewandte Statistik*; Springer Verlag: Berlin, 1984; p 77.