Mutagenicity Studies. The mutagenicity of the nitrosamines was assessed with *Salmonella* tester strain TA 1535, which detects base-pair substitution mutations, and hamster Aroclor 1254 induced S9 mix instead of rat S9, since nitroso compounds have been reported to be more sensitive to hamster S9 activation.[2] The protein content of the added S9 was 3 mg/plate. The dose-response study used duplicate plates over a 10-point range of 1-1000 g/plate. The plate incorporation test was performed as recommended by Ames et al.[13] with the modifications of Andrews et al.[14] Plates were incubated at 37 °C for 48 h and counted by using a hand-held tally. A compound was considered to be mutagenic only if there were two consecutive doses which showed revertant numbers that were greater than twice the mean of the current controls.

Partition Coefficients. The octanol/water partition coefficients were measured by the shake procedure as previously described.[6] Quantitation of the nitrosamine in the aqueous layer was determined by HPLC.

Acknowledgment. We thank Corinthia Brown for her expert technical help with the Ames assay and Dr. Y. Tondeur and John Roman for the mass spectrometric data.

Dipole Moment in Relation to H_2 Receptor Histamine Antagonist Activity for Cimetidine Analogues

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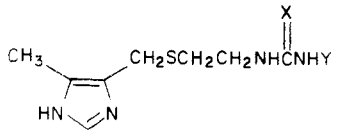
The activities of a series of H_2 receptor histamine antagonists structurally related to cimetidine (1) have been compared to investigate the effect of replacing the cyanoguanidine moiety by other neutral, dipolar groups. Antagonist activity, as measured in vitro on the histamine-stimulated guinea pig right atrium, was found to be very sensitive to relatively minor structural changes. Differences in H_2 antagonist activity are accounted for by dipole moment orientation and lipophilicity and are rationalized in terms of an optimum requirement for alignment of a hydrogen-bonding moiety in the antagonist with respect to the receptor and desolvation effects at the receptor. The most active compound in the series is the 2-amino-3-nitropyrrole derivative **5**, which combines a near-optimal dipole orientation with high lipophilicity.

The success of cimetidine (1) in the treatment of peptic ulcer disease has promoted a great deal of research interest in H_2 receptor antagonists as clinically effective agents.

The search for H_2 antagonists of increased potency by the structural modification of cimetidine has led to the discovery of several new compounds, notable amongst which are ranitidine[1] and tiotidine,[2] in which imidazole has been replaced by the highly effective [(dimethylamino)-methyl]furan and guanidinothiazole moieties, respectively. At the opposite end of the cimetidine molecule, suitable replacement of the cyanoguanidine group has provided antagonists of equivalent or increased potency, including the 5-substituted aminopyrimidinone derivative, oxmetidine.[3]

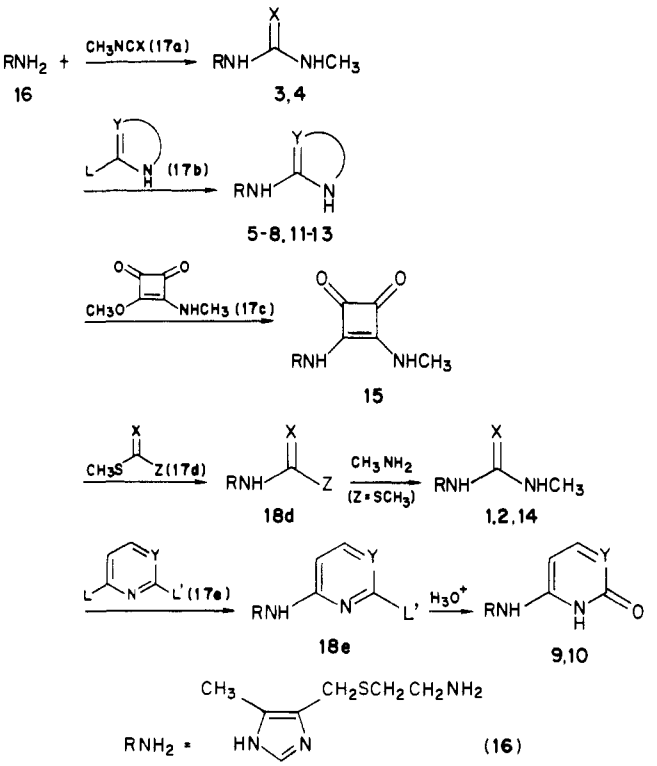
In a recent investigation,[4,5] a series of 12 cimetidine analogues were compared in order to analyze differences in antagonist activity on replacement of the cyanoguanidine group. For most compounds, a reasonable relationship was found between in vitro H_2 antagonist activity and a lipophilicity parameter (octanol/water log P of a cyanoguanidine or corresponding alternative model compound). A notable anomaly, however, was the nitrodiaminoethene analogue (**2**), whose activity was only poorly predicted, and it was concluded that some other property was making a marked contribution to activity.



