Zwitterionic Analogues of Cimetidine as H_2 Receptor Antagonists

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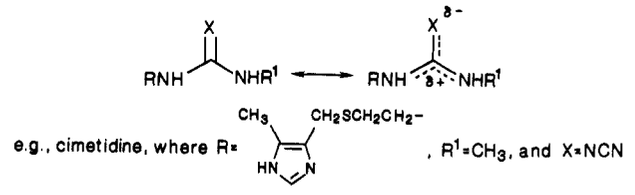
A series of analogues of the H_2 receptor histamine antagonist cimetidine have been synthesized in which the dipolar cyanoguanidine group has been replaced by a number of zwitterionic moieties. Although none of the compounds is more effective than cimetidine in blocking histamine-stimulated tachycardia on the isolated guinea pig atrium, the activities of most of the compounds possessing rigid dipoles can be accounted for on the basis of dipole orientation relative to the common side chain and by considering the active species in each case to be the zwitterion. These findings are in general agreement with those found for analogues having conjugated groups as dipoles.

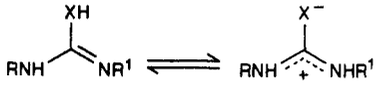
Structural modifications to the H_2 receptor histamine antagonist cimetidine, *N*-cyano-*N'*-methyl-*N''*-[2-[[(4-methyl-5-imidazolyl)methyl]thio]ethyl]guanidine, have recently been described[1] in which the cyanoguanidine moiety is replaced by alternative uncharged, polar groups. One property shared by these groups is a high dipole moment that arises mainly as the result of π-electron delocalization, as shown in Scheme I, where X is an electronegative atom or group.

In a series of 15 such analogues, it was found that most of the variance in in vitro H_2 antagonist activity could be accounted for by the orientation of the dipole of the polar group rather than its moment. Originally, however, it was thought that these groups might undergo direct dipole-mediated interactions with the receptor and that antagonist potency might be enhanced by increasing dipole moment. In seeking replacements for the cyanoguanidine group with higher dipole moments, the possibility of introducing zwitterionic groups possessing fully separated charges was considered. Suitable zwitterionic groups might be generated, for example, by encouraging the transfer of a proton from an acidic group, XH, to a basic amidine group within the same structural fragment, as shown in Scheme II. A number of cyclic and acyclic zwitterionic amidines derived in this way have thus been incorporated into H_2 antagonists and are the subject of this paper.

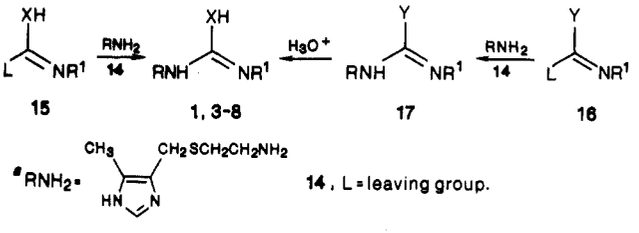
Scheme I. Neutral, Conjugated Dipoles



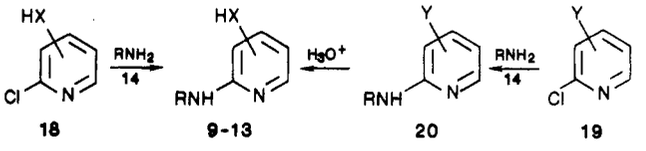
Scheme II. Zwitterionic Dipoles



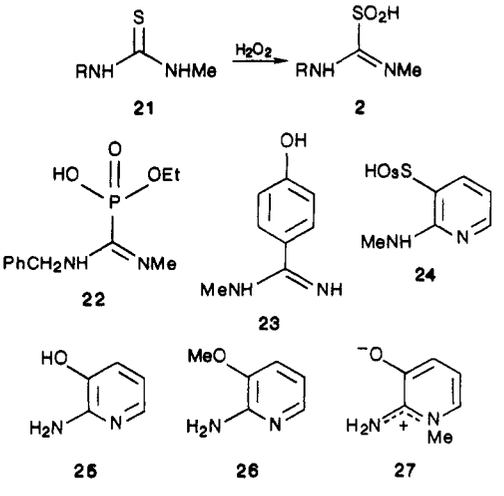
Scheme III[a]



Scheme IV



Scheme V



Chemistry

Most of the antagonists were prepared either by direct displacement of a leaving group from intermediates **15** or **18** by the parent amine **14** or by reaction of intermediates **16** or **19** with amine **14** to give **17** and **20**, respectively, followed by acidic hydrolysis of the group Y to give an acidic function, XH, in the appropriate antagonists, as shown in Schemes III and IV.

Model amidinophosphonate, hydroxybenzamidine, and aminopyridinesulfonic acid compounds (**22–24**) were prepared in a similar way with intermediates **15** (XH = EtOP(=O)OH, L = MeS, R^1 = Me), **15** (XH = 4-C_6H_4OH, L = EtO, R^1 = H), and **18** (XH = 3-SO_3H), respectively. The amidinosulfinic acid derivative **2** was prepared directly by partial oxidation of the parent thiourea **21**[2] with H_2O_2 (Scheme V). 2-Amino-3-methoxypyridine (**26**) was prepared by a known method,[3] and the 2-amino-3-hydroxypyridinium betaine **27** was obtained by ring N-methylation of 2-amino-3-hydroxypyridine (**25**). 2-Amino-3-hydroxypyridine was a commercial sample (Aldrich Chemical Co.) and was used without further purification.

Results and Discussion

The H_2 receptor antagonist activities (-log K_B) of 13 zwitterionic analogues of cimetidine have been measured

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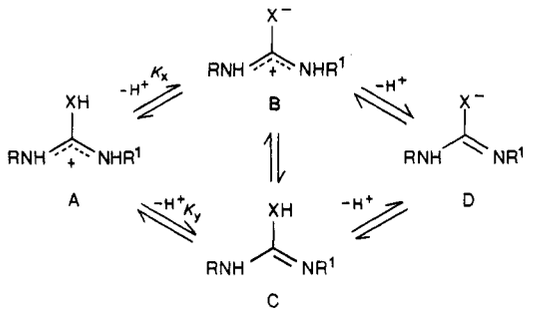
Scheme VI. Prototropic Equilibria in Substituted Formamidines[a]



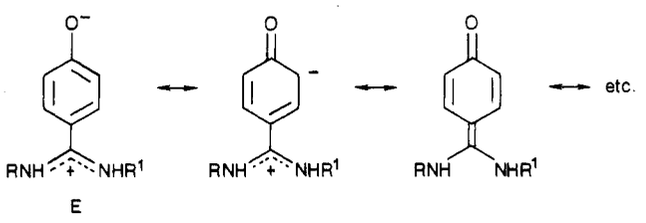
XH = CO_2H, SO_2H, SO_3H, $CH_3OP(=O)OH$, $NHP(=O)(OH)OCH_2CH_3$, CH_2CO_2H, $^4C_6H_4CO_2H$, $^4C_6H_4OH$

[a] For convenience, C and D are each shown as one of two possible tautomers.

