

Zwitterionic Analogues of Cimetidine as H₂ Receptor Antagonists

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A series of analogues of the H₂ receptor histamine antagonist cimetidine have been synthesized in which the dipolar cyanoguanidine group has been replaced by a number of zwitterionic moieties.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 H₂ receptor histamine antagonist cimetidine, *N*-cyano-*N'*-methyl-*N''*-[2-[[4-methyl-5-imidazolyl)methyl]thio]ethyl]guanidine, have recently been described¹ 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.

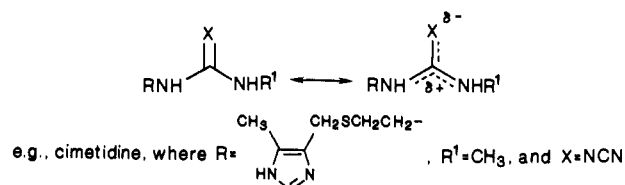
In a series of 15 such analogues, it was found that most of the variance in *in vitro* H₂ antagonist activity could be accounted for by the orientation of the dipole of the polar group rather than its moment. Originally, however, it was thought that these groups might undergo direct dipole-mediated interactions 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 H₂ antagonists and are the subject of this paper.

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, R¹ = Me), 15 (XH = 4-C₆H₄OH, L = EtO, R¹ = H), and 18 (XH = 3-SO₃H), respectively. The amidinosulfonic acid derivative 2 was prepared directly by partial oxidation of the parent thiourea 21² with H₂O₂ (Scheme V). 2-Amino-3-methoxy-pyridine (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.)

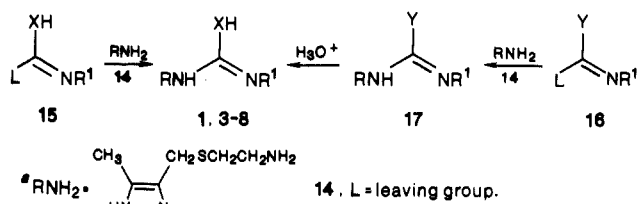
Scheme I. Neutral, Conjugated Dipoles



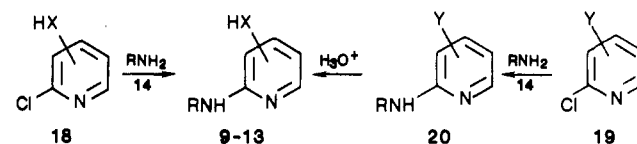
Scheme II. Zwitterionic Dipoles



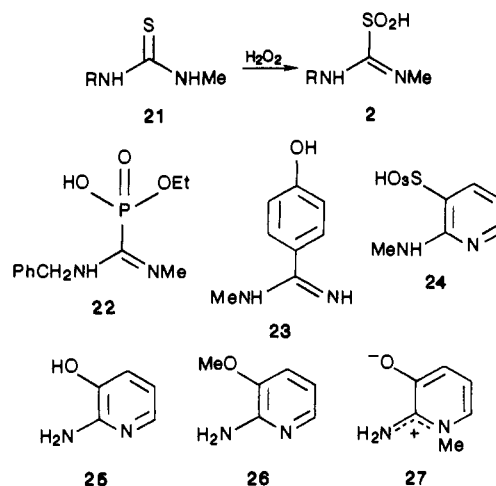
Scheme III^a



Scheme IV



Scheme V

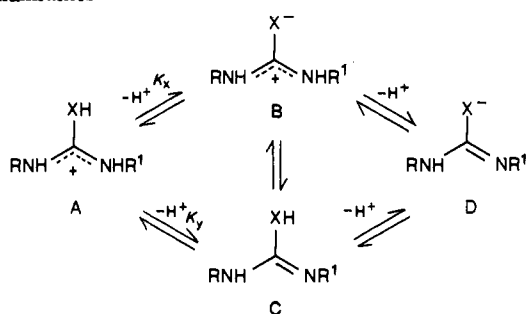


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and was used without further purification.