1, X = NCN; Y = CH_3
2, X = $CHNO_2$; Y = CH_3

One property which cyanoguanidine shares with other neutral moieties found in active analogues of cimetidine is its polarity. Simple derivatives of urea, thiourea,

Scheme I



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cyanoguanidine, and 1-nitro-2,2-diaminoethene have high dipole moments, especially in aqueous solution, where large contributions from charge-separated canonical species are believed to occur.[6]

To investigate the importance of dipole moment for H_2 antagonist activity, the dipole moments of model compounds corresponding to the neutral, dipolar moieties in selected cimetidine analogues have been compared.

Chemistry. All antagonists discussed in this investigation were prepared from the common amine **16**, by reaction with a suitably activated synthon, **17a–e**, and in the case of **17d** and **17e** by subsequent hydrolysis or aminolysis of intermediates **18d** and **18e** (Scheme I).

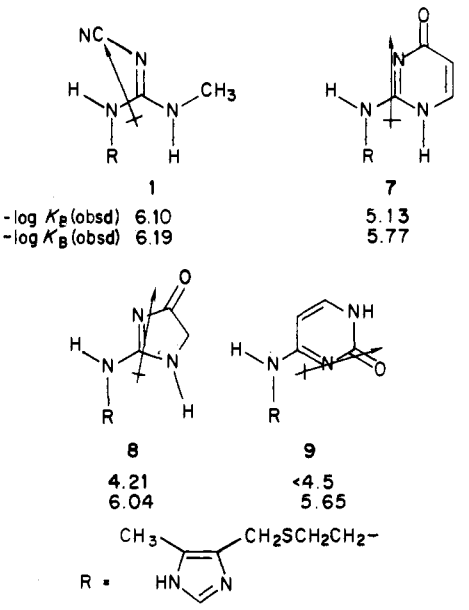
Preparation of the urea, thiourea, cyanoguanidine, and nitroguanidine antagonists (**1**, **3**, **4**, **14**) has been described elsewhere.[7] The 1-nitro-2,2-diaminoethene derivative **2** was prepared by analogy with the cyanoguanidine, by reacting the amine **16** with intermediate **17d** (X = $CHNO_2$, Z = SCH_3) followed by treatment of intermediate **18d** with methylamine. The aminopyrrole **5**, aminodihydropyrrole **6**, aminopyrimidinone **7**, aminoimidazolinone **8**, aminopyridones **11** and **12**, and the thiadiazine dioxide **13** were prepared by reacting amine **16** with intermediates **17b** having suitable leaving groups L (L = CH_3SO for **5**, CH_3S for **6–8** and **13**, and Br for **11** and **12**). The 4-aminopyrimidin-2-one **9** was synthesized by reacting 2,4-dimercaptopyrimidine (**17e**, L = L′ = SH; Y = N) with amine **16**, followed by hydrolysis of the intermediate **18e**. In a similar way, the 2-aminopyrid-6-one derivative **10** was prepared from amine **16** and 2-bromo-6-ethoxypyridine (**17e**, L = Br; L′ = OEt; Y = CH) to give intermediate **18e**, which was subsequently hydrolyzed. The intermediate **17c** was reacted with amine **16** to furnish the diaminocyclobutenedione **15** by methoxide displacement (Scheme I).

Results and Discussion

The H_2 receptor antagonist activities ($-\log K_B$) of 15 cimetidine analogues, measured in vitro on the guinea pig right atrium, are presented in Table I. In compounds possessing acyclic, dipolar groups, such as cimetidine, only the terminally N-methylated derivatives (Y = CH_3) have been included in this study. It was previously shown[4,5] that these derivatives were fairly consistently more potent as H_2 receptor antagonists than their desmethyl analogues (Y = H), and that these increments could be related to their increased lipophilicity. Dipole moment values available for model compounds, RNHC(=X)NHY,[6,9,10] corresponding to the dipolar moieties in the antagonists, are given in Table I.