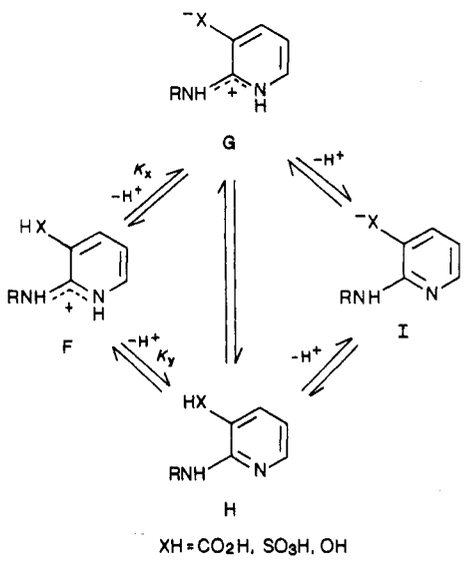
in vitro against histamine stimulation of the rate of beating on the guinea pig right atrium preparation and are shown in Table I. Although none of the compounds is more active than cimetidine ($-\log K_B = 6.10^4$), the zwitterionic species, assumed to be the biologically active form, is not the most favored species at the assay pH of 7.4 in every case. In order to estimate the relative populations of zwitterions existing under assay conditions, the relevant ionic and tautomeric equilibria must be considered. These are shown for substituted formamidines in Scheme VI and for 3-substituted 2-aminopyridine derivatives in Scheme VIII. Estimates of the microscopic pK_a values corresponding to dissociation of the conjugate acids (A and F) by loss of a proton from the XH group (pK_x) and from the amidinium cation (pK_y) are given in Table I together with measured macroscopic pK_a values, where available.

Amidine-Based Zwitterions. In compounds 1–4 and 6 the polar groups are expected to be neutral (i.e., zwitterionic) over a wide pH range. Although the exact microscopic pK_x values are not known, the acidifying effect of the strongly electron-withdrawing amidinium group ($\sigma_m = 0.65$[6]) should result in values considerably lower than those of the simple acids indicated in Table I. The microscopic pK_y values for these compounds, which have been calculated by using the correlation equation of Charton,[8] are all considerably higher than pK_x, suggesting an overwhelming preference for dissociation of XH

Scheme VII. Canonical Forms of the 4-Hydroxybenzamidine Zwitterion



Scheme VIII. Prototropic Equilibria in 3-Substituted 2-Aminopyridines[a]



XH = CO_2H, SO_3H, OH

[a] H and I are both shown as the tautomer considered to be preferred.[25]

(Scheme VI), leading to the zwitterion (B). Preference for the zwitterion in amidinoformic, -sulfinic, and -sulfonic acids has already been suggested by others.[20-23] The guanidinophosphonate moiety in compound 5 is appreciably more acidic than its amidinophosphonate counterpart (in 4), as suggested by model compounds (Table I), and it is estimated that 50% will be neutral at pH 7.4. In addition, the large difference between the microscopic pK_x and pK_y values for 5 indicate that the neutral form should be completely zwitterionic (i.e., 50% of the total species will be present as the zwitterion).

The prototropic equilibria for compounds 7 and 8 in which the two ionizable groups are separated by a benzene ring are shown in Scheme VI. The microscopic ionization constants for the 4-amidinobenzoic acid moiety have been estimated by comparing the effects of 4-substituents on the ionization of benzoic acid[17] and the effects of 4-substituents on the ionization of benzamidinium ions (eq 1, Table II). Ionization of the carboxyl group (calcd $pK_x = 3.55$) is expected to precede that of the amidinium cation (calcd $pK_y = 10.62$) and to result in a predominance of the zwitterion at pH 7.4.

The model 4-hydroxybenzamidine (23) is a fairly basic compound with a measured pK_a of 7.95, and at pH 7.4, it is expected that 8 will exist mainly as the cation. Nevertheless, a significant proportion (22%) will be unprotonated, and it is estimated, by comparing microscopic pK_x and pK_y values (Table I), that proton loss will take

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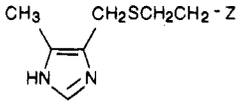
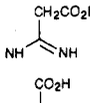
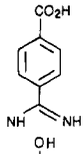
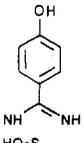
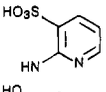
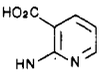
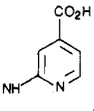
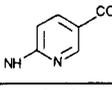
(23) Walter, W.; Randau, G. *Liebigs Ann. Chem.* **1969**, *722*, 98.

Table I. Structures, Activities, and Physical Properties of H_2 Receptor Antagonists



compd	Z	H_2 receptor antagonist activity ($-\log K_B$) obsd (95% limits)[a]	corrected[b]	pred (eq 6)	macroscopic pK_a of Z[c] pK_1	pK_2	microscopic pK_a of Z[d] pK_x	pK_y	% zwitterion at pH 7.4	ψ[e]
cimetidine		6.10 (6.04–6.17)								
1		5.41 (5.12–5.67)	5.41	5.58	2.22[f]	11.04[f]	<4.76[g]	7.03[h]	100	0[i]
2		5.73 (5.51–5.89)	5.73	5.58	1.97[f]		<2.11[j]	4.27[h,k]	100	0[l]
3		5.87 (5.11–6.72)	5.87	5.58			<−1.20[m]	4.87[h]	100	0[n]
4		4.25 (3.80–4.86)	4.25	5.58		11.22[o]	<1.29[p]	6.43[h,q]	100	−[r]
5		4.48 (4.12–4.86)	4.78	–	−0.31[s]	7.4[t]	<1.29[p]	5.52[u]	50	−[r]
6		3.30 (2.69–3.98)[v]	3.30	–			<4.76[g]	10.86[h,w]	100	−[r]
7		3.70 (3.39–4.09)[x]	3.70	5.58			3.55[y]	10.62[z]	100	0
8		4.20 (3.88–4.75)	4.86	5.58	7.95[aa]	>12.7[aa,bb]	8.48[cc]	11.66[z]	~22	0
9		3.77[dd]	6.07	6.08		5.10[aa]	<2.55[ee]	3.42[ff]	0.5	28
10		5.89 (5.66–6.16)	5.99	6.07	6.03[gg]	9.51[gg]	5.99[c,hh]	6.58[c,ii]	~80[jj]	26
11		5.09 (4.65–5.53)	6.03	6.08	2.25[gg,kk]	6.54[gg,kk]	<4.20[ll]	4.63[ff]	12	31
12		3.76 (2.98–4.49)	4.83	4.94	1.95[gg,kk]	6.37[gg,kk]	<4.20[ll]	5.17[mm]	9	−16
13		<3.3	<4.3	2.35			<4.20[ll]	4.68[nn]	~10	−55

