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Original paper

Isocytosine H_2-receptor histamine antagonists II. Synthesis and evaluation of biological activity at histamine H_1- and H_2-receptors of 5-(heterocyclyl)methylisocytosines

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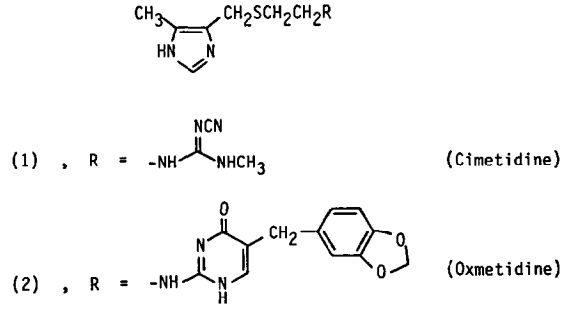
Summary — A series of 2-[2-(5-methyl-4-imidazolylmethylthio)ethylamino]-4-pyrimidones was synthesised based on oxmetidine **2**, in which the methylenedioxyphenyl group of **2** was replaced by a heterocyclic ring. Good H_2-receptor antagonist activity was retained over a range of basic and neutral heterocyclic substituents. Replacement of the 5-methyl-4-imidazolyl ring in selected compounds with 2-thiazolyl and, particularly, 3-bromo-2-pyridyl rings gave a series of compounds which have both H_1- and H_2-receptor histamine antagonist activities. Some structure—activity and structure—toxicity correlations are discussed. Compound **6d**, 2-[2-(5-methyl-4-imidazolylmethylthio)ethylamino]-5-(6-methylpyrid-3-yl)-4-pyrimidone, has the most favourable combination of properties for H_2-antagonism and has been evaluated further as an anti-secretory agent.

Résumé — **Les isocytosines comme antagonistes des récepteurs histamine-H_2 II. Synthèse et évaluation de l'activité biologique des (hétérylméthyl)-5 isocytosine sur les récepteurs histamine-H_1 et -H_2.** *On a synthétisé une série de [(méthyl-5 imidazolyl-4 méthylthio)-2 éthylamino]-2 pyrimidones-4 basées sur l'oxmétidine* **2**, *dans laquelle le groupe méthylènedioxyphényle est remplacé par un noyau hétérocyclique. Une gamme de groupes hétérocycliques basiques et neutres possèdent tous une bonne activité vis-à-vis des récepteurs histaminiques-H_2. Si l'on remplace dans certains produits le noyau méthyl-5 imidazolyl-4 par le noyau thiazolyl-2, et en particulier, bromo-3 pyridyl-2, on obtient une série de composés qui possèdent à la fois une activité antagoniste envers les récepteurs histaminiques H_1 et H_2. Certaines corrélations structure—activité et structure—toxicité sont discutées. Le produit* **6d**, *[(méthyl-5 imidazolyl-4 méthylthio)-2] ethylamino-2 (méthyl-6 pyridyl-3)-5 pyrimidone-4, possède la combinaison de propriétés la plus favorable pour l'antagonisme des récepteurs histaminiques-H_2 et a de plus été évalué comme agent anti-sécrétoire.*

H_2-receptor antagonists / combined H_1- and H_2-receptor antagonists / imidazoles / thiazoles / bromopyridines / 2-amino-pyrimidin-4-ones (isocytosines)

Introduction

The introduction of H_2-receptor histamine antagonists has revolutionised drug therapy for hypersecretory states. Cimetidine **1** (Tagamet®) was the first clinically effective agent in this class and was introduced in 1976. Recently we described [1] a series of H_2-receptor antagonists in which the cyanoguanidine group of cimetidine was replaced by a 2-amino-4-pyrimidone (isocytosine) ring. Manipulation of substituents in the pyrimidone ring led to the clinically effective agent oxmetidine **2**, containing a 5-(3,4-methylenedioxy)benzyl group.