In a previous study[11] of compounds **1–9**, it was reported that there was no simple relationship between antagonist activity and either measured dipole moment or lipophilicity alone. However, a combination of those two parameters gave a reasonable correlation for seven analogues (compounds **1–7**), as shown in eq 1, suggesting that activity

Scheme II



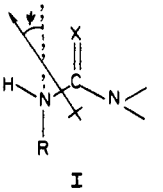
might be optimized by combining a high dipole moment with high lipophilicity. Here, n is the number of compounds considered, r is the correlation coefficient, s is the standard deviation, and the values in parentheses are the 95% confidence limits of the regression coefficients.

$$-\log K_B = \underset{(\pm 0.17)}{0.23\mu} + \underset{(\pm 0.85)}{1.08 \log P} + \underset{(\pm 2.30)}{2.74} \quad (1)$$

$$n = 7,\ r = 0.910,\ s = 0.426$$

The relatively weak activities of compounds **8** and **9** were only poorly predicted by eq 1 (see Table I), and it was thought that these discrepancies might be explained by deviations in the orientations of their dipoles from that of cyanoguanidine, as shown qualitatively in Scheme II. The dipolar aminoheterocyclic groups in compounds **7–9** are tautomeric systems, which, for the purpose of this study, have been considered in forms reported to be major contributing species in aqueous solution.[12-14]

To investigate the importance of dipole orientation in more detail, CNDO/2 molecular orbital calculations[15] were performed for the relevant dipolar groups, and estimates were made of their dipole orientations with respect to the R–N bond (angle ψ), considering the planar configuration I common to structures **1–9**. On this basis, acyclic moieties



I

such as the cyanoguanidine group in cimetidine (i.e., **1**, in its *E,Z* form, Scheme II) can be compared with cyclic moieties such as the aminopyrimidinone moiety in the corresponding antagonist **7**. The values calculated for ψ are given in Table I.

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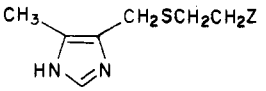
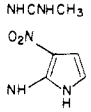
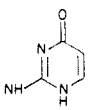
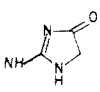
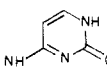
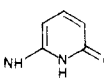
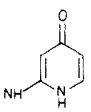
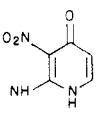
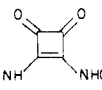
(15) Program No. 261, Quantum Chemistry Program Exchange, Indiana University Chemistry Department, Bloomington, IN.

Table I. Physical Properties and H_2 Receptor Antagonist Activities



					H_2 receptor antagonist activity ($-\log K_B$)		
compd	Z	dipole moment[a]	log P[b]	ψ[c]	obsd[d] (95% limits)	predicted (eq 1)	predicted (eq 8) (95% limits)
1		13.1	0.40	13	6.10 (6.04–6.17)	6.19	6.25 (±0.35)
2		15.1	−0.40	33	5.85 (5.79–5.92)	5.78	6.16 (±0.43)
3		10.0	0.55	0	6.04 (5.82–6.13)	5.63	5.52 (±0.37)
4		8.3[e]	−0.06	0	4.69 (4.19–5105)[j]	4.58	5.15 (±0.27)
5		14.2	1.04	27	7.31 (7.02–7.80)[k]	7.13	7.03 (±0.61)
6		17.8	−0.87	28	6.31 (5.99–6.58)	5.89	5.88 (±0.56)
7		13.1	0.02	2	5.13 (4.70–5.51)	5.77	5.36 (±0.26)
8		16.7	−0.5[g]	−6	4.21 (3.27–4.78)	6.04	4.37 (±0.43)
9		15.0[f]	−0.4[g]	−143	<4.5	5.65	−2.95 (±2.65)
10			0.79	−82	<4.0		−2.24 (±2.67)
11			0.8[h]	−5	4.80 (4.40–5.13)		5.24 (±0.50)
12			−0.2[i]	17	6.44 (6.14–6.85)[l]		6.05 (±0.35)
13			−0.74	0	4.57 (3.96–5.05)		4.74 (±0.44)
14			0.13	13	5.84 (5.56–6.11)		6.09 (±0.31)
15			−0.08	−15	4.23 (3.75–4.59)[m]		3.69 (±0.62)

[a] References 6, 9, and 10. [b] Measured in octanol/borax buffer at pH 9.0 and 37 °C. [c] Dipole moment orientation relative to R–N bond (see text). [d] Tested in the histamine-stimulated guinea pig right atrium and analyzed by Schild plot.[8] Slopes of log $(X-1)$ plotted against log B were not significantly different from unity (±95% limits) unless indicated. [e] Upper limit. [f] Approximate value. [g] Estimated log P, calculated as log P(HZ) + π(N=CHNHCMe=CCH$_2$SCH$_2$CH$_2$), where π(N=CHNHCMe=CCH$_2$SCH$_2$CH$_2$) = log P(1) − log P(H$_2$NC(NCN)NHCH$_3$) = 0.40−(−0.77) = 1.17 and log P(HZ) for model compounds corresponding to 8 and 9 = −1.69 and −1.55, respectively. [h] Assumed equivalent to 10. [i] Estimated log P, calculated as log P(CH$_3$Z) + π(N=CHNHCMe=CCH$_2$SCH$_2$CH$_2$) − π(CH$_3$), where log P(CH$_3$Z) = −0.99 and π(CH$_3$) is taken as log P(CH$_3$Z) − log P(HZ) for the isocytosine group in 7, ie., −0.55 − (−0.97) = 0.42. [j] Slope 0.70 ± 0.12. [k] Slope 0.63 ± 0.17. [l] Slope 0.68 ± 0.22. [m] Slope 0.78 ± 0.11.