[a] Tested on the histamine-stimulated guinea pig right atrium and analyzed by Schild plot. Slopes of log $(X - 1)$ plotted against log B were not significantly different from unity (±95% limits) unless indicated. [b] Corrected for proportion of zwitterion at pH 7.4 (see text). [c] Determined potentiometrically (see Experimental Section). [d] pK_a values taken from Perrin's compilation[5] or calculated by using equations shown in Table II or from literature and σ values from Hansch and Leo.[6] [e] Approximate dipole orientation relative to R–N bond (see text), estimated using standard bond lengths and angles or crystal dimensions where available, as described previously.[7] [f] Value for antagonist. [g] pK_a of $MeCO_2H$ at 25 °C.[5] [h] Calculated using equation of Charton.[8] [i] Crystal structure of amidinoformic acid from Glover.[9] [j] pK_a of $BuSO_2Na$ at 20 °C.[10] [k] Using σ_m for SO_2Me. [l] Although the SO_2 plane subtends an angle of 68° with the NCN plane in the amidinosulfinic acid crystal,[11] ψ can be considered to be 0°. [m] pK_a of $MeSO_3H$ at 25 °C.[12] [n] Crystal structure of (*N*,*N*-dimethylamidino)sulfonic acid from Walter and Holst.[13] [o] R = $PhCH_2$, ethyl ester. [p] pK_a of $(MeO)_2PO_2H$ at 25 °C.[14] [q] Using σ_m for $PO(OMe)_2$. [r] Complicated by bond rotation (see text). [s] First pK_a of *N*,*N*-dimethyl-N^1-guanidinophosphonic acid at 30.5 °C.[15] [t] Second pK_a of benzyl guanidinophosphonate.[15] [u] Calculated by using eq of Charton,[8] and σ_I for $PO(OMe)_2$. [v] Slope 1.65 ± 0.91. [w] σ_m for CH_2CO_2H = 0.05 calculated from σ_I and σ_p values of 0.11 and −0.07, respectively, using $\sigma_m = (2\sigma(I) + \sigma_p)/3$.[16] [x] Slope 1.61 ± 0.73. [y] Calculated by using Hammett's eqation.[17] [z] Calculated by using eq 1, Table II. [aa] R = Me. [bb] Determined by UV spectrophotometry. [cc] Calculated by using equation of Jaffe.[17] [dd] Estimated from two experiments, slope 1.04. [ee] pK_a of $PhSO_3H$ at 25 °C.[5] [ff] Calculated by using equation 2, Table II. [gg] R = H. [hh] pK_a of **27**. [ii] pK_a of **26**. [jj] % zwitterion (G) in the mixture with H estimated from data in Figure 1 to be 85% by using a standard dual-wavelength (293 and 317 nm) analysis of a two-component mixture; the value estimated from the pK_a values of **26** and **27** using the expression $pK_y - pK_x = \log K$ is 80%; a small correction for ionization to the cation (F, 4.1%) and the anion (I, 0.8%) was also made. [kk] Hirai.[18] [ll] pK_a of $PhCO_2H$ at 25 °C.[5] [mm] Calculated by using eq 3, Table II. [nn] Calculated by using eq 4, Table II.

Table II. Correlations Used for Estimating pK_a Values

	n^a	r^b	s^c	p^d	eq no.
3- and 4-substituted *N,N*-dibutylbenzamidines[e]					
$pK_a = 11.20 - 1.28\sigma$	5	0.951	0.099	<0.01	1
3-substituted 2-aminopyridines[f,g]					
$pK_a = 6.99 - 6.38\sigma_m$	5	0.996	0.164	<0.001	2
4-substituted 2-aminopyridines[f,h]					
$pK_a = 6.75 - 3.52\sigma_p$	6	0.990	0.155	<0.001	3
5-substituted 2-aminopyridines[f,i]					
$pK_a = 6.83 - 5.80\ \sigma_m$	5	0.997	0.136	<0.001	4

[a] Number of data points used in regression. [b] Correlation coefficient. [c] Standard deviation from regression line. [d] Level of significance (*t* test). [e] Using pK_a values in 50% MeOH at 25 °C for 3-Cl, 3-OMe, 4-Cl, 4-OMe, and unsubstituted compounds (10.68, 11.20, 10.90, 11.50, and 11.27, respectively)[19] and σ values from Hansch and Leo.[6] [f] σ values from Hansch and Leo.[6] [g] Using pK_a values for 3-H, Me, CO_2Me, CO_2Et, and NO_2 compounds (6.82, 7.48, 4.78, 4.73, and 2.33, respectively).[5] [h] Using pK_a values for 4-H, Me, OMe, CO_2Me, CO_2Et, and Cl compounds (6.82, 7.38, 7.62, 5.21, 5.25, and 5.70, respectively).[5] [i] Using pK_a values for 5-H, Me, Cl, CN, and NO_2 compounds (6.82, 7.22, 4.83, 3.41, and 2.78, respectively).

place predominantly at the phenolic OH group. In the resulting zwitterion (E, Scheme VII), the charged centers are in conjugation, and it is possible that a number of other canonical forms, including a vinylogous urea, may contribute. Comparison of the measured dipole moment of 4-hydroxybenzamidine[24] (23 D) with the value for the zwitterion calculated as described previously[7] (31 D, assuming standard bond lengths and angles) suggests that there should be a large contribution from E in water.