Results and Discussion

The H₂ receptor antagonist activities ($-\log K_B$) of 13 zwitterionic analogues of cimetidine have been measured

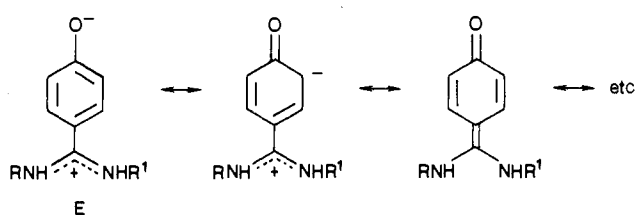
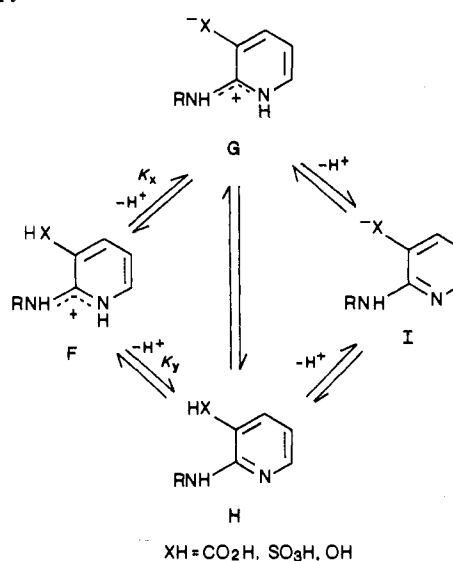
Scheme VI. Prototropic Equilibria in Substituted Formamidines^a

XH = CO₂H, SO₂H, SO₃H, CH₃OP(=O)OH, NHP(=O)(OH)OCH₂CH₃, CH₂CO₂H, *C₆H₄CO₂H, †C₆H₄OH

^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-Hydroxybenzamidinium Zwitterion**Scheme VIII.** Prototropic Equilibria in 3-Substituted 2-Aminopyridines^a

XH = CO₂H, SO₃H, 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 acid¹⁷ 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-hydroxybenzamidinium (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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Table I. Structures, Activities, and Physical Properties of H₂ Receptor Antagonists

compd	Z	H ₂ receptor antagonist activity (-log K _B)			macroscopic pK _a of Z ^c		microscopic pK _a of Z ^d		% zwitterion at pH 7.4	ψ ^e
		obsd (95% limits) ^a	corrected ^b	pred (eq 6)	pK ₁	pK ₂	pK _x	pK _y		
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 ^e	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 compilation⁵ 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 MeCO₂H at 25 °C.⁵ ^h Calculated using equation of Charton.⁸ ⁱ Crystal structure of amidinoformic acid from Glover.⁹ ^j pK_a of BuSO₂Na at 20 °C.¹⁰ ^k Using σ_m for SO₂Me. ^l Although the SO₂ plane subtends an angle of 68° with the NCN plane in the amidinosulfonic acid crystal,¹¹ ψ can be considered to be 0°. ^m pK_a of MeSO₂H at 25 °C.¹² ⁿ Crystal structure of (N,N-dimethylamidino)sulfonic acid from Walter and Holst.¹³ ^o R = PhCH₂, ethyl ester. ^p pK_a of (MeO)₂PO₂H 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-N¹-guanidinophosphonic acid at 30.5 °C.¹⁵ ^t Second pK_a of benzyl guanidinophosphonate.¹⁵ ^u Calculated by using eq of Charton,⁸ and σ₁ for PO(OMe)₂. ^v Slope 1.65 ± 0.91. ^w σ_m for CH₂CO₂H = 0.05 calculated from σ₁ and σ_p values of 0.11 and -0.07, respectively, using σ_m = (2σ(I) + σ_p)/3.¹⁶ ^x Slope 1.61 ± 0.73. ^y Calculated by using Hammett's equation.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 PhSO₃H 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 (Z) 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 PhCO₂H 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 <i>N,N</i> -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, CO₂Me, CO₂Et, and NO₂ compounds (6.82, 7.48, 4.78, 4.73, and 2.33, respectively).⁵ ^h Using pK_a values for 4-H, Me, OMe, CO₂Me, CO₂Et, 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 NO₂ 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-hydroxybenzamide²⁴ (23 D) with the value for the zwitterion calculated as described previously⁷ (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,