The possible existence of an optimum value for ψ within the series could now be examined by calculating the deviation (θ) of group dipole orientations (ψ) from various arbitrary angles (relative to the R–N bond) and assessing their biological significance. In this way, surprisingly good correlations were obtained between antagonist activity and cos θ alone, the best, shown in eq 3, Table II, for compounds 1–8 is for an optimum reference angle ψ of 22°. Thus, for these eight antagonists, dipole orientation alone accounts for 75% of the variance in biological activity, and the "t test" indicates this parameter to be significant at greater than the 99% level. As can be seen from Table

Table II. Correlation Equations for H_2 Antagonist Activity

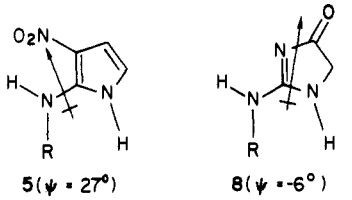
	n^a	r^b	s^c	eq no.
$-\log K_B = 1.27 \log P + 0.172\mu + 3.34$ (±1.50) (±0.292) (±4.04)	8	0.705	0.828	2
$-\log K_B = 20.4 \cos \theta^d - 13.8$ (±11.9) (±11.4)	8	0.863	0.539	3
$-\log K_B = 0.099\mu \cos \theta^d + 4.43$ (±0.292) (±3.87)	8	0.318	1.01	4
$-\log K_B = 1.29 \log P + 0.209\mu \cos \theta^d + 2.97$ (±1.23) (±0.238) (±3.16)	8	0.796	0.707	5
$-\log K_B = 0.509 \log P + 18.5 \cos \theta^d - 12.0$ (±0.751) (±11.2) (±10.7)	8	0.917	0.466	6
$-\log K_B = 0.717 \log P + 10.3 \cos \theta^e - 3.86$ (±0.636) (±5.3) (±4.89)	8	0.937	0.406	7
$-\log K_B = 0.600 \log P + 9.12 \cos \theta^e - 2.71$ (±0.458) (±2.93) (±2.64)	13	0.906	0.409	8

[a] Number of data points used in regression. [b] Correlation coefficient. [c] Standard deviation from regression line. [d] θ calculated relative to reference angle $\psi = 22°$. [e] θ calculated relative to reference angle $\psi = 30°$.

I, the ψ value of 22° lies almost midway between that of two of the most active compounds, the cyanoguanidine **1** ($\psi = 13°$) and the aminonitropyrrole **5** ($\psi = 27°$).

In contrast, only a very poor correlation was obtained with use of the dipole moment vector term, $\mu \cos \theta$ (eq 4, Table II), and replacement of the μ parameter in eq 2 by $\mu \cos \theta$ in eq 5 gave no useful improvement in significance. In each case, $\mu \cos \theta$ failed to reach significance at the 95% level.

Modification of eq 3 to include the log P term again resulted in no useful improvement (eq 6, Table II), with the latter term failing to reach significance at the 90% level. However, redefining the angle θ relative to a reference angle ψ of 30° resulted in an improved relationship (eq 7, Table II), in which the log P term reached significance at the 95% level and 88% of the variance in the biological data could be accounted for. The high antagonist activity of the aminonitropyrrole derivative **5** may now be explained by its near-optimal orientation and relatively high lipophilicity, while the weakly active aminoimidazolinone derivative **8** has an unfavorable orientation and is hydrophilic.