Pyridine-Based Zwitterions. The ionic and tautomeric equilibria for the 3-substituted 2-aminopyridine derivatives **9–11** are shown in Scheme VIII. The exact values of the microscopic pK_x constants for **9** and **11** are not known, but these should be significantly lower than the pK_a values of the corresponding benzene derivatives cited in Table I, due to the presence of the charged amidine system. The microscopic pK_y values for compounds **9** and **11** have been calculated by using eq 2 (Table II). In compound **9**, pK_x is significantly lower than pK_y, suggesting that the zwitterion (G) predominates over the neutral species (H). The system is, however, fairly acidic, and only a small proportion (0.5%) of G will exist at pH 7.4. In compound **11**, although pK_x is lower than pK_y the difference has not been quantified. Spectroscopic evidence,[18] however, suggests that 2-aminonicotinic acid is almost exclusively zwitterionic in water. As with **9**, **11** is acidic, and at pH 7.4 it is estimated that 12% exists as the zwitterion (G). The isomeric isonicotinic and 6-aminonicotinic acid derivatives (compounds **12** and **13**, respectively) are similarly acidic. The microscopic pK_y values for these two groups have been calculated by using eq 3 and 4 (Table II), and the zwitterion is thought to be the predominant neutral form.[18]

Prototropic preferences in the 2-amino-3-hydroxypyridine derivative **10** have been estimated with model compounds. A comparison of the ultraviolet absorption spectra of buffered, aqueous solutions of 2-amino-3-hydroxypyridine (**25**), 2-amino-3-methoxypyridine (**26**), and 1-methyl-2-aminopyridinium 3-oxide betaine (**27**) is shown in Figure 1. The marked similarity between the spectra of **25** and **27** strongly supports a preference for the zwitterionic form G at pH 7.4, and the ratio of G to H is estimated to be approximately 5:1. This result is in good agreement with the ratio calculated from the pK_a values of **26** and **27** (see Table I). Unlike the substituted pyridine moieties in **9** and **11**, however, the 2-amino-3-hydroxypyridine in **10** is only weakly acidic and will exist predominantly as a mixture of G and H (95%) at pH 7.4.

If it is assumed that the zwitterionic forms of compounds **1–13** are solely responsible for their antagonist activities,

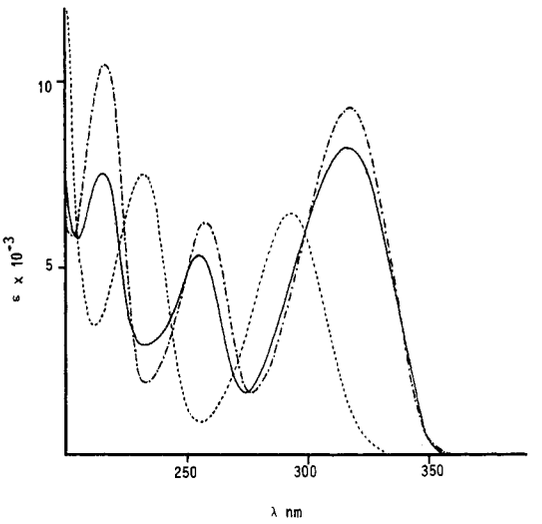
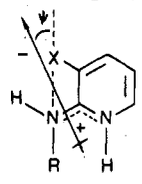


Figure 1. Ultraviolet absorption spectra of **25–27** in aqueous buffers at pH 7.4.

	25 (–)			**26** (---)		**27** (·-·)		
λ_{max}	317	255	215	293	231	317	257	216
$\Delta\epsilon \times 10^{-3}$	8.21	5.33	7.55	6.45	7.54	9.21	6.16	10.43

$$\Delta\epsilon = \epsilon\lambda_{max} - \epsilon_{400}$$

useful comparisons can be made of their $-\log K_B$ values corrected for the relative populations of these species expected under assay conditions. These "corrected" values are given in Table I. One obvious result of applying these correction factors is to largely remove the differences between the activities of the three 3-substituted pyridine derivatives, **9–11**, making this the most active class of zwitterions investigated. It is also interesting to note that the dipoles of these three zwitterionic moieties are orientated in a similar direction relative to the R–N bond (see J) and that their orientation angles, ψ, are close to 30°, the

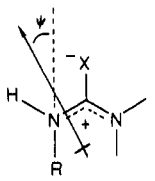


J

value proposed as optimal in a series of derivatives of dipolar, conjugated systems studied previously[1] (see K and Table I).

Comparison of the three aminopyridinecarboxylic acid derivatives **11–13** shows the effect of moving the negative end of the dipole around the ring. As seen from Table I, H_2 antagonist activity falls progressively from 2-aminonicotinic through 2-aminoisonicotinic to 6-aminonicotinic acid derivatives, while ψ decreases from 31° to –16° to –55°

(24) Young, R. C.; Ganellin, C. R.; Graham, M. J.; Roantree, M. L.; Grant, E. H. *Tetrahedron Lett.* **1985**, *26*(15), 1897.



K

(Table I), supporting the idea that the optimum may be near to 30°.

The simple amidino acids **1–3**, which are completely zwitterionic, comprise another class with fairly similar but slightly lower antagonist activities. Here, the dipoles are all orientated 30° from the proposed optimum (i.e., ψ = 0° in K).

On the basis of dipole orientation alone, the 4-amidinobenzoic acid and 4-hydroxybenzamidine derivatives **7** and **8** might have been expected to be similar in their antagonist activity to the structurally simpler amidino acids **1–3**. Compounds **7** and **8** are, however, relatively weakly active even after correcting for ionization in **8**.

Compounds **4–6** are also much more weakly active than the related simple amidines **1–3**. The amidinophosphonic acid **4**, although somewhat analogous to **2** in having the center of its negative charge displaced from the central C–X bond axis, has greater steric requirements, and the preferred conformation of this group is uncertain. In **5** and **6**, rotation about the C–X bond is possible, thus making the dipole orientation ambiguous. Moreover, bond rotation in the amidinoacetic acid moiety will be relatively free and the dipole will lack the rigidity that might be required for effective alignment with the receptor.

For those active compounds that possess rigid dipoles with defined orientations (**1–3** and **7–12**), the relationship between H_2 antagonist activity, corrected for the proportion of zwitterionic species, and the dipole orientation parameter, cos θ (where θ is defined[1] as the deviation of dipole orientation from the proposed optimum angle ψ of 30°, i.e., $\theta = 30 - \psi$), is given by eq 5. Clearly, cos θ does

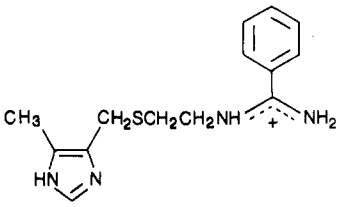
$$-\log K_B(\text{corr}) = 4.59 \cos\theta + 1.29 \quad (5)$$
$$(\pm 5.97) \qquad (\pm 5.35)$$
$$n = 9,\ r = 0.567,\ s = 0.698$$

not adequately account for activity within this group of analogues, and it is evident that **7** and **8** are outliers. If these two compounds are withdrawn, a highly significant relationship ($p < 0.005$) is obtained (eq 6), with dipole orientation accounting for 87% of the variance in the corrected biological data. Presumably there will be a limit

$$-\log K_B(\text{corr}) = 3.73 \cos\theta + 2.35 \quad (6)$$
$$(\pm 1.67) \qquad (\pm 1.51)$$
$$n = 7,\ r = 0.932,\ s = 0.177$$

to the distance separating the charges of a zwitterion for effective dipole-mediated alignment of antagonist with receptor,[1] and **7** and **8** might be considered to be more analogous to antagonists lacking a negatively charged X group (Scheme VI), for example, the benzamidine derivative[26] (**28**), which is also a relatively weakly active H_2 antagonist ($-\log K_B$ = 4.53 (3.76–5.11), Schild slope = 1.20 ± 0.28).

