Potential Histamine H_2-Receptor Antagonists. 1. Aminoethylimidazo[1,2-*a*]pyridines and -imidazo[1,5-*a*]pyridines

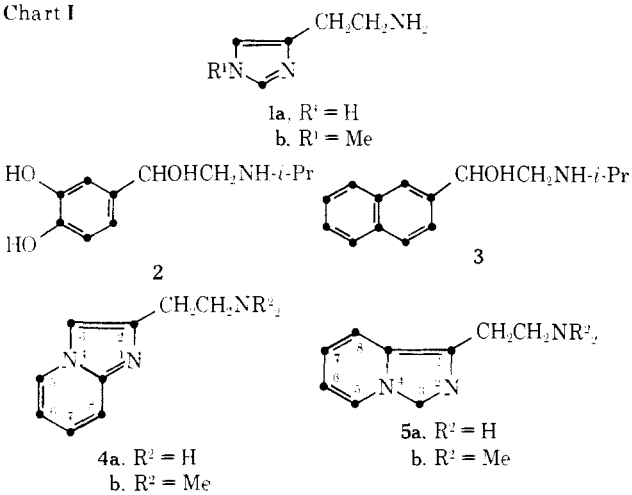
Graham J. Durant,* John M. Loynes, and Stanley H. B. Wright

The Research Institute, Smith Kline and French Laboratories, Ltd., Welwyn Garden City, Hertfordshire, England. *Received June 6, 1973*

Based on an analogy with adrenergic β-receptor stimulants and their antagonists, several aminoethylimidazo[1,2-a]pyridines and -imidazo[1,5-a]pyridines including their tetrahydro derivatives were synthesized as potential histamine H_2-receptor antagonists. Neither agonist nor antagonist activity at H_2 receptors was detected. 2-(2-Aminoethyl)imidazo[1,2-a]pyridines were, however, found to be moderately active H_1-receptor agonists.

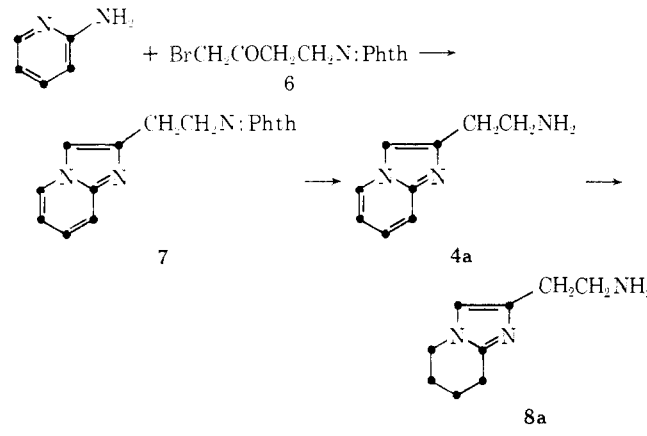
The receptors mediating certain physiological actions of histamine (1a) have been classified into two distinct types, designated H_1 and H_2.[1,2] The effect of histamine at its H_1 receptor may be blocked specifically by conventional antihistaminic drugs, such as mepyramine.[1] Other effects of histamine, such as the stimulation of gastric acid secretion, are not blocked. Work aimed at discovering an antagonist of these non-H_1 effects was started in these laboratories in 1964 and led to the eventual synthesis and characterization of the H_2-receptor antagonist, burimamide.[2] Many different approaches to the problem were explored in our early investigations, one of which was based on a simple analogy with adrenergic β-receptor stimulants and their antagonists. We noted that structural modification of isoproterenol (2), a typical adrenergic β-receptor agonist, had furnished pronethalol (3), its antagonist.[3] These two compounds are structurally related by their hydroxyethylamine side chains but differentiated by their rings. It seemed to us that two features had been incorporated into this structural modification: acidic hydrogen atoms which appeared to be essential for agonist activity[4] had been removed and a fused benzene ring had been added. The latter extends the planar region of the molecule, enhances lipid solubility, and probably contributes substantially to receptor binding ability (affinity[5]). The strict analogy for modifying histamine to produce its antagonist required us therefore to alter the ring but leave intact the ethylamine side chain. We had already found that the simple removal of the ring-mobile proton as in 3-methylhistamine (1b) virtually eliminated agonist properties (subsequently reported[2]) without providing an antagonist. To complete the catecholamine analogy we sought therefore to extend the planar imidazole nucleus of histamine by a benzene ring, fused either at imidazole positions 1 and 2 or 1 and 5 to give the bicyclic compounds 2-(2-aminoethyl)imidazo[1,2-a]pyridine (**4a**) and 1-(2-aminoethyl)imidazo[1,5-a]pyridine (**5a**). In this paper we describe the synthesis of these and related compounds and the results of tests for antagonism at H_2 receptors and for agonism at both H_2 and H_1 receptors (Chart I).