In searching for a more general relationship, eq 7 has been extended to include all the compounds shown in Table I whose log K_B values could be determined experimentally. The resulting equation (eq 8, Table II) is highly significant and spans a range of H_2 antagonist activity of more than 3 orders of magnitude. Observed and predicted H_2 antagonist activities for the 13 compounds are shown in Table I and compared graphically in Figure 1. Two compounds which were not included in the correlation set are **9** and **10**, the aminopyrimidinone (cytosine) and the aminopyridone analogues, respectively. In aqueous solution, the 4-aminopyrimidin-2-one tautomer of **9** is expected to predominate[13,14] and in this form, its dipole orientation will be far from the proposed ideal orientation (i.e., $\theta > 90°$). This compound had no measurable H_2 antagonist activity in the atrium up to a dose of 486 μM, and using eq 8, its extrapolated activity was negative, with wide associated confidence limits. Likewise, derivative **10**, with

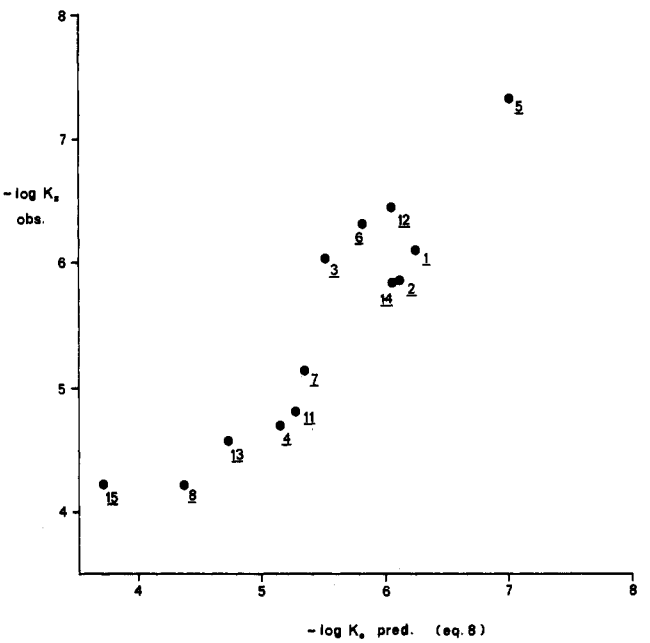


Figure 1. Comparison of observed and predicted H_2 receptor antagonist activities of 13 cimetidine analogues.

a similarly unfavorable dipole orientation, was also predicted to be inactive, as observed. The isomeric 2-aminopyrid-4-one **11** which has a more favorable dipole orientation, is a weak antagonist whose activity is reasonably well predicted by eq 8. Introduction of a nitro substituent at the pyridine ring 3-position of **11** resulted in a large increase in H_2 antagonist activity, to give compound **12**. Again, this result is in accord with prediction and can be explained by the favorable effect on dipole orientation, which outweighs a drop in lipophilicity. The dihydrothiadiazine dioxide derivative **13**,[16] which is a cyclic sulfonylguanidine, has a dipole oriented parallel to the R–N bond ($\psi = 0°$) and a very low partition coefficient. Prediction of its activity by eq 8 agrees well with that observed.

The nitroguanidine group in compound **14** has a dipole which is orientated in a similar direction with respect to the side chain, as the cyanoguanidine group in cimetidine. It is, however, more hydrophilic, and this could account

(16) Durant, G. J.; Emmett, J. C.; Ganellin, C. R. (Smith Kline & French Labs Ltd.) G.B. Patent 1 419 994, 1976.

for its slightly lower H_2 antagonist activity.

The diaminocyclobutenedione derivative **15**,[17] which does not strictly conform to structure I, has also been included for comparison. Here, the geometry of the four-membered ring structure causes its dipole to be oriented in an unfavorable direction with respect to the R–N bond ($\psi = -15°$). Unexpectedly, the weak H_2 antagonist activity of this compound is predicted fairly well by eq 8. The diaminocyclobutenedione moiety has recently been employed in conjunction with different side chains in compounds such as BMY 25,368[18] and, in contrast, found to give very potent H_2 receptor antagonists. It is thought, however, that different structure–activity relationships may apply in these cases.

The interpretation of eq 8 is not immediately clear. Because antagonist activity is primarily related to dipole orientation rather than magnitude, it might reasonably be assumed that the amidine-type moiety in this series of compounds has an orientational function rather than being involved in direct dipole–dipole or dipole–charge interactions at the receptor. Extensive charge delocalization results not only in a dipole moment but also serves to acidify the amidine NH functions, making them potential hydrogen-bond donors. The cyanoguanidine group has been shown[19] to be an effective hydrogen-bond donor from its ability to interact with the imidazole ring (N_π) nitrogen in cimetidine. It might therefore be speculated that the cyanoguanidine and related moieties interact with the H_2 receptor by hydrogen bonding and that the strength of interaction is determined by the dipole's ability to align with the receptor. Moreover, as the orientational term in eq 8 was defined by reference to the R–N bond in structure I, it can also be considered to relate to the N–H bond involving the same nitrogen atom. This might therefore suggest a role for the (R)–NH group in hydrogen bonding to the H_2 receptor.