Equation 6 predicts a $-\log K_B$(corr) value for compound **13** of 2.35 (Table I) corresponding to an uncorrected $-\log K_B$ of 1.4, which is not in disagreement with the experimental observation that no antagonist activity could be detected on the atrium up to a dose of 486 μM.



28

In a previous study[1] where the H_2 antagonist activities of a series of analogues of cimetidine possessing alternative uncharged, dipolar groups were considered, dipole orientation was also found to be highly correlated, and for 13 compounds eq 7 is obtained. For these compounds, dipole

$$-\log K_B = 9.10 \cos\theta - 2.69 \quad (7)$$
$$(\pm 3.75) \qquad (\pm 3.39)$$
$$n = 13,\ r = 0.849,\ s = 0.531$$

orientation accounts for 72% of the variance in the activity data. Thus for analogues of cimetidine incorporating both zwitterionic and neutral dipolar groups, cos θ (calculated with reference to an optimum angle ψ of 30°) appears to be highly correlated with H_2 antagonist activity. It is interesting, however, to note that the coefficient of this parameter in eq 7 is more than twice as great as that in eq 6. This might be explained by a difference in the degree of hydration between the zwitterionic and conjugated dipolar groups. Previously it was suggested[1] that hydrophobic effects might be involved in the interaction of cimetidine analogues with the H_2 receptor and that in order to fully realize their hydrogen-bonding and dipolar potential these polar antagonists would have to undergo loss of a water solvation shell. The zwitterions, being composed of localized charges, would be expected to be more highly hydrated and it is possible that their ability to align with a suitable receptor site might be diminished, thus making the antagonist activity relatively insensitive to dipole orientation.

Experimental Section

Synthesis. NMR spectra were recorded on a Varian A60A, a JEOL PFT 100P, or a Bruker AM250 spectrometer, using Me_4Si for reference. Microanalytical data are within 0.4% of theoretical values, and melting points are uncorrected.

[*N*-[2-[[(4-Methyl-5-imidazolyl)methyl]thio]ethyl]-amidino]formic Acid (1). Trilead tetroxide (43.0 g, 0.063 mol) was added to a solution of **15** (XH = CO_2H, L = SH, R^1 = H)[27] (4.90 g, 0.046 mol) and **14**[2](8.00 g, 0.046 mol) in MeOH (200 mL). The mixture was stirred at room temperature for 4 h and filtered to remove the lead compounds. The product was isolated by chromatography (SiO_2–EtOAc/*i*-PrOH) to give a solid, which was dissolved in MeOH and precipitated with Et_2O to give **1** (2.75 g, 25%) as the hemietherate: mp 174–176 °C dec; NMR (Me_2SO-d_6, 60 MHz) δ 1.10 (t, 1.8 H, Et_2O), 2.16 (s, 3 H), 2.67 (t, 2 H), 3.40 (q, 1.2 H, Et_2O), 3.55 (t, 2 H), 3.71 (s, 2 H), 7.50 (s, 1 H). Anal. ($C_9H_{14}N_4O_2 \cdot 0.5(C_2H_5)_2O$) C, H, N, S.

[*N*-Methyl-*N'*-[2-[[(4-methyl-5-imidazolyl)methyl]thio]-ethyl]amidino]sulfinic Acid (2). Thiourea **21**[2] (2.93 g, 0.012 mol) in MeOH (12 mL) was treated dropwise with 30% H_2O_2 (2.72 g, 0.024 mol) with stirring in an ice bath. The resulting clear solution was stored overnight at 0 °C to yield a white, crystalline solid, which was filtered off and dried to give **2** (1.01 g, 30%), mp 120–121 °C. Anal. ($C_9H_{16}N_4O_2S_2$) C, H, N, S.

[*N*-Methyl-*N'*-[2-[[(4-methyl-5-imidazolyl)methyl]thio]-ethyl]amidino]sulfonic Acid (3). A solution of **14** (1.43 g, 0.0085 mol) in dry MeCN (150 mL) was added dropwise, with stirring, to a solution of **15** (XH = SO_3H, L = SMe, R^1 = Me[28] (1.43 g,

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0.0084 mol) in dry MeCN (150 mL) at 50 °C, giving immediate precipitation. After warming for a further hour at 70 °C, the mixture was evaporated to dryness and chromatographed (SiO_2–EtOAc/MeOH) to give a crude product, which was crystallized from *i*-PrOH to give **3** (0.460 g, 19%), mp 162.5–163.5 °C. Anal. $C_9H_{16}N_4O_3S_2$) C, H, N, S.

Methyl [*N*-Methyl-*N'*-[2-[[(4-methyl-5-imidazolyl)methyl]thio]ethyl]amidino]phosphonate (4). A mixture of redistilled MeNCS (7.30 g, 0.10 mol) and dimethyl phosphite (11.0 g, 0.10 mol) was treated with NaOEt (ca. 0.6 g) until the exothermic reaction had ceased. The mixture was kept at 110 °C for 2 h, cooled, washed with H_2O, and extracted with Et_2O. Chromatography of the latter (SiO_2–EtOAc/petroleum ether (40–60 °C)) afforded dimethyl [*N*-(methylthio)carbamoyl]-phosphonate.

The above product (1.83 g, 0.010 mol) was dissolved in MeI (10 mL) and the solution was heated under reflux for 3 h. After the solution was kept at room temperature for 3 days under anhydrous conditions, **15** (XH = MeOP(=O)OH, L = SMe, R^1 = Me) crystallized out. This product (1.56 g, 0.0080 mol) was dissolved in MeCN (50mL) and treated with **14** (1.36 g, 0.0080 mol) and, after being allowed to stand at room temperature for 16 h, afforded a solid, which was recrystallized three times from MeOH/Me_2CO to give **4**, mp 170–171 °C. Anal. ($C_{10}H_{19}N_4O_3PS$) C, H, N.