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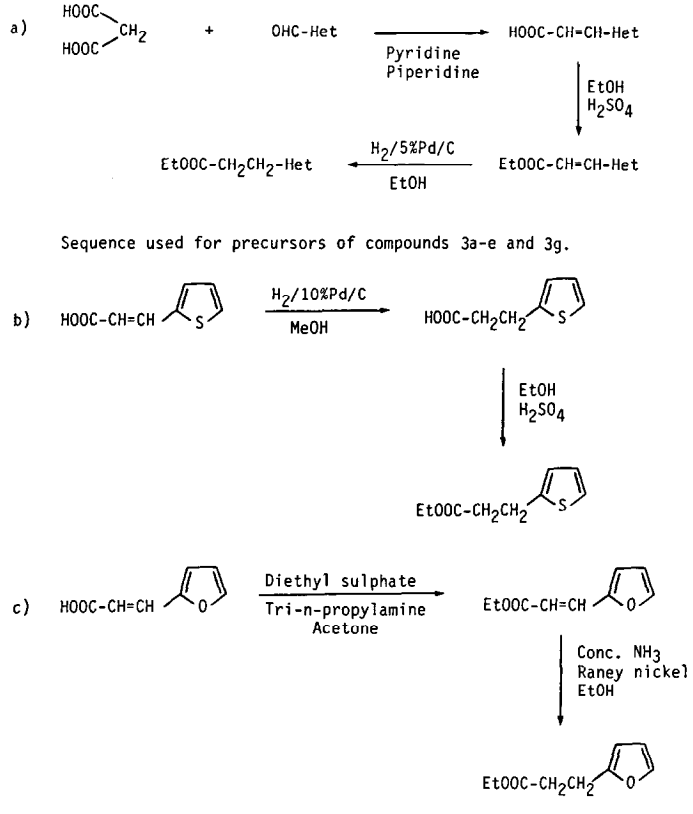
Because of the excellent H_2-antagonist activity of oxmetidine and its analogues [1] together with the possibility that the relatively high lipophilicity of oxmetidine (oxmetidine octanol—water partition P at pH 8.5 and 37.5°C = 130; cimetidine = 2.5 [2]) might lead to solubility problems in injectable drug administration, we describe in this paper the replacement of the methylenedioxyphenyl moiety with heterocyclic rings. Reduced lipophilicity and potentially increased solubility is achieved by the nature of the heterocycle itself and/or by virtue of it containing an additional basic centre for protonation at physiological pH.

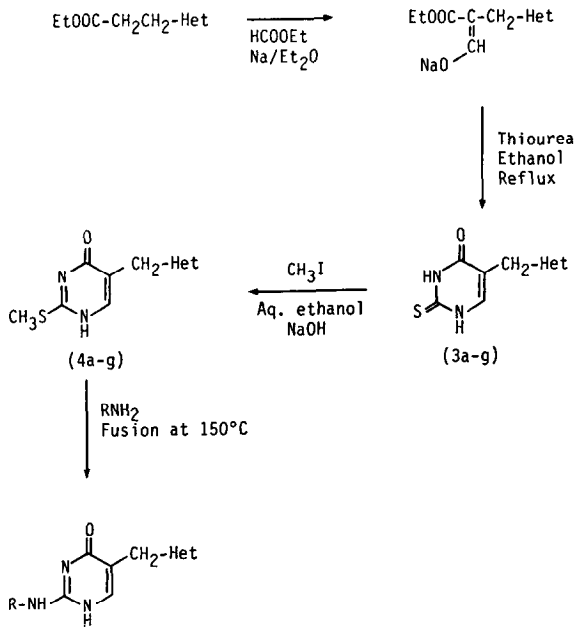
In addition, we describe the replacement of the imidazole ring in the side chain of these new molecules, with alternative heterocyclic rings as previously described in the cyanoguanidine series [3]. This leads to compounds with an interesting combination of histamine H_2- and H_1-antagonist activities.

Chemistry

The general synthetic strategy for the preparation of the desired compounds was similar to that previously described for the preparation of oxmetidine **2** [1], although some improvements were incorporated and modifications were necessary for specific compounds. The synthetic sequences for all the compounds are outlined in Schemes 1—3 and described below. Physical properties and analytical data

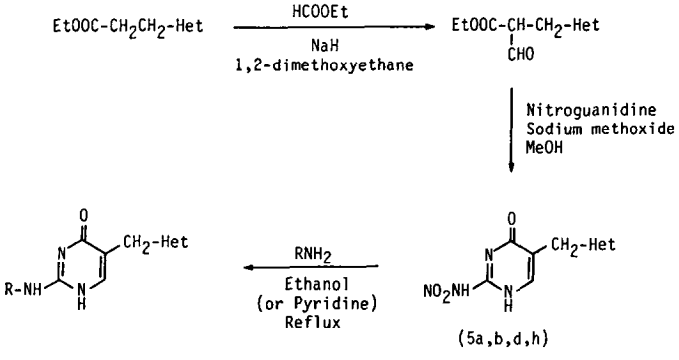


Scheme 1. Preparation of ethyl β-(heterocyclyl)propionates.



(Compounds **6a-c, 6e-g, 7d-e, 8a-d**)
Identities of Het and R as shown in Table V.

Scheme 2. Preparation of isocytosines (first route).



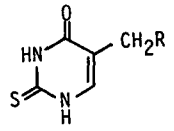
(Compounds **6d, 6h, 7a-b, 9-11**)
Identities of Het and R as shown in Table V.

Scheme 3. Preparation of isocytosines (second route).

of the new compounds prepared are outlined in Tables I—IV.