The inclusion of the log P parameter in eq 8 and its high statistical significance support the earlier suggestion[4,5] that lipophilicity might be related to H_2 antagonist activity. Since the molecules are very polar, the log P parameter may represent a hydrophobic effect; if so, this might suggest the involvement of desolvation effects at the receptor. One may envisage that the drug molecules in aqueous solution are in a water solvent shell and have to undergo desolvation in order to fully realize the hydrogen bonding and dipolar interactions at the receptor.

Experimental Section

Synthesis. NMR spectra were recorded on a Varian A60A or a JEOL PFT 100P spectrometer, using $(CH_3)_4Si$ for reference. Microanalytical data are within ±0.4% of theoretical values and melting points are uncorrected.

1-Nitro-2-(methylamino)-2-[[2-[[(4-methyl-5-imidazolyl)methyl]thio]ethyl]amino]ethene (2). A solution of 16[7] (1.71 g, 0.010 mol) in *t*-BuOH (30 mL) was added to a solution of 1-nitro-2,2-bis(methylthio)ethene[20] (1.66 g, 0.010 mol) in MeCN (20 mL) at room temperature. After heating under reflux for 3 h, the solution was evaporated to dryness and chromatographed (SiO_2–MeAc) to give **18d** (X = $CHNO_2$, Z = SCH_3) (1.58 g, 55%), mp 151–153 °C. A sample recrystallized from MeCN had mp 152–153 °C. Anal. ($C_{10}H_{16}N_4O_2S_2$) C, H, N, S.

A mixture of the above product (0.67 g, 0.0023 mol) and 33% $MeNH_2$ in EtOH (4 mL) was heated in a sealed tube at 70–80 °C for 1 h. Concentration, followed by chromatographic purification (SiO_2–MeAc) and recrystallization from MeCN, gave **2** (0.39 g, 63%), mp 141–143 °C. A further recrystallization from *i*-PrOH gave mp 148–151 °C. Anal. ($C_{10}H_{17}N_5O_2S$) C, H, N, S.

2-[[2-[[(4-Methyl-5-imidazolyl)methyl]thio]ethyl]amino]-3-nitropyrrole (5). A solution of 2-(methylthio)-3-nitropyrrole[21] (2.5 g, 0.016 mol) in glacial AcOH (70 mL) and H_2O_2 (30%, 2 mL, 0.017 mol) was heated at 60 °C for 4.5 h. The solvent was removed in vacuo (after first checking that no peroxide remained), and the residue was recrystallized from *i*-PrOH to give 2-(methylsulfinyl)-3-nitropyrrole (2.3 g, 85%), mp 162–164 °C. Anal. ($C_5H_6N_2O_3S$) C, H, N, S.

A solution of the above product (2.0 g, 0.011 mol) and **16** (2.0 g, 0.012 mol) in MeOH (50 mL) was heated under reflux for 7 days. After evaporating to dryness, the residue was chromatographed (SiO_2–EtOAc), evaporated to dryness, and recrystallized from *i*-PrOH to yield **5** (0.96 g, 31%), mp 161–162 °C. Anal. ($C_{11}H_{15}N_5O_2S$) C, H, N, S.

2-[[2-[[(4-Methyl-5-imidazolyl)methyl]thio]ethyl]amino]-3-nitro-4,5-dihydropyrrole (6). A solution of 1-nitro-2-(methylthio)-2-(methylsulfinyl)ethene[22] (2.0 g, 0.011 mol) and aziridine (0.5 g, 0.012 mol) in MeOH (20 mL) was stirred at room temperature for 1 h. The solid which crystallized out was filtered off to afford 1-nitro-2-(methylthio)-2-aziridinoethene (1.3 g, 74%): mp 107.5–110 °C; NMR ($CDCl_3$) δ 2.4 (s, CH_2CH_2), 2.56 (s, CH_3), 7.15 (s, HC=).

N_2 was passed through a solution of the above product (0.5 g, 0.003 mol) in dry MeAc (15 mL) for 15 min and the temperature was raised to 35 °C. Addition of KI (2.5 g, 0.015 mol) to the solution yielded a yellow precipitate, which was washed with H_2O and then MeAc to give 2-(methylthio)-3-nitro-4,5-dihydropyrrole (0.17 g, 34%) mp 207–209 °C. Anal. ($C_5H_8N_2O_2S$) C, H, N, S. A solution of **16** (1.3 g, 0.008 mol) and 2-(methylthio)-3-nitro-4,5-dihydropyrrole (1.2 g, 0.008 mol) in EtOH (50 mL) was refluxed for 1.5 h. On cooling a solid formed, which was filtered off and recrystallized from $MeOH/H_2O$ to give **6** (1.4 g, 66%), mp 207.5–208 °C. Anal. ($C_{11}H_{17}N_5O_2S$) C, H, N, S.