Ethyl [*N*-Methyl-*N'*-[2-[[(4-methyl-5-imidazolyl)methyl]thio]ethyl]guanidino]phosphonate Hydrobromide (5). An ice-cooled mixture of redistilled benzyl alcohol (10.8 g, 0.10 mol) and Et_3N (10.1 g, 0.10 mol) was added dropwise, with stirring, to a solution of ethyl dichlorophosphate (16.3 g, 0.10 mol) in THF (100 mL) over 30 min. After 2 h of stirring at room temperature, the solution was filtered and almost all of the THF evaporated at 25 °C under reduced pressure to give benzyl ethyl chlorophosphate as an oil. This was diluted with $CHCl_3$ (80 mL) and, while cooling in an ice bath, treated first with a cold solution of *N*,*S*-dimethylisothiouronium iodide (23.2 g, 0.10 mol) in H_2O (25 mL) and then with vigorous stirring over 30 min a solution of NaOH (8.00 g, 0.20 mol) in H_2O (15 mL). After addition was complete, the cooling bath was removed, and vigorous stirring was continued for a further 2 h. the organic phase was then separated, washed successively with dilute H_2SO_4, $NaHCO_3$ solution, and H_2O, and dried over Na_2SO_4. After evaporating to dryness, the mixture was chromatographed (SiO_2–EtOAc/petroleum ether (40–60 °C)) to give **16** (Y = NHP(=O)(OEt)-(OCH_2Ph), L = SMe, R^1 = Me) as an oil.

To a stirred mixture of the above product (3.05 g, 0.010 mol) with **14** (1.71 g, 0.010 mol) and 4A molecular sieves (1 g) in dry *i*-PrOH (50 mL) was added Ag_2O (2.32 g, 0.010 mol) in several portions during 30 min. After 3 h the reaction mixture was filtered and evaporated. The residue was chromatographed (SiO_2–Me_2CO/MeOH) to give **17** (Y = NHP(=O)(OEt)(OCH_2Ph), R^1 = Me) (2.30 g). This product (1.27 g, 0.0030 mol) was dissolved in Me_2CO (10 mL) and 48% aqueous HBr (1.1 mL, 0.0060 mol) was added. MeOH (1 mL) was added and the solution was kept for 18 h, after which **5** crystallized out (0.900 g, 75%), mp 170–172 °C dec. Anal. ($C_{11}H_{22}N_5O_3PS$·HBr) C, H, N, Br.

[*N*-[2-[[(4-Methyl-5-imidazolyl)methyl]thio]ethyl]-amidino]acetic Acid Dihydrochloride (6). A mixture of **16** (Y = CH_2CO_2Et, L = OEt, R^1 = H)[29] (13.0 g, 0.065 mol) and **14** (6.00 g, 0.035 mol) in EtOH (100 mL) was left to react for 2 days. After evaporation of solvent in vacuo, the resulting oily residue solidified on triturating with Et_2O. Recrystallization from MeCN afforded **17** (Y = CH_2CO_2Et, R^1 = H) (7.50 g), mp 124–126.5 °C.

A solution of the above product (0.500 g, 0.0020 mol) in 2.5 N HCl (40 mL) was heated under reflux for 2 h and then allowed to stand overnight. After evaporation to dryness in vacuo, the residue was solidified on trituration with Et_2O, filtered, and washed with Et_2O to give **6** (0.500 g, 77%), mp 237–239 °C. Anal. ($C_{10}H_{16}N_4O_2S$·2HCl) C, H, N, S, Cl.

Sodium 4-[*N*-[2-[[(4-Methyl-5-imidazolyl)methyl]thio]-ethyl]amidino]benzoate Hydrochloride (7). A mixture of **16** (Y = 4-$C_6H_4CO_2Et$, L = OEt, R^1 = H) free base (prepared from the hydrochloride[30] (2.76 g, 0.011 mol) by treatment with NaOEt (from Na, 0.246 g, 0.011 g-atom) in EtOH) and **14** (0.917 g, 0.0054 mol) in EtOH (50 mL) was left to stand at room temperature for 10 days. The resulting mixture was filtered, evaporated to dryness, and chromatographed (SiO_2/$CHCl_3$) to give **17** (Y = 4-$C_6H_4CO_2Et$, R^1 = H) as an oil. The above product (1.65 g, 0.0047 mol) was hydrolyzed with aqueous HCl (40 mL, 50%) at 70 °C for 4 h. The resulting mixture was then basified to pH 8.5 by slow addition of 2 N NaOH, filtered, and evaporated to an oil. This was dissolved in a minimum amount of *i*-PrOH, filtered to remove inorganic material, evaporated to an oil, and treated with EtOH and EtOAc to give a solid precipitate in three crops. These were combined and recrystallized again from EtOH/EtOAc to afford **7** (0.325 g, 16%), mp 206 °C. Anal. ($C_{15}H_{17}N_4O_2SNa$·HCl) C, H, N, Cl.

***N*-[2-[[(4-Methyl-5-imidazolyl)methyl]thio]ethyl]-4-hydroxybenzamidine Dihydrochloride (8).** The hydrochloride of **15** (XH = 4-C_6H_4OH, L = OEt, R^1 = H)[31] (4.43 g, 0.022 mol) was basified by adding to a solution of K_2CO_3 (3.46 g, 0.025 mol) in H_2O (15 mL) and shaking with Et_2O (100 mL). The Et_2O layer was dried over $MgSO_4$ and added to a solution of **14** (1.88 g, 0.011 mol) in EtOH (15 mL). After the solution was allowed to stand at room temperature for 7 days, a solid had deposited and was filtered off. Acidification with EtOH/HCl, followed by recrystallization from EtOH/Et_2O gave **8** (1.28 g, 32%), mp 225–228 °C. Anal. ($C_{14}H_{18}N_4OS$·2HCl) C, H, N, S, Cl.

2-[[2-[[(4-Methyl-5-imidazolyl)methyl]thio]ethyl]-amino]pyridine-3-sulfonic Acid (9). A mixture of **18** (XH = 3-SO_3H)[32] (2.50 g, 0.013 mol) and **14** (3.43 g, 0.020 mol) was heated at 135 °C for 21 h and allowed to cool. The resulting glass was chromatographed (SiO_2–$CHCl_3$/*i*-PrOH) and the product evaporated to dryness. The residue was next dissolved in a little H_2O, treated with excess concentrated NH_3 solution, and washed with several portions of $CHCl_3$, and the aqueous solution was evaporated to dryness, azeotroping with EtOH to leave a yellow glass, which was crystallized from *i*-PrOH to give **9** (0.200 g, 5%), softening with no distinct mp >50 °C. Anal. ($C_{12}H_{16}N_4O_3S_2$) C, H, N, S.