A two-carbon homologation of the heterocyclic aldehydes (Het-CHO in Scheme 1), using malonic acid gave β-substituted acrylic acids which, in the majority of cases, were esterified and reduced to the appropriate ethyl 3-(heterocyclyl) propionates (Scheme 1a). For the 2-thienyl analogue, reduction of the propionate ester was extremely slow, even at elevated temperatures, so it was preferable to carry out the reduction at the acrylic acid stage [4] and esterify the propionic acid (Scheme 1b). The acid-labile β-(2-furyl)-acrylic acid was esterified under basic conditions using the method of Stodola [5]. Attempted reduction of ethyl β-(2-furyl)acrylate with the usual 5% palladium catalyst

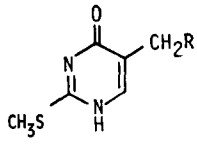
Table I. — 2-Thiouracils.



Compd. No.[a]	R	Molecular formula[b]	Crystallisation solvent	mp (°C)	Yield[c] (%)
3a	4-pyridyl	$C_{10}H_9N_3OS$	precipitated washed with EtOH	320—324 (dec.)	48
3b	3-pyridyl	$C_{10}H_9N_3OS$	MeCOOH/H_2O	271—274 (dec.)	47
3c	2-pyridyl	$C_{10}H_9N_3OS$	MeCOOH/H_2O	262—267 (dec.)	29
3d	6-methyl-3-pyridyl	$C_{11}H_{11}N_3OS$	MeCOOH/H_2O	240—241	47
3e	3-quinolinyl	$C_{14}H_{11}N_3OS$	MeCOOH/H_2O	281—286 (dec.)	31
3f	2-thienyl	$C_9H_8N_2OS_2$[d]	EtOH	213—215	38
3g	2-thiazolyl	$C_8H_7N_3OS_2$	MeCOOH	275—280 (dec.)	29

[a]Numbers correspond to compounds in Table II. Thus, for example, **3a** is the precursor of compound **4a** in Table II.
[b]Problems were encountered in obtaining satisfactory elemental analyses due to residual solvent (glacial acetic acid). Identity and purity of the compounds were checked by NMR and thin—layer chromatography and they were then methylated to give compounds of Table II which were fully analysed.
[c]Yields from substituted ethyl propionates.
[d]Anal. $C_9H_8N_2OS_2$ (C, H, N, S).

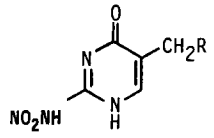
Table II. — 2-Methylthio-4-pyrimidones.



Compd. No.	R	Molecular formula[a]	Crystallisation solvent	mp (°C)	Yield[b] (%)
4a	4-pyridyl	$C_{11}H_{11}N_3OS$	EtOH/H_2O	174—175	79
4b	3-pyridyl	$C_{11}H_{11}N_3OS$	EtOH/MeCOOH	247—249	44
4c	2-pyridyl	$C_{11}H_{11}N_3OS \cdot HI$	EtOH	195—197.5	69
4d	6-methyl-3-pyridyl	$C_{12}H_{13}N_3OS$	EtOH/MeCOOH	197—198.5	59
4e	3-quinolinyl	$C_{15}H_{13}N_3OS$	EtOH	215.5—218	75
4f	2-thienyl	$C_{10}H_{10}N_2OS_2$	EtOH	170.5—171.5	89
4g	2-thiazolyl	$C_9H_9N_3OS_2$	EtOH	181—182.5	77

[a]All micro-analytical data for C, H, N and S to within ±0.4% of theory.
[b]Yields from 2-thiouracils in Table I.

Table III. — 2-Nitroamino-4-pyrimidones.



Compd. No.	R	Molecular formula[a]	Crystallisation solvent	mp (°C)	Yield[b] (%)
5a	4-pyridyl	$C_{10}H_9N_5O_3$	MeCOOH/H_2O	240—243	45
5b	3-pyridyl	$C_{10}H_9N_5O_3$	MeCOOH/H_2O	230.5—232 (dec.)	39
5d	6-methyl-3-pyridyl	$C_{11}H_{11}N_5O_3$	precipitated from alkaline solution with MeCOOH at pH = 5	229—231	33
5h	2-furyl	$C_9H_8N_4O_4$	MeCOOH	183—184	22

[a]Micro-analytical data for C, H and N to within ±0.4% of theory.
[b]Yields from substituted ethyl propionate.

Table IV. — Chemical characteristics of isocytosines in Table V.

Compd. No.	Molecular formula	Crystallisation solvent	mp (°C)	Yield[a] (%)	Route by scheme
6a	$C_{17}H_{20}N_6OS \cdot 3\ HCl$[b]	MeOH/EtOH	228—233	40	2
6b	$C_{17}H_{20}N_6OS \cdot 3\ HCl$[c]	MeOH/H_2O	237—241	69	2
6c	$C_{17}H_{20}N_6OS \cdot 3\ HCl \cdot 0.5\ H_2O$	EtOH/H_2O	207—210	36	2
6d	$C_{18}H_{22}N_6OS \cdot 3\ HCl$	MeOH/EtOH	209—212	67	3
6e	$C_{21}H_{22}N_6OS \cdot 2.8\ HCl \cdot 1.2\ H_2O$	EtOH/H_2O	184—189	68	2
6f	$C_{16}H_{19}N_5OS_2 \cdot 2\ HBr$	EtOH/MeCN	199—203	68	2
6g	$C_{15}H_{18}N_6OS_2 \cdot 3\ HCl$	EtOH/H_2O	201—205	34	2
6h	$C_{16}H_{19}N_5O_2S$	MeOH/EtOH	180—183	59	3
7a	$C_{16}H_{17}N_5OS_2 \cdot 3\ HCl$[d]$\cdot 0.5\ H_2O$	MeOH	190—195 (Sinters)	75	3
7b	$C_{16}H_{17}N_5OS_2 \cdot 3\ HCl$	EtOH/H_2O	178—180.5	76	3
7d	$C_{17}H_{19}N_5OS_2 \cdot 3\ HCl$	H_2O	187—190	57	2
7e	$C_{20}H_{19}N_5OS_2 \cdot 3\ HCl$[e]	EtOH/H_2O	202—205	50	2
8a	$C_{18}H_{18}BrN_5OS \cdot 3\ HBr$	MeOH/H_2O	258—264 (dec.)	57	2
8b	$C_{18}H_{18}BrN_5OS \cdot 3\ HBr$	MeOH/H_2O	218.5—221.5	58	2
8c	$C_{18}H_{18}BrN_5OS \cdot 3\ HBr$[f]	MeOH/H_2O	225—230 (dec.)	45	2
8d	$C_{19}H_{20}BrN_5OS \cdot 3\ HCl$	H_2O	193—196	67	2
9	$C_{18}H_{22}N_6O \cdot 3\ HCl$	H_2O	242—246	70	3
10	$C_{18}H_{22}N_6OS \cdot 3\ HCl$	EtOH/MeOH	233—236	45	3
11	$C_{16}H_{18}N_6O \cdot 3\ HCl \cdot 0.75\ H_2O$	H_2O	208.5—212	43	3

[a]Yield from 2-methylthio-4-pyrimidones (Table II, Scheme 2) or 2-nitroamino-4-pyrimidones (Table III, Scheme 3).
[b]Cl^-: theory 22.8%; found 22.0%.
[c]Cl^-: theory 22.8%; found 22.0%. N: theory 18.0%; found 17.4%.
[d]Cl^-: theory 22.3%; found 21.7%.
[e]Cl^-: theory 20.5%; found 19.8%.
[f]Br^-: theory 35.5%; found 35.0%.
All other micro-analytical data for C, H, N, S and halogen to within ±0.4% of theory.

led to appreciable ring reduction, so Raney nickel was used as catalyst in the presence of ammonium hydroxide to prevent ring reduction [6] (Scheme 1c). The ethyl 3-(heterocyclyl) propionates were then converted into the required isocytosines by one of two routes (Schemes 2 and 3).

In the first route (Scheme 2) the substituted propionate esters were subjected to a formylation reaction using ethyl formate and sodium wire in dry ether as base, to give 2-formyl-3-(heterocyclyl) propionate esters. These were reacted *in situ* with thiourea to give 2-thiouracils (Table I), which in turn were alkylated with methyl iodide, to give the 2-methylthio-4-pyrimidones (Table II). Finally, the 2-methylthio-4-pyrimidones were treated at high temperature, under fusion conditions, in a nucleophilic displacement with the primary amines to give the target isocytosines (Table IV: Route shown in Table).

In the second route (Scheme 3), the substituted propionate esters were formylated with ethyl formate in 1,2-dimethoxyethane in the presence of sodium hydride as base. (This formylation procedure is more convenient than that described in Scheme 2 above and gives more consistent yields). The resulting 2-formyl-3-(heterocyclyl) propionate esters, as their sodium enolates, were treated with nitroguanidine in methanol to give 2-nitroamino-4-pyrimidones (Table III), which were refluxed in a suitable solvent in the presence of the selected primary amine to give isocytosines (Table IV: Route shown in Table).

Although it was shown that in Scheme 2 modest yields of isocytosines could be obtained from the 2-methylthio compounds by replacing the fusion conditions with refluxing pyridine, Scheme 3 proved much more convenient [1] and during the course of this work replaced Scheme 2 as the method of choice for the preparation of isocytosine histamine antagonists.

A brief general description of typical preparations *via* Schemes 1—3 is given under Experimental protocols.

Pharmacology

Compounds were assayed *in vitro* for H_2-receptor histamine antagonist activity by measurement of the antagonism of histamine-stimulated tachycardia in the guinea pig isolated right atrial preparation [7] and activities were expressed as pA_2 values when possible. Some of the compounds were slow to reach equilibrium (see Table V) and were difficult to wash out of the tissue.

Anti-secretory activities of the compounds were obtained by measurement of the inhibition of histamine-stimulated gastric acid secretion in the lumen-perfused stomach of the anaesthetised rat after rapid intravenous injection and, for selected compounds, in the conscious Heidenhain—pouch dog by intravenous injection or oral administration [7].