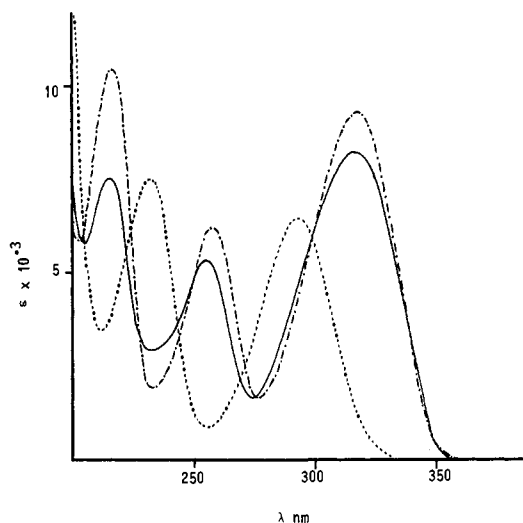
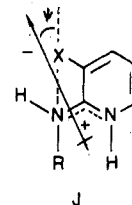


Figure 1. Ultraviolet absorption spectra of 25–27 in aqueous buffers at pH 7.4.

	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

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

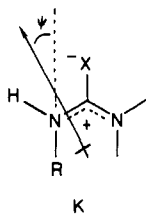
useful comparisons can be made of their $-\log K_B$ values corrected for the relative populations of these species expected under assay conditions. These “corrected” values are given in Table I. One obvious result of applying these correction factors is to largely remove the differences between the activities 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



value proposed as optimal in a series of derivatives of dipolar, conjugated systems studied previously¹ (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, H₂ antagonist activity falls progressively from 2-aminonicotinic through 2-aminoisonicotinic to 6-aminonicotinic acid derivatives, while ψ decreases from 31° to –16° to –55°

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(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., $\psi = 0^\circ$ in K).

On the basis of dipole orientation alone, the 4-amidinobenzoic acid and 4-hydroxybenzamidino 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, $\cos \theta$ (where θ is defined¹ 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, $\cos \theta$ does

$$-\log K_B(\text{corr}) = 4.59 \cos \theta + 1.29 \quad (5)$$

(±5.97) (±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

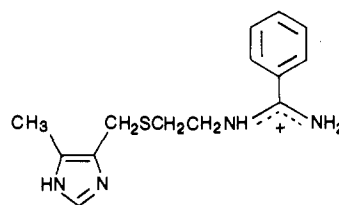
$$-\log K_B(\text{corr}) = 3.73 \cos \theta + 2.35 \quad (6)$$

(±1.67) (±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 benzamidino derivative²⁶ (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 $-\log K_B(\text{corr})$ 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 experi-



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mental observation that no antagonist activity could be detected on the atrium up to a dose of $486 \mu\text{M}$.

In a previous study¹ 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

$$-\log K_B = 9.10 \cos \theta - 2.69 \quad (7)$$

(±3.75) (±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, $\cos \theta$ (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 suggested¹ 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-(4-methyl-5-imidazolyl)methyl]thio]ethyl]amidino]formic Acid (1). Trilead tetraoxide (43.0 g, 0.063 mol) was added to a solution of 15 ($\text{XH} = \text{CO}_2\text{H}$, $\text{L} = \text{SH}$, $\text{R}^1 = \text{H}$)²⁷ (4.90 g, 0.046 mol) and 14² (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 ($\text{Me}_2\text{SO}-d_6$, 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. ($\text{C}_9\text{H}_{14}\text{N}_4\text{O}_2 \cdot 0.5(\text{C}_2\text{H}_5)_2\text{O}$) C, H, N, S.

[*N*-Methyl-*N*'-[2-[[4-(4-methyl-5-imidazolyl)methyl]thio]ethyl]amidino]sulfonic Acid (2). Thiourea 21² (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. ($\text{C}_9\text{H}_{16}\text{N}_4\text{O}_2\text{S}_2$) C, H, N, S.

[*N*-Methyl-*N*'-[2-[[4-(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 ($\text{XH} = \text{SO}_3\text{H}$, $\text{L} = \text{SMe}$, $\text{R}^1 = \text{Me}$)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 (SiO₂-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. C₉H₁₆N₄O₃S₂) 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 H₂O, and extracted with Et₂O. Chromatography of the latter (SiO₂-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, R¹ = Me) crystallized out. This product (1.56 g, 0.0080 mol) was dissolved in MeCN (50 mL) 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/Me₂CO to give 4, mp 170–171 °C. Anal. (C₁₀H₁₉N₄O₃PS) 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 Et₃N (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 CHCl₃ (80 mL) and, while cooling in an ice bath, treated first with a cold solution of *N,S*-dimethylisothiuronium iodide (23.2 g, 0.10 mol) in H₂O (25 mL) and then with vigorous stirring over 30 min a solution of NaOH (8.00 g, 0.20 mol) in H₂O (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 H₂SO₄, NaHCO₃ solution, and H₂O, and dried over Na₂SO₄. After evaporating to dryness, the mixture was chromatographed (SiO₂-EtOAc/petroleum ether (40–60 °C)) to give 16 (Y = NHP(=O)(OEt)(OCH₂Ph), L = SMe, R¹ = 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 Ag₂O (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 (SiO₂-Me₂CO/MeOH) to give 17 (Y = NHP(=O)(OEt)(OCH₂Ph), R¹ = Me) (2.30 g). This product (1.27 g, 0.0030 mol) was dissolved in Me₂CO (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. (C₁₁H₂₂N₅O₃PS·HBr) C, H, N, Br.

[*N*-[2-[[4-Methyl-5-imidazolyl)methyl]thio]ethyl]amidino]acetic Acid Dihydrochloride (6). A mixture of 16 (Y = CH₂CO₂Et, L = OEt, R¹ = 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 Et₂O. Recrystallization from MeCN afforded 17 (Y = CH₂CO₂Et, R¹ = 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 Et₂O, filtered, and washed with Et₂O to give 6 (0.500 g, 77%), mp 237–239 °C. Anal. (C₁₀H₁₆N₄O₂S·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-C₆H₄CO₂Et, L = OEt, R¹ = H) free base (prepared from the hydrochloride³⁰ (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 (SiO₂/CHCl₃) to give 17 (Y = 4-C₆H₄CO₂Et, R¹ = 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. (C₁₅H₁₇N₄O₂SNa·HCl) C, H, N, Cl.

***N*-[2-[[4-Methyl-5-imidazolyl)methyl]thio]ethyl]-4-hydroxybenzamide Dihydrochloride (8).** The hydrochloride of 15 (XH = 4-C₆H₄OH, L = OEt, R¹ = H)³¹ (4.43 g, 0.022 mol) was basified by adding to a solution of K₂CO₃ (3.46 g, 0.025 mol) in H₂O (15 mL) and shaking with Et₂O (100 mL). The Et₂O layer was dried over MgSO₄ 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/Et₂O gave 8 (1.28 g, 32%), mp 225–228 °C. Anal. (C₁₄H₁₈N₄OS·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-SO₃H)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 (SiO₂-CHCl₃/*i*-PrOH) and the product evaporated to dryness. The residue was next dissolved in a little H₂O, treated with excess concentrated NH₃ solution, and washed with several portions of CHCl₃, 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. (C₁₂H₁₆N₄O₃S₂) 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 Me₂SO 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 H₂O to precipitate out an oil, which was extracted with CHCl₃, washed with 1 N NaOH solution, and dried over anhydrous MgSO₄. After removal of the solvent, 19 (Y = 3-OCH₂Ph) 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 (SiO₂/CHCl₃) to yield 20 (Y = 3-OCH₂Ph) 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. (C₁₂H₁₆N₄OS·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-CO₂H) (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 H₂O and neutralized by slow addition of 2 N NaOH. At pH 6 solid precipitated out of solution. This was filtered off and recrystallized from H₂O to afford 11 (1.04 g, 36%), which sublimed at 98 °C. Anal. (C₁₃H₁₆N₄O₂S) 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 (SiO₂/CHCl₃) to give an oil, which solidified on trituration with petroleum ether (40–60 °C). Recrystallization from CH₂Cl₂/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. (C₁₃H₁₆N₃O₂S·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-CONH₂) (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 (SiO₂-EtOAc/*i*-PrOH) to afford 20 (Y = 5-CONH₂).

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 H₂O, basified with 10 N NaOH to pH 12, and evaporated to dryness in vacuo to remove NH₃. The remaining solid was redissolved in H₂O, 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. (C₁₃H₁₆N₃O₂S·2HCl) C, H, N, S.