2-[[2-[[(4-Methyl-5-imidazolyl)methyl]thio]ethyl]-amino]-3-hydroxypyridine Dihydrochloride (10). 2-Chloro-3-pyridinol (9.47 g, 0.073 mol) was added to a solution of NaOEt in EtOH (from Na, 1.67 g, 0.073 g-atom). Sufficient Me_2SO was added to dissolve all of the solid, and EtOH was removed in vacuo. To the resulting solution was added benzyl chloride (9.30 g, 0.073 mol) with cooling and stirring, and the reaction mixture was left to stir under reflux for 6 h. Unreacted benzyl chloride and solvent were evaporated off in vacuo on a boiling water bath, and the residue was treated with H_2O to precipitate out an oil, which was extracted with $CHCl_3$, washed with 1 N NaOH solution, and dried over anhydrous $MgSO_4$. After removal of the solvent, **19** (Y = 3-OCH_2Ph) was obtained as an oil.

The above product (11.6 g, 0.053 mol) was mixed with **14** (18.1 g, 0.11 mol) and heated at 120 °C for 9 days. The resulting mixture was chromatographed (SiO_2/$CHCl_3$) to yield **20** (Y = 3-OCH_2Ph) as a red oil. The latter product (1.85 g, 0.0052 mol) was hydrolyzed with concentrated HCl (10 mL), heating at 60 °C for 4 h. The reaction mixture was evaporated to dryness in vacuo to a green oil and dissolved in MeOH, EtOAc was added, and the mixture was left to stand for 2 days. The red crystals obtained were filtered off and recrystallized from MeOH/EtOAc to give **10** (0.170 g, 10%), mp 210–212 °C. Anal. ($C_{12}H_{16}N_4OS$·2HCl) C, H, N, S, Cl.

2-[[2-[[(4-Methyl-5-imidazolyl)methyl]thio]ethyl]-amino]nicotinic Acid (11). An intimate mixture of **18** (XH = 3-CO_2H) (1.73 g, 0.011 mol) and **14** (1.71 g, 0.010 mol) was heated at 150 °C for 6 h. The resulting cooled glass was dissolved in a little H_2O and neutralized by slow addition of 2 N NaOH. At pH 6 solid precipitated out of solution. This was filtered off and recrystallized from H_2O to afford **11** (1.04 g, 36%), which sublimed at 98 °C. Anal. ($C_{13}H_{16}N_4O_2S$) C, H, N, S.

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2-[[2-[[(4-Methyl-5-imidazolyl)methyl]thio]ethyl]-amino]isonicotinic Acid Dihydrochloride (12). Compound **19** (Y = 4-CN)[33] (14.0 g, 0.10 mol) was mixed with **14** (34.6 g, 0.20 mol) in pyridine (300 mL) and heated under reflux for 3 h. After evaporating to dryness, the mixture was chromatographed ($SiO_2/CHCl_3$) to give an oil, which solidified on trituation with petroleum ether (40–60 °C). Recrystallization from CH_2Cl_2/petroleum ether (60–80 °C) gave **20** (Y = 4-CN).

The above product (2.00 g, 0.0073 mol) was hydrolyzed by heating with concentrated HCl (20 mL) at 60 °C for 3 h. The mixture was reduced in volume to about 4 mL and allowed to stand, yielding **12** (0.610 g, 24%), mp 238–240 °C. Anal. ($C_{13}H_{16}N_3O_2S\cdot 2HCl$) C, H, N, S, Cl.

6-[[2-[[(4-Methyl-5-imidazolyl)methyl]thio]ethyl]-amino]nicotinic Acid Dihydrochloride (13). A mixture of **19** (Y = 5-$CONH_2$) (5.03 g, 0.032 mol) and **14** (14.5 g, 0.085 mol) was heated with stirring at 130 °C for 6 h. After the mixture was cooled, the residue was chromatographed (SiO_2–EtOAc/*i*-PrOH) to afford **20** (Y = 5-$CONH_2$).

The above product (6.40 g, 0.022 mol) was hydrolyzed by heating with concentrated HCl (30 mL) at 80 °C for 1.5 h and then evaporated to dryness in vacuo. The residual solid was dissolved in H_2O, basified with 10 N NaOH to pH 12, and evaporated to dryness in vacuo to remove NH_3. The remaining solid was redissolved in H_2O, treated with concentrated HCl to pH 1, and then azeotroped to dryness with EtOH. Recrystallization from *i*-PrOH (after removing insoluble inorganics) yielded **13** (1.00 g, 12%), mp >230 °C. Anal. ($C_{13}H_{16}N_3O_2S\cdot 2HCl$) C, H, N, S.

Ethyl (*N*-Methyl-*N'*-benzylamidino)phosphonate (22). Diethyl (*N*-methylthiocarbamoyl)phosphonate[34] (2.11 g, 0.010 mol) was dissolved in MeI (10 mL), and the solution was heated under reflux for 2 h and then left at room temperature for a further 24 h. Ethyl (*N,S*-dimethylthioimidoyl)phosphonate, which solidified, was recrystallized from MeCN, mp 142–147 °C.

The above product (0.400 g, 0.0020 mol) was dissolved in dry MeCN (10 mL) and treated with benzylamine (0.300 g, 0.0030 mol). After a few minutes, a solid began to form. This was collected and recrystallized from MeOH/EtOAc to give **22**, mp 224 °C dec. Anal. ($C_{11}H_{17}N_2O_3P$) C, H, N.

***N*-Methyl-4-hydroxybenzamidine (23).** Compound **15** (XH = 4-C_6H_4OH, L = OEt, R^1 = H) hydrochloride (2.00 g, 0.010 mol) was basified as described above and treated with excess $MeNH_2$/EtOH (5 mL, 33%), and the mixture was allowed to stand at room temperature for 17 days. The solid that had deposited was collected and recrystallized twice from H_2O to give **23** (0.360 g, 24%), mp 249–250 °C. Anal. ($C_8H_{10}N_2O$) C, H, N.

2-(Methylamino)pyridine-3-sulfonic Acid (24). Compound **18** (XH = 3-SO_3H) (1.00 g, 0.0052 mol) was mixed with excess $MeNH_2$/EtOH (4 mL, 33%) and heated in a sealed glass tube at 130 °C for 9 h. After cooling, the crude product was carefully removed and purified by ion exchange (IRC-50(H)). The aqueous product was azeotroped to dryness with EtOH and the resulting solid was recrystallized from MeOH to afford **24** (0.150 g, 16%), mp 259 °C. Anal. ($C_6H_8N_2O_3S$) C, H, N.