Compounds were assayed *in vitro* for H_1-receptor histamine antagonist activity by measurement of the inhibition of histamine-induced contractions of the guinea pig isolated ileum [7] and activities were expressed as pA_2 values.

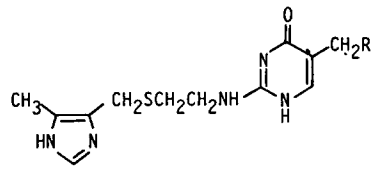
Results and Discussion

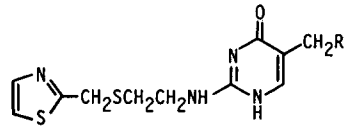
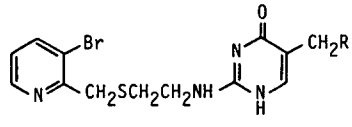
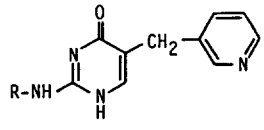
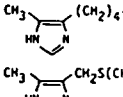
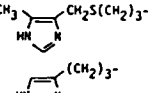
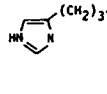
The *in vitro* and *in vivo* H_2-antagonist and *in vitro* H_1-antagonist activities of the compounds under discussion are shown in Table V. In addition, because of the high acute toxicity observed in some examples from the previously described [1] series of isocytosine H_2-antagonists, the LD_{50}'s (mouse) of selected compounds in the present series were measured (Table V).

The series of compounds containing a 2-(5-methyl-4-imidazolylmethylthio)ethylamino side chain **6a—h** are direct analogues of oxmetidine **2** and the activity profile of this compound is included in Table V for comparison. Replacement of the 3,4-methylenedioxyphenyl group of **2** by pyridyl gave the three isomers **6a—c**. The 2- and 3-pyridyl isomers are very potent H_2-receptor antagonists, with the latter **6b** being slightly more active than oxmetidine *in vivo*, but both compounds have relatively high acute toxicity. The 4-pyridyl isomer **6a** has lower H_2-antagonist activity but is less acutely toxic. This pattern is similar to that seen in the oxmetidine series, when the introduction of a substituent into the phenyl ring of the 5-benzyl group *para* to the $-CH_2-$ linkage gave compounds with reduced toxicity [1]. In this series, the pyridyl ring nitrogen of **6a** appears to be having the same effect. The introduction into **6b** of a methyl group *para* to the $-CH_2-$ linkage gave **6d**, a potent H_2-receptor antagonist with reduced toxicity. The quinolyl analogue of **6b**, compound **6e** however, is appreciably less potent at the H_2-receptor and shows slightly greater H_1-antagonist activity than other compounds in this series. Compounds **6f—h**, although potent H_2-receptor antagonists, lack a strategically-placed substituent, are thus toxic or potentially toxic and were not studied further.

Replacement of the 5-methyl-4-imidazolyl ring of cimetidine **1** with alternative nitrogen-containing heterocycles has been described [3], such compounds being the first non-imidazole H_2-receptor antagonists. When similar modifications on selected compounds were carried out in the present series, interesting combined H_1- and H_2-antagonist activities were observed. Thus the 2-thiazolyl compounds **7a, b, d, e**, have H_2-antagonist activities very similar to the corresponding 5-methyl-4-imidazolyl analogues described above, but H_1-antagonist activity is increased. In the 3-bromo-2-pyridyl series **8a—d** H_2-antagonist activity is, in most cases, marginally lower for a given 5-substituent, but H_1-antagonist activity is further increased and for some compounds (*e.g.*, **8d**) the pA_2 at the H_1-receptor (guinea pig ileum) is greater than that at the H_2-receptor (guinea pig atrium). It should be noted, however, that the H_1-receptor antagonist activity of these compounds is still substantially lower than for the classical 'anti-histamines' (*e.g.*, mepyramine pA_2 (g.p. ileum) = 9.36 [8]). Moving from 4-methyl-5-imidazolyl through 2-thiazolyl to 3-bromo-2-pyridyl rings increases the lipophilicity within a given series of compounds (estimated increase in octanol/water partition, log P, + 0.5 and + 0.6, respectively, (R.C. Mitchell, unpublished results, measured in [3])) and there is a corresponding increase in H_1-antagonist activity (*e.g.*, **6d** → **7d** → **8d**). For compounds with a given isocytosine 5-substituent, the order of acute toxicity was 5-methyl-4-

Table V. Biological activity of isocytosines.



Compound No.	R	H_2-Antagonist		H_1-Antagonist	Acute Toxicity
		pA_2 (Slope)[a] (G.P. Atrium)	ED_{50} (rat)[b] (μmol./kg)	pA_2 (Slope)[c] (G.P. Ileum)	LD_{50} (Mouse)[d] (μmol/kg-i.v.)
2 (oxmetidine)	C_6H_3,3,4-OCH_2O-	*6.9 (30',0.65)	0.09	5.44 (1.11) [2]	260
6a	4-Pyridyl	6.46 (0.85)	1.15	4.20 (0.78)	160
6b	3-Pyridyl	6.98 (1.01)	0.05	*5.23 (1.39)	24
6c	2-Pyridyl	7.13 (60', 0.94)	0.23	5.02 (1.08)	20
6d	6-Methyl-3-pyridyl	7.05 (30', 1.15)	0.09	5.49 (0.88)	120
6e	3-Quinolinyl	6.12 (30', 1.1)	0.34	5.93 (1.0)	130
6f	2-Thienyl	*6.4 (2.2)	0.1	*5.85 (1.41)	1.5
6g	2-Thiazolyl	7.38 (0.9)	0.07	5.05 (1.33)	17
6h	2-Furyl	7.08 (60', 0.9)	0.27	5.17 (1.08)	-
					
7a	4-Pyridyl	6.36 (1.0)	2.4	5.66 (0.81)	-
7b	3-Pyridyl	*7.2 (30', 0.61)	0.09	6.08 (0.85)	180
7d	6-Methyl-3-pyridyl	7.21 (30', 0.75)	0.27	6.48 (0.81)	480
7e	3-Quinolinyl	*6.3 (30', 1.7)	1.49	6.18 (0.85)	-
					
8a	4-Pyridyl	6.37 (0.92)	1.27	6.58 (0.87)	240
8b	3-Pyridyl	6.89 (30', 0.84)	0.36	7.03 (0.76)	56
8c	2-Pyridyl	*6.8 (0.66)	2.72	6.25 (1.02)	80
8d	6-Methyl-3-pyridyl	6.85 (30', 0.88)	0.18	7.15 (0.87)	120
					
9		6.62 (30', 0.75)	0.125	5.55 (1.19)	-
10		*6.1 (0.6)	1.3	*5.5 (0.65)	-
11		5.44 (30', 0.94) (Partial Agonist: 31% Histamine 47% Maximum).	4.07	5.65 (0.93)	-

[a]Antagonism of histamine-stimulated tachycardia in guinea pig right atrium *in vitro*. For some compounds, preliminary experiments showed that antagonism had not reached equilibrium within the normal 8 min period but it had been achieved within the time shown. Where indicated, this equibration time was therefore used in the determination of pA_2 values.

For those compounds marked * the pA_2 values must only be considered approximate figures, since the slope of the Schild plot was significantly different from unity.

[b]Antagonism of histamine-stimulated gastric acid secretion in the lumen-perfused stomach of the anaesthetised rat. Compounds were given by rapid intravenous injection during a near maximal plateau of acid secretion. The ED_{50} is the dose required to produce 50% inhibition and was estimated from the linear regression of log $[I/100-I]$ on log dose, where I is the percentage inhibition.

[c]Antagonism of histamine-induced contractions of the isolated guinea pig ileum *in vitro*. Equilibration was achieved within 2 min and pA_2 values determined. For those compounds marked * the pA_2 values must only be considered approximate figures, since the slope of the Schild plot was significantly different from unity.

[d]Groups of 5 or 10 mice dosed by i.v. injection *via* the tail vein using a suitable range of doses. Mortalities were recorded for up to 7 days. Medium lethal dose was estimated using the method of Litchfield and Wilcoxon [25]. All tests were completed some years ago, before such tests were dicontinued at SK&F.

imidazolyl > 3-bromo-2-pyridyl > 2-thiazolyl, as indicated by increasing LD_{50} values.

Using the 5-(3-pyridylmethyl) isocytosine moiety as a model system, further modifications to the amino side chain have been made. Thus, replacement of the sulphur atom in **6b** with a $-CH_2-$ group to give **9** reduces H_2-antagonist activity. A similar reduction in activity in other series of H_2-receptor antagonists has been rationalised [9] by consideration of the tautomerism of the imidazole ring. Extending the linking chain of **6b** by an extra $-CH_2-$ group to give the methylthiopropyl analogue **10** leads to a further reduction in H_2-antagonist activity. Replacement of the (5-methyl-4-imidazolylmethylthio)ethyl side chain of **6b** with 3-(4-imidazolyl)propyl led to a compound **11** which has the properties of a weak partial agonist. This is of interest, since the 3-(4-imidazolyl)propyl moiety is a feature of the potent, selective H_2-agonist, impromidine [10]. The H_1-antagonist activities of **9—11** are similar to that of **6b**.

Compound **6d** has the best combination of low acute toxicity and good selectivity for the H_2-receptor and was further evaluated in the Heidenhain—pouch dog by both intravenous and oral routes of administration and compared to oxmetidine **2** and cimetidine **1** (Table VI). When given

Table VI. Anti-secretory activity in the conscious Heidenhein—pouch dog measured as the % inhibition of maximally stimulated acid secretion at a given dose[a].

Compd.	i.v. dose (μmol/kg)	Inhibition (%)	Oral dose (μmol/kg)	Inhibition (%)
6d	0.5	87	5.0	41
	0.25	50		
Oxmetidine **2**	0.5	61 [2]	5.0	53 [2]
Cimetidine **1**	4.0	68 [26]	2.0	82 [26]

[a]Acid secretion stimulated by a continuous intravenous infusion of histamine at a rate of 20 μmol/h.

by the i.v. route, **6d** is somewhat more potent than oxmetidine in inhibiting histamine-stimulated gastric acid secretion and has a similar duration of action. Oral activity was somewhat lower. Compound **6d** underwent preliminary studies as a parenterally administered H_2-antagonist but was not evaluated clinically, being replaced by the more potent, longer-acting agent donetidine (**SK&F 93574**) [11].

However, the 5-(6-methyl-3-pyridylmethyl)isocytosine moiety of **6d** became the basis, on furthur modification of the group in the 2-position, for a series of clinically effective agents with differing pharmacological profiles. Thus, icotidine (**SK&F 93319**), an antagonist of histamine at both H_1- and H_2-receptors [12], temelastine (**SK&F 93944**), a potent, selective, non-sedative H_1-antagonist [13] and lupitidine (**SK&F 93479**), a potent, selective, long-acting H_2-antagonist [14], all contain this isocytosine group and will be the focus of future medicinal chemistry publications.

Experimental protocols

Chemistry

All new compounds quoted in the Tables were fully characterized spectroscopically. NMR spectra were recorded on a Jeol PFT 100P or a Varian AC60 spectrometer using $(CH_3)_4Si$ for reference. Infra-red spectra were recorded on a Perkin—Elmer 577 or a Perkin—Elmer 580B spectrophotometer and samples were presented as a nujol mull or a KBr disc.

Thin—layer chromatograms (TLC) were run on pre-coated silica gel 60 F_{254} plates with ethyl acetate:methanol:880 NH_3 (5:1:1), as the mobile phase. Micro-analytical data are within ± 0.4% of theoretical values unless quoted otherwise.

Melting points were recorded in open capillaries on an electrothermal apparatus and are uncorrected.

Starting materials used in Scheme 1

The aldehydes used as starting materials in Scheme 1 were all obtained commercially except 6-methylnicotinaldehyde and 2-thiazolealdehyde which were prepared by published procedures from commercially available 2-methyl-5-vinylpyridine [15] and from 2-hydroxymethylthiazole [16], respectively. 2-Hydroxymethylthiazole was prepared from commercially available 2-bromothiazole [16].

Primary amines

The side chain primary amines used in the final stage of Schemes 2 and 3 to prepare the isocytosines in Table IV were prepared according to literature procedures as indicated below: 4-[[(2-aminoethyl)thio]-methyl]-5-methylimidazole [17]; 2-[[(2-aminoethyl)thio]methyl]thiazole [10]; 2-[[(2-aminoethyl)thio]methyl]-3-bromopyridine [3]; 4-(3-aminopropyl)imidazole [18]; 4-(4-aminobutyl)-5-methylimidazole [17]; 4-[[(3-aminopropyl)thio]methyl]-5-methylimidazole [3].

Procedures for the preparation of ethyl 3-(heterocyclyl) propionates [19]

β-(Heterocyclyl) acrylic acids

The appropriate aldehydes were converted to β-substituted acrylic acids by the general method of Marvel *et al.* [20], using malonic acid in pyridine containing a small quantity of piperidine (yields 70—90%).

Ethyl 3-(heterocyclyl) propionates

(Where heterocyclic ring is 2,3 or 4-pyridyl, 6-methyl-3-pyridyl, 3-quinolinyl and 2-thiazolyl).

The β-(heterocyclyl) acrylic acids were esterified in ethanol in the presence of concentrated sulphuric acid [21] to give ethyl β-(heteroethyl 3-(heterocyclyl) propionates. The reduction step could be accelerated by warming the reaction mixture to ~ 45°C and this was partiethyl 3-(heterocyclyl) propionates. The reduction step could be accelerated by warming the reaction mixture to ~ 45°C and this was particularly useful in the case of the 2-thiazolyl analogue when reduction at room temperature was very slow.

Ethyl 3-(2-thienyl) propionate

β-(2-Thienyl) acrylic acid was reduced in methanol (H_2/10% Pd/C/50°C/50 psi) to give 3-(2-thienyl) propionic acid in 84% yield. (mp: 49—50°C from ether/40—60 petroleum ether; literature mp: 48—49°C [4]). 3-(2-Thienyl) propionic acid was esterified in the usual way with ethanol in concentrated sulphuric acid to give ethyl 3-(2-thienyl) propionate in 74% yield.

Ethyl 3-(2-furyl) propionate [6]

To a solution of β-(2-furyl) acrylic acid (20 g, 0.144 mol) in acetone (200 ml) was added, dropwise and simultaneously, diethyl sulphate (22.2 g, 0.144 mol) and tri-*n*-propylamine (21.5 g, 0.150 mol). The reaction mixture was then heated at reflux temperature for 2 h, cooled, poured onto ice (300 g) and extracted with diethyl ether (4 × 100 ml). The ether extracts were washed (aq. K_2CO_3 and then H_2O), dried ($MgSO_4$) and evaporated to give ethyl β-(2-furyl) acrylate (24 g, ~ 100% yield) as a brown oil.

A solution of ethyl β-(2-furyl) acrylate in ethanol and conc. NH_4OH was reduced by the method described in [6] (H_2/Raney nickel) to give ethyl 3-(2-furyl) propionate in 80% yield.

All intermediates in this section were checked for purity/identity by TLC and NMR and/or IR.

Isocytosines [19] [23] (Table IV)

2-Thiouracils [19] (Table I)
The ethyl 3-(heterocyclyl) propionates (1 eq) and ethyl formate (1 eq) were added over a period of 6 h to a stirred mixture of sodium wire (1 eq) in dry ether (60 ml/0.1 mol of ester) cooled in an ice—salt bath. The mixture was stirred for 18 h at room temperature and evaporated to dryness to give the ethyl 2-formyl-3-(heterocyclyl) propionates as their sodium enolates. The residue was refluxed for 7 h with thiourea (1 eq based on starting ester) and ethanol (70 ml/0.1 mol of thiourea). The mixture was evaporated to dryness and the residue was dissolved in water. Acetic acid was added until the mixture attained pH = 4. The white precipitate was collected by filtration, washed well with water and crystallised from a suitable solvent (see Table I).

2-Methylthio-4-pyrimidones [19] (Table II)
A solution of substituted 2-thiouracil (1 eq), methyl iodide (1 eq) and sodium hydroxide (1 eq) in water (100 ml/0.1 mol of 2-thiouracil) and ethanol (200 ml/0.1 mol of 2-thiouracil) was stirred at 60°C. A white solid began to precipitate almost immediately. Stirring was continued for 30 min and the mixture allowed to cool. The solid was collected, washed well with water, dried and crystallised from an appropriate solvent (see Table II).

*Isocytosines (compounds **6a—c, 6e—g, 7d—e, 8a—d**) Scheme 2*
An intimate mixture of substituted 2-methylthio-4-pyrimidone (1 eq) and primary amine base (1 eq, see Table IV) was heated at 145—150°C for 4—5 h. After cooling the reaction mixture was triturated with water to give the required isocytosine as the free base.

This was converted into a suitable crystalline salt by *either*: 1) dissolution in ethanolic hydrogen chloride, evaporation and crystallisation, *or* 2) dissolution in a suitable solvent (methanol or ethanol), treatment with 2 N HBr, evaporation to dryness and crystallisation.

2-Nitroamino-4-pyrimidones [23, 24] (Table III)
To a stirring suspension of sodium hydride (50% in oil, 1.25 eq) in 1,2-dimethoxyethane (25 ml/0.1 mol of NaH) were added dropwise at 0°C over a 2h period the ethyl β-(heterocyclyl) propionate (1 eq) and ethyl formate (1.5 eq). Frothing occurred and the mixture was allowed to stand at room temperature for 20 h, poured onto ice and the resulting solution extracted with ether (× 3). The aqueous solution was acidified to pH = 6 with 2 N H_2SO_4 to precipitate the ethyl 2-formyl-3-(heterocyclyl) propionate as a white solid which was collected, washed with water, dried and used immediately without further purification (yields 50—70%).

Nitroguanidine (1 eq) was added to sodium methoxide (from 1.1 eq of sodium) in methanol (100 ml/0.1 mol of nitroguanidine) and the mixture was heated under reflux for 45 min. The ethyl 2-formyl-3-(heterocyclyl) propionate (1 eq) was added over 1 h, the mixture heated under reflux for 18 h and then evaporated to dryness. The residue was dissolved in water and the solution was extracted with chloroform. The residual aqueous phase was adjusted to pH = 5 with glacial acetic acid when the title compounds precipitated as white solids and were crystallised, if necessary, from a suitable solvent (see Table III).

*Isocytosines (compounds **6d, 6h, 7a—b, 9—11**) Scheme 3*
A mixture of substituted 2-nitroamino-4-pyrimidone (1 eq) and primary amine base (1 eq, see Table IV) was dissolved in absolute ethanol (200 ml/0.1 mol) and heated under reflux for 24 h. The ethanol was evaporated and the residue washed with water. Alternatively, refluxing dry pyridine (200 ml/0.1 mol) could be used as solvent (reaction time 12 h) when greater care was needed at the water-washing stage to remove all residual pyridine.

Purification of the isocytosines was achieved by crystallisation of the base (*e.g.*, compound **6h**) or conversion to a suitable salt as described previously.

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