2-[[2-[[(4-Methyl-5-imidazolyl)methyl]thio]ethyl]amino]pyrimidin-4-one Dihydrochloride (7). A mixture of **16** (2.6 g, 0.015 mol) and 2-(methylthio)-4-pyrimidone (1.4 g, 0.010 mol) was heated to 160 °C over a period of 2.5 h. After cooling, the mixture was triturated under H_2O to give the crude product, which was filtered off, dissolved in 5 N HCl, evaporated to dryness, and recrystallized from $H_2O/EtOH$ to give **7** (2.1 g, 79%), mp 246–248 °C. Anal. ($C_{11}H_{17}Cl_2N_5OS$) C, H, N, S, Cl.

2-[[2-[[(4-Methyl-5-imidazolyl)methyl]thio]ethyl]amino]-2-imidazolin-4-one Dihydrochloride (8). A solution of **16** (3.4 g, 0.020 mol) and 2-(methylthio)-2-imidazolin-4-one hydriodide[12] (2.6 g, 0.010 mol) in dry EtOH (20 mL) was left to stand at room temperature for 4 days. The crude product was filtered off and dissolved in dilute HCl and the solution rebasified with K_2CO_3 in H_2O. The pure base (1.1 g, 43%, mp 224–225 °C) was converted to the dihydrochloride by dissolving in dilute HCl, evaporating to dryness, and recrystallizing from $EtOH/H_2O$ to give **8**, mp 226–228 °C. Anal. ($C_{10}H_{17}Cl_2N_5OS$) C, H, N, S, Cl.

4-[[2-[[(4-Methyl-5-imidazolyl)methyl]thio]ethyl]amino]pyrimidin-2-one (9). A solution of **16** (7.4 g, 0.043 mol) and 2,4-dimercaptopyrimidine (4.1 g, 0.028 mol) in H_2O (150 mL) was heated under reflux for 12 h. After cooling, the precipitated oil was separated, washed with water, and dissolved in 2 N HCl. The solution was evaporated to dryness and the residue recrystallized from EtOH to give **18e** (Y = N, L′ = SH) (3.0 g, 30%), mp 254–257 °C. Anal. ($C_{11}H_{17}Cl_2N_5S_2$) C, H, N, S.

A solution of the above product (1.0 g, 0.003 mol) and chloroacetic acid (0.35 g, 0.004 mol) in H_2O (5 mL) was heated on a steam bath for 40 min. Concentrated HCl (8 mL) was added, and the solution was heated under reflux for 2 h, followed by evaporation to dryness. The residual oil was dissolved in H_2O (5 mL)

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and basified with NH_4OH and the precipitate washed with hot H_2O to give **9** (0.28 g, 38%), mp 249–251 °C. Anal. ($C_{11}H_{15}N_5OS$) C, H, N, S.

2-[[2-[[(4-Methyl-5-imidazolyl)methyl]thio]ethyl]amino]-1*H*-pyrid-6-one (10). A mixture of **16** (20 g, 0.12 mol) and 2-bromo-6-ethoxypyridine[23] (11.9 g, 0.059 mol) was heated with stirring at 160 °C for 4 h. After cooling, the mixture was dissolved in 20% aqueous HBr and the solution was washed with ether. The aqueous solution was rebasified with K_2CO_3, extracted into $CHCl_3$, and washed with H_2O. The dried extract was evaporated to dryness and chromatographed (SiO_2–EtOAc/MeOH/$CHCl_3$) to give an oil (3.4 g, 20%), which was treated with picric acid in EtOH to give **18e** (Y = CH, L′ = OEt) dipicrate: mp 172 °C; MS, *m/e* 292. A solution of the base of the above product (3.4 g, 0.012 mol) in 5 N HCl (100 mL) was heated under reflux for 2.5 h. The resulting solution was evaporated to dryness, dissolved in a minimum amount of H_2O, and then basified with aqueous K_2CO_3. After washing of the solution once with $CHCl_3$ and allowing it to stand at 0 °C overnight, a solid crystallized out. This was collected and recrystallized from H_2O to give **10** (0.85 g, 27%). Anal. ($C_{12}H_{16}N_4OS$) C, H, N, S. A further recrystallization from H_2O gave a pure sample, mp 85 °C. Anal. ($C_{12}H_{16}N_4OS$) C, H, N, S.