2-Amino-3-methoxypyridine (26). This was prepared by the method of Den Hertog,[3] by treating a solution of 2-bromo-3-methoxypyridine (1.10 g, 0.0058 mol) in Et_2O with KNH_2 in liquid NH_3 (from K, 1.05 g, 0.027 mol in NH_3, 80 mL). The crude product was chromatographed ($SiO_2/CHCl_3$) to give an oil, which crystallized on standing. This was purified by sublimation at 100 °C to give **26** (0.290 g, 40%): mp 79–80 °C; NMR ($CDCl_3$, 250 MHz) δ 3.84 (s, 3 H), 4.67 (s, 2 H), 6.60 (m, 1 H), 6.90 (m, 1 H), 7.65 (m, 1 H). Anal. ($C_6H_8N_2O$) C, H, N.

1-Methyl-2-aminopyridinium 3-Oxide (27). A solution of **25** (1.00 g, 0.0091 mol) in Me_2CO (80 mL) was treated with MeI (13.0 g, 0.092 mol) and heated under reflux for 4.5 h. After removal of the solvent, the resulting green oil was chromatographed (SiO_2–MeCN/NH_4OH (10:1)) to give a crude product, which was extracted into hot $CHCl_3$, filtered, and diluted with Et_2O to give crystalline **27** (0.710 g, 63%): mp >170 °C dec; NMR (Me_2SO-d_6, 250 MHz) δ 3.61 (s, 3 H), 6.06 (m, 1 H), 6.40 (m, 1 H), 6.56 (m, 1 H), 7.29 (br s, 2 H). Anal. ($C_6H_8N_2O$) C, H, N.

***N*-[2-[[(4-Methyl-5-imidazolyl)methyl]thio]ethyl]benzamidine Dihydrochloride (28).** Ethyl benzimidate hydrochloride[35] (10.8 g, 0.058 mol) was basified with K_2CO_3 (8.07 g, 0.058 mol) in H_2O and extracted into Et_2O. Treatment with **14** (5.00 g, 0.029 mol) in EtOH at room temperature for 6 days followed by concentration gave an oil, which was converted to the hydrochloride with excess HCl/EtOH. The resulting solution was concentrated to an oily solid and recrystallized from *i*-PrOH/Et_2O and then EtOH/Et_2O to give **28** (7.64 g, 75%), mp 221–222.5 °C. Anal. ($C_{14}H_{18}N_4S\cdot 2HCl$) C, H, N, S, Cl.

Physical Measurements. pK_a values were measured potentiometrically at 25 °C. Compounds of approximately 0.005 M were titrated in 0.1 M KCl against 0.1 N KOH or 0.1 N HCl.

The ultraviolet absorption spectra of **25–27** were recorded at concentrations of (5–10) × 10^{-5} M in aqueous KH_2PO_4/Na_2HPO_4 buffer (pH 7.4) at 37 °C with a Perkin-Elmer Lambda 5 spectrophotometer. Extinction coefficients, ϵ, were measured at absorption maxima and corrected for any base-line absorbance at 400 nm.

Pharmacology. H_2 receptor histamine antagonist activity was determined in the isolated guinea pig right atrium against histamine-stimulated tachycardia as described by Parsons et al.[36] 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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Registry No. **1**, 64794-70-3; **2**, 108082-64-0; **3**, 71543-51-6; **4**, 70385-39-6; **5**·HBr, 70385-43-2; **6**·2HCl, 108103-17-9; **7**·Na·HCl, 108082-65-1; **8**·2HCl, 57785-51-0; **9**, 108082-66-2; **10**·2HCl, 85608-35-1; **11**, 85608-29-3; **12**·2HCl, 108082-67-3; **13**·2HCl, 108082-68-4; **14**, 108082-69-5; **15** (XH = CO_2H, L = SH, R^1 = H), 39894-60-5; **15** (XH = SO_3H, L = SMe, R^1 = Me), 63299-68-3; **15** (XH = MeOP(O)OH, L = SMe, R^1 = Me), 73992-64-0; **15** (XH = 4-C_6H_4OH, L = OEt, R^1 = H)·HCl, 54998-28-6; **16** (Y = NHP(O)(OEt)(OCH_2Ph), L = SMe, R^1 = Me), 73992-65-1; **16** (Y = CH_2CO_2Et, L = OEt, R^1 = H), 27317-59-5; **16** (Y = 4-$C_6H_4CO_2Et$, L = OEt, R^1 = H), 57870-22-1; **16** (Y = 4-$C_6H_4CO_2Et$, L = OEt, R^1 = H)·HCl, 66631-28-5; **17** (Y = NHP(O)(OEt)-(OCH_2Ph), R^1 = Me), 73992-60-6; **17** (Y = CH_2CO_2Et, R^1 = H), 108082-70-8; **17** (Y = 4-$C_6H_4CO_2Et$, R^1 = H), 108082-71-9; **18** (XH = 3-SO_3H), 6602-56-8; **18** (XH = 3-CO_2H), 2942-59-8; **19** (Y = 3-OCH_2Ph), 108082-72-0; **19** (Y = 4-CN), 33252-30-1; **19** (Y = 5-$CONH_2$), 6271-78-9; **20** (Y = 3-OCH_2Ph), 108082-73-1; **20** (Y = 4-CN), 108082-74-2; **20** (Y = 5-$CONH_2$), 108103-18-0; **21**, 34839-70-8; **22**, 108082-75-3; **23**, 99463-01-1; **24**, 108082-76-4; **25**, 16867-03-1; **26**, 10201-71-5; **27**, 108082-77-5; **28**·2HCl, 57785-49-6; MeNCS, 556-61-6; dimethyl phosphite, 868-85-9; cimetidine, 51481-61-9; ethyl dichlorophosphate, 1498-51-7; ethyl dichlorophosphate, 1498-51-7; dimethyl [*N*-(methylthio)carbamoyl]-phosphate, 73992-63-9; benzyl ethyl chlorophosphate, 73992-66-2; *N,S*-dimethylisothiouronium iodide, 41306-45-0; 2-chloro-3-pyridinol, 6636-78-8; diethyl (*N*-methylthiocarbamoyl)-phosphonate, 70385-36-3; ethyl (*N,S*-dimethylthioimidoyl)-phosphonate, 70385-37-4.

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