Ethyl (*N*-Methyl-*N'*-benzylamidino)phosphonate (22). Diethyl (*N*-methylthiocarbamoyl)phosphonate³⁴ (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. (C₁₁H₁₇N₂O₃P) C, H, N.

N-Methyl-4-hydroxybenzamidino (23). Compound 15 (XH = 4-C₆H₄OH, L = OEt, R¹ = H) hydrochloride (2.00 g, 0.010 mol) was basified as described above and treated with excess MeNH₂/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 H₂O to give 23 (0.360 g, 24%), mp 249–250 °C. Anal. (C₈H₁₀N₂O) C, H, N.

2-(Methylamino)pyridine-3-sulfonic Acid (24). Compound 18 (XH = 3-SO₃H) (1.00 g, 0.0052 mol) was mixed with excess MeNH₂/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. (C₆H₈N₂O₃S) 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 Et₂O with KNH₂ in liquid NH₃ (from K, 1.05 g, 0.027 mol in NH₃, 80 mL). The crude product was chromatographed (SiO₂/CHCl₃) 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 (CDCl₃, 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. (C₆H₈N₂O) C, H, N.

1-Methyl-2-aminopyridinium 3-Oxide (27). A solution of 25 (1.00 g, 0.0091 mol) in Me₂CO (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 (SiO₂-MeCN/NH₄OH (10:1)) to give a crude product, which was extracted into hot CHCl₃, filtered, and diluted with Et₂O to give crystalline 27 (0.710 g, 63%); mp >170 °C dec; NMR (Me₂SO-*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. (C₆H₈N₂O) C, H, N.

N-[2-[[4-Methyl-5-imidazolyl)methyl]thio]ethyl]benzamidino Dihydrochloride (28). Ethyl benzimidate hydrochloride³⁵ (10.8 g, 0.058 mol) was basified with K₂CO₃ (8.07 g, 0.058 mol) in H₂O and extracted into Et₂O. 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/Et₂O and then EtOH/Et₂O to give 28 (7.64 g, 75%), mp 221–222.5 °C. Anal. (C₁₄H₁₈N₄S·2HCl) C, H, N, S, Cl.

Physical Measurements. p*K*_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 KH₂PO₄/Na₂HPO₄ 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. H₂ 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 $K_B = B/(X - 1)$.

Acknowledgment. We gratefully acknowledge the contributions of A. J. Hayter, M. Jones, D. S. Kay, N. E. Sore, and C. E. Williams in the synthesis of compounds, Dr. M. E. Parsons and R. C. Blakemore in providing the pharmacological test data, and Dr. G. J. Durant for useful discussions.

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 = CO₂H, L = SH, R¹ = H), 39894-60-5; 15 (XH = SO₃H, L = SMe, R¹ = Me), 63299-68-3; 15 (XH = MeOP(O)OH, L = SMe, R¹ = Me), 73992-64-0; 15 (XH = 4-C₆H₄OH, L = OEt, R¹ = H)·HCl, 54998-28-6; 16 (Y = NHP(O)(OEt)(OCH₂Ph), L = SMe, R¹ = Me), 73992-65-1; 16 (Y = CH₂CO₂Et, L = OEt, R¹ = H), 27317-59-5; 16 (Y = 4-C₆H₄CO₂Et, L = OEt, R¹ = H), 57870-22-1; 16 (Y = 4-C₆H₄CO₂Et, L = OEt, R¹ = H)·HCl, 66631-28-5; 17 (Y = NHP(O)(OEt)(OCH₂Ph), R¹ = Me), 73992-60-6; 17 (Y = CH₂CO₂Et, R¹ = H), 108082-70-8; 17 (Y = 4-C₆H₄CO₂Et, R¹ = H), 108082-71-9; 18 (XH = 3-SO₃H), 6602-56-8; 18 (XH = 3-CO₂H), 2942-59-8; 19 (Y = 3-OCH₂Ph), 108082-72-0; 19 (Y = 4-CN), 33252-30-1; 19 (Y = 5-CONH₂), 6271-78-9; 20 (Y = 3-OCH₂Ph), 108082-73-1; 20 (Y = 4-CN), 108082-74-2; 20 (Y = 5-CONH₂), 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*-dimethylisothiuronium 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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