2-[[2-[[(4-Methyl-5-imidazolyl)methyl]thio]ethyl]amino]-1*H*-pyrid-4-one Dihydrochloride (11). A mixture of **16** (7.6 g, 0.044 mol) and 2-bromopyrid-4-one[24] (3.8 g, 0.022 mol) was heated with stirring at 160 °C for 3 h. After cooling, the mixture was chromatographed (SiO_2–*i*-PrOH/EtOAc and then *i*-PrOH/EtOH). The fractions containing a mixture of product and starting amine were combined, evaporated to dryness, and purified further by ion-exchange chromatography (IRA 400, OH form 0.2 N HCl). Evaporation of the eluate gave the crude product (1.1 g, 15%), which was recrystallized from *i*-PrOH/EtOAc to give **11**: mp 212–214 °C; MS, *m/e* 264; NMR (D_2O) δ 8.72 (s, im 2 H), 7.86 (d, pyr 6 H), 6.62 (q, pyr 3 H), 5.45 (d, pyr 5 H), 3.98 (s, im CH_2), 3.62 (t, NCH_2), 2.92 (t, SCH_2), 2.38 (s, CH_3).

2-[[2-[[(4-Methyl-5-imidazolyl)methyl]thio]ethyl]amino]-3-nitropyrid-4-one Hydrochloride (12). A mixture of **16** (2.34 g, 0.014 mol) and 2-bromo-3-nitropyrid-4-one[25] (3.0 g, 0.014 mol) was heated at 170 °C for 0.5 h. The cold residue was washed with MeOH and dissolved in boiling HCl/EtOH. Insoluble residue was filtered off and the filtrate was evaporated to a residue, which was recrystallized from MeOH/EtOAc and purified further by ion-exchange chromatography (IRA 400, OH form −2% HCl). Evaporation of the eluate to dryness and recrystallization from MeOH gave **12** as a mixture of the mono- and dihydrochlorides (0.52 g, 10%), mp 228–230 °C. Anal. ($C_{12}H_{15}N_5O_3S$·1.5HCl) C, H, N, S, Cl.

3-[[2-[[(4-Methyl-5-imidazolyl)methyl]thio]ethyl]amino]-5,6-dihydro-1,2,4-thiadiazine 1,1-Dioxide (13). A mixture of **16** (4.0 g, 0.023 mol) and 3-(methylthio)-5,6-dihydro-1,2,4-thiadiazine 1,1-dioxide[26] (4.2 g, 0.023 mol) was heated in an oil bath at 140 °C for 4 h. The product was chromatographed (SiO_2–EtOH/EtOAc) and then recrystallized from EtOH/Et_2O to give **13** (2.2 g, 32%), mp 146–147 °C. Anal. ($C_{10}H_{17}N_5O_2S_2$) C, H, N.

1-(Methylamino)-2-[[2-[[(4-methyl-5-imidazolyl)methyl]thio]ethyl]amino]cyclobut-1-ene-3,4-dione (15). Into an ethereal solution of dimethyl squarate[27] (5.58 g, 0.039 mol) was passed $MeNH_2$ gas, and the mixture was stirred for 30 min at room temperature. The solid precipitate was filtered off, dried, and recrystallized from EtOAc to give **17c** (2.40 g, 43%), mp 177–178 °C. Anal. ($C_6H_7NO_3$) C, H, N. A mixture of **17c** (1.2 g, 0.009 mol) and **16** (1.95 g, 0.011 mol) was heated at 170 °C with stirring for 40 min. After allowing to cool, the resulting residue was chromatographed (SiO_2–$CHCl_3$/EtOH), and the product was recrystallized twice from EtOH to give **15** (0.19 g, 8%), mp 207.5–208.5 °C. Anal. ($C_{12}H_{16}N_4O_2S$) C, H, N, S.

Dipole Moments. Measurement of dipole moments was performed with a Boonton 33A bridge, as described previously.[28] Because of poor solubility in the usual nonpolar solvents, permittivity measurements of model compounds, corresponding to cyanoguanidine replacement groups in the antagonists, were made in water or ethanediol. Comparability between measurements in these two solvents has been noted.[9,10] Values of the "effective dipole moment", μ (i.e., $g^{1/2}\mu$, assuming that g, the Kirkwood correlation coefficient is unity) are given in Table I.[9]

Pharmacology. Histamine H_2 receptor blocking activity was determined in the isolated guinea pig right atrium against histamine-stimulated tachycardia by the method described by Parsons et al.[8] Dose ratios (X) were calculated as the ratio of histamine concentrations required to produce half-maximal responses in the presence and absence of different concentrations (B) of antagonist, and dissociation constants (K_B) were derived from the equation $K_B = B/(X - 1)$.

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