Chart I



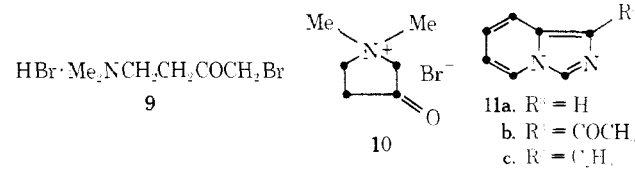
Imidazo[1,2-*a*]pyridines. The classical route to imidazo[1,2-a]pyridines which is the Tchitchibabin synthesis from 2-aminopyridine and α-halo ketones[6] was used to give **4a** (Scheme I). The bromo ketone **6**[7] condensed smoothly with 2-aminopyridine in DMF containing

Scheme I



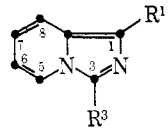
N:Phth = phthalimido

$NaHCO_3$ to form the imidazo[1,2-a]pyridine (**7**). Acid hydrolysis then yielded **4a** as the dihydrochloride. The related tertiary amine **4b** was prepared from 1-bromo-4-dimethylaminobutan-2-one hydrobromide (**9**)[8] and 2-aminopyridine but in low yield because of the competing cyclization of **9** to 1-methylpyrrolidin-3-one methobromide (**10**). Catalytic hydrogenation, preferentially in the pyridine ring,[6] gave 2-(2-aminoethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine (**8a**) from the amine hydrochloride **4a** and PtO_2 in an acidic medium.



Imidazo[1,5-*a*]pyridines. Synthesis of the histamine analog **5a** containing the little known imidazo[1,5-a]pyridine ring presented a more serious problem. Direct cyclization methods allied to the original ring synthesis of Bower and Ramage[9] were unattractive, as inaccessible picolylamine derivatives were required. More promising for the synthesis of **5** was the discovery by Bower and Ramage[9] that electrophilic substitution of imidazo[1,5-a]pyridine (**11a**) took place readily and moreover that Friedel-Crafts acylation appeared to give the 1-acetyl derivative **11b**. Acyl seemed a suitable group for conversion to **5a** but first the structure of the Friedel-Crafts acetylation product had to be confirmed. This was done by Wolff-

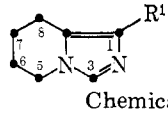
Table I. Proton Chemical Shift Positions of Some Imidazo[1,5-*a*]pyridines



Compd	Substituents R¹	Substituents R³	Chemical shift[a,b] (δ), ppm 1-H	3-H	5-H	6,7-H	8-H	Solvent
11a[d]	H	H	7.45 (s)	8.10 (s)	7.90 (m)	6.35–6.81 (m)	7.35 (m)	$CDCl_3$
11a[e]	H	H	7.27	7.97	7.88	6.41, 6.58	7.34	CCl_4
11c[d]	CH_2CH_3	H		8.07 (s)	7.82 (m)	6.33–6.77 (m)	7.37 (m)	$CDCl_3$
5a	$CH_2CH_2NH_2$	H		8.18 (s)	7.98 (m)	6.41–7.00 (m)	7.43 (m)	D_2O
18[e]	$CH(OH)CH_2NH_2$·picrate	H		8.35 (s)	8.25 (m)	6.51–6.93 (m)	7.6 (m)	$(CD_3)_2SO$
20	H	CH_2CH_2N:Phth	7.33 (s)		7.90 (m)	6.51–6.83 (m)	7.40 (m)	$CDCl_3$
		Imidazo[1,5-*a*]pyridinium Salts						
11a[f]	H	H	7.94 (s)	9.32 (s)	8.44 (m)	7.12–7.44 (m)	7.81 (m)	D_2O
5b[g]	$CH_2CH_2NMe_2$·HCl	H		9.33 (s)	8.43 (m)	7.08–7.42 (m)	7.89 (m)	D_2O
21[g]	H	$CH_2CH_2NH_2$·HCl	8.01 (s)		8.44 (m)	7.18–7.50 (m)	7.92 (m)	D_2O

[a]Multiplicity in parentheses: singlet (s); doublet (d); multiplet (m). [b]Aliphatic protons not included. [c]Data of W. W. Paudler and J. E. Kuder, *J. Heterocycl. Chem.*, **3**, 33 (1966). [d]Reference 9. [e]Additional peak at δ 8.58 (s) assigned to picric acid protons. [f]Perchlorate. [g]Dihydrochloride.

Table II. Proton Chemical Shift Positions of 5,6,7,8-Tetrahydroimidazo[1,5-*a*]pyridines[a]



Compd	R¹ substituents	Chemical shift[a,b] (δ), ppm 1-H	3-H	Solvent
19c[c]	H	7.36 (d)	8.97 (s)	$(CD_3)_2SO$
19a[d]	$CH_2CH_2NH_2$·HCl		8.57 (s)	D_2O
19d[d]	$CH_2CH_2NMe_2$·HCl		8.55 (s)	D_2O

[a,b]See footnotes in Table I. [c]Picrate; additional peak at δ 8.63 (s) assigned to picric acid protons. [d]Dihydrochloride.

Kishner reduction to the ethyl derivative **11c** in which the position of substitution was shown clearly by nmr (Table I). The Friedel-Crafts synthesis using chloroacetyl chloride then gave the chloro ketone **12** (Scheme II). A subsequent Gabriel reaction afforded the amino ketone **14a** *via* the phthalimido derivative **13**. Final conversion into **5a** required reduction of the carbonyl group to methylene but both Clemmensen and Wolff-Kishner reduction methods resulted in extensive decomposition. Because of the lability of the amino ketone **14** a much milder technique was sought. Since 1-acyl derivatives of imidazo[1,5-*a*]pyridine are "electron-rich" carbonyl compounds (vinylogous amides), they should be susceptible to electrophilic attack by diborane and reduced to the alkane analogously to acylpyrroles and -indoles.[10,11] Reduction of either the amino ketone **14a** or the azido ketone **17** with diborane generated internally from BF_3–$NaBH_4$ completed the synthesis of **5a**. Yields were low, due mainly to difficulties of isolation from boron-containing complexes. However, by the same method **5b** was obtained from the dimethylamino ketone **14b** in excellent yield. Reduction of **14b** with $NaBH_4$ yielded the unstable ethanolamine **18** characterized as a monopicrate. Hydrogenation of **5a,b** with Pd/C afforded the 5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridines **19a,b**. The imidazo[1,5-*a*]pyridine **21** analogous to "isohistamine" (**23**)[12] was prepared from 2-picolylamine (Scheme III). Acid hydrolysis of the phthalimido derivative **20** gave low yields of **21** presumably because of extensive ring cleavage, 2-picolylamine hydrochloride being isolated from the reaction.

The position of the aminoethyl substituent in the imidazo[1,5-*a*]pyridines was confirmed by the chemical shifts of the ring protons in the nmr spectra of the bases and salts (Table I). Additional evidence was obtained from the chemical shifts of the ring protons in the 5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridines **19a,b** when compared with the parent heterocycle **19c** (Table II).

Biological Results and Discussion

The compounds were investigated for interactions with H_2 receptors in anesthetized rats, firstly as agonists by their ability to stimulate gastric acid secretion and then as antagonists by their ability to inhibit histamine-stimulated gastric secretion.[2] Neither **4a** and **5a**, the imidazopyridines directly analogous to histamine, nor any of the other compounds tested (Tables III and IV) was a stimulant.

Scheme II

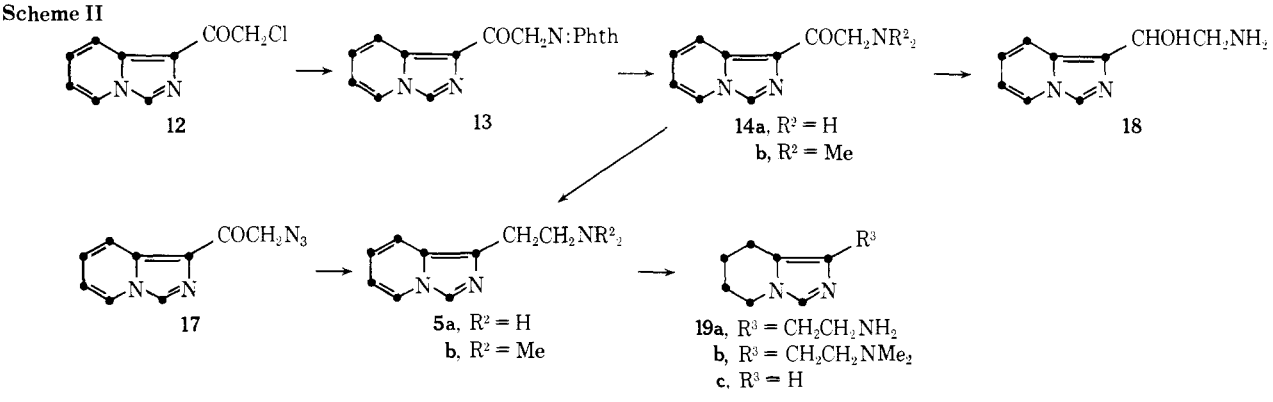
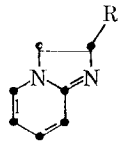
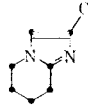


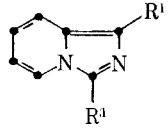
Table III. Imidazo[1,2-*a*]pyridines

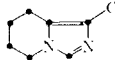
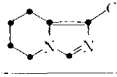


No.	R	Salt	Yield, %	Mp, °C	Crystn solvent	Molecular formula[a]	H_2-receptor antagonism Test I[b]	H_2-receptor antagonism Test II[c]	Agonist activity relative to histamine (=100) H_2 receptor[d]	Agonist activity relative to histamine (=100) H_1 receptor[e]
4a	$CH_2CH_2NH_2$	2HCl	55	285–290	EtOH	$C_9H_{11}N_3 \cdot 2HCl$	−ve (128)	−ve (25)	wk (128)	~11[f]
4b	$CH_2CH_2NMe_2$	2HBr	3	262–264	MeOH	$C_{11}H_{15}N_3 \cdot 2HBr$		−ve (12.5)	−ve (128)	
8a		$2HNO_3$	63	180–182.5	EtOH	$C_9H_{15}N_3 \cdot 2HNO_3$		−ve (12.5)	wk (256)	~3[g]

[a]All compounds were analyzed for C, H, and N and **4a** also for Cl. The results obtained were within 0.4% of the theoretical values. [b]Tested for inhibition of gastric acid secretion in anesthetized rats stimulated by continuous iv infusion of histamine:[2] −ve indicates no detectable inhibition of histamine response up to maximum dose administered (μmol/kg iv in parentheses). [c]Tested for inhibition of gastric acid secretion in anesthetized rats, stimulated with single iv doses of histamine, by intravenous infusion of compound: −ve indicates no detectable inhibition of histamine response up to maximum dose administered (μmol/kg/min in parentheses) for a minimum period of 60 min. [d]Tested for stimulation of gastric acid secretion in anesthetized rats: −ve indicates no detectable activity up to maximum dose administered (μmol/kg iv in parentheses); wk indicates that response produced by maximum dose (μmol/kg iv in parentheses) is weaker than that produced by 0.5 μmol/kg iv of histamine, *i.e.*, activity <1% histamine. [e]Tested for stimulation of contraction of isolated guinea-pig ileum in the presence of atropine.[2] [f]Approximate value from average of five cumulative doses against histamine (maximum response of compound 82% of histamine maximum; 50% contraction produced at 1.9 nmol/ml; *cf.* histamine produced 50% contraction at 0.21 nmol/ml). [g]Approximate value from average of four cumulative doses against histamine (maximum response of compound 61% of histamine maximum; 50% contraction produced at 6.8 nmol/ml, *cf.* histamine 50% contraction at 0.21 nmol/ml).

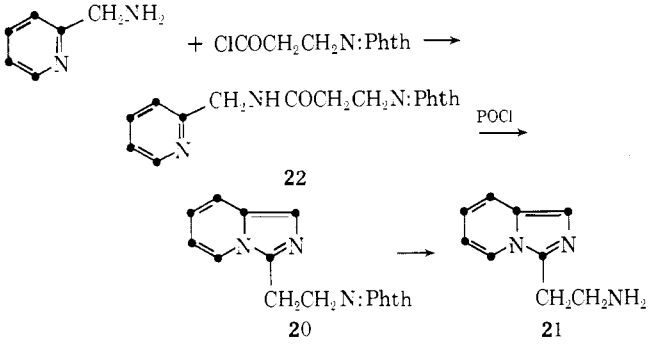
Table IV. Imidazo[1,5-*a*]pyridines



No.	R^1	R^3	Salt	Yield, %	Mp, °C	Crystn solvent	Molecular formula[a]	H_2-receptor antagonism Test I[b]	H_2-receptor antagonism Test II[c]	Agonist activity H_2 receptor[d]	Agonist activity H_1 receptor[e,f]
5a	$CH_2CH_2NH_2$	H	HCl	*g*	215–218	EtOH Et_2O	$C_9H_{11}N_3 \cdot HCl$	−ve (256)		wk (64)	−ve (10)
5b	$CH_2CH_2NMe_2$	H	2HCl	77	243–248	MeOH–Et_2O	$C_{11}H_{15}N_3 \cdot 2HCl$	−ve (200)		−ve (128)	
14a	$COCH_2NH_2$	H	HCl	18	>350 dec	*i*-PrOH–MeOH–EtOAc	$C_9H_9N_3O \cdot HCl$	−ve (256)		wk (128)	−ve (0.9)
14b	$COCH_2NMe_2$	H		51	95–97	*i*-PrOH–H_2O	$C_{11}H_{13}N_3O$	−ve (256)		wk (128)	−ve (0.8)
18	$CHOHCH_2NH_2$	H	2HCl	51	Dec	MeOH–Et_2O	$C_9H_{11}N_3O \cdot 2HCl$	−ve (100)		wk (128)	−ve (6.4)
21	H	$CH_2CH_2NH_2$	2HCl	9	262–266	EtOH–H_2O	$C_9H_{11}N_3 \cdot 2HCl$		−ve (6.25)	wk (64)	−ve (2.1)
19a			2HCl	67	238–243	EtOH	$C_9H_{13}N_3 \cdot 2HCl$	−ve (256)		−ve (128)	−ve (0.8)
19b			2HCl	90	229–233	*i*-PrOH–Et_2O	$C_{11}H_{19}N_3 \cdot 2HCl$	−ve (512)	−ve (12.5)	−ve (64)	−ve (0.4)

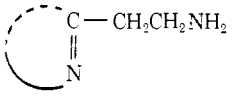
[a]See footnote in Table III. Compounds **5a,b**, **14a**, and **19a** were also analyzed for Cl. [b–e]See footnotes in Table III. [f]−ve indicates no significant activity up to maximum concentration tested (mmol/ml in parentheses), *i.e.*, activity <0.01% histamine. [g]See Experimental Section.

Scheme III

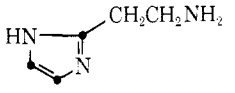


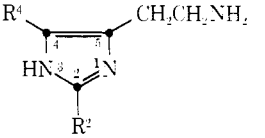
This was in accord with the expectation that removal of the mobile ring proton would eliminate agonist properties. However, neither 4a nor **5a** was an antagonist. Thus the relationship between isoproterenol and its antagonist, pronethalol, which led us to fuse a benzenoid ring on to histamine, does not appear to hold for histamine H_2-receptor activity. We extended our search for potential antagonists to tertiary amines by analogy with the conventional antihistamines (H_1-receptor antagonists) where it is well known that a high level of activity is associated with the tertiary amine structure. However, neither of the dimethylamino derivatives **4b** and **5b** was active as an H_2-receptor antagonist. Imidazo[1,5-*a*]pyridine has a second position "ortho" to the basic nitrogen atom. Since the position of substitution in a heterocyclic ring may be critical for activity at histamine receptors (*e.g.*, the H_1-receptor agonist activity of aminoethylthiazoles is much greater for the 2 than for the 4 isomer[13]), 3-(2-aminoethyl)imidazo[1,5-*a*]pyridine (**21**), isomeric with **5a** and an analog of "isohistamine" (**23**),[12] was investigated. However, it, too, was found to be devoid of H_2-receptor antagonist activity. The partially saturated compounds **8a** and **19a,b**, the amino ketones **14a,b**, and the ethanolamine **18** also showed no signs of H_2-receptor antagonism.

Compounds were tested as H_1-receptor agonists by their ability to stimulate the contraction of an isolated piece of guinea-pig terminal ileum suspended in oxygenated Tyrode solution at 37° in the presence of atropine. Whereas no activity could be found in any of the imidazo[1,5-*a*]pyridines (Table IV), appreciable agonist activity was detected in the aminoethylimidazo[1,2-*a*]pyridine (**4a**, *ca.* 11% histamine) and its tetrahydro derivative **8a** (*ca.* 3%).† Subsequent antagonism by mepyramine confirmed that the agonist action of 4a and **8a** results from an H_1-receptor response. The active imidazo[1,2-*a*]pyridines satisfy the purported minimum requirements for H_1-receptor histamine-like activity[14-16] in that they derive from a heterocyclic ring containing the structural unit



but these appear to be the first bicyclic analogs of histamine with reported H_1-receptor agonist activity.[13,16] The difference in activity between the aminoethylimidazo[1,2-*a*]pyridines (**4a** and **8a**, formally 2,3-disubstituted derivatives of histamine) and -imidazo[1,5-*a*]pyridines (*e.g.*, **5a** and **19a**, formally 3,4-disubstituted derivatives of histamine) is of particular interest when compared with the relative activities of 2- and 4-methylhistamine.‡ 4-Methylhistamine (**24b**) is considerably weaker than 2-





24a, $R^2 = CH_3$; $R^1 = H$
b, $R^2 = H$; $R^1 = CH_3$

methylhistamine (**24a**) as an H_1-receptor agonist (activities are respectively 0.2 and 16.5% of histamine[2]) and it has been proposed that this could be a consequence of the restricted rotation and influence on ring orientation caused by interactions between the protons of the 4-methyl group and the methylenic protons α to the side-chain amino group.[18] It is of interest therefore to find from inspection of CPK space-filling molecular models of **5a** and **19a** that there appears to be a steric interaction between the 8 proton of the imidazo[1,5-*a*]pyridine ring and the methylenic protons α to the side-chain amino group which would similarly restrict rotation and influence ring orientation. The activity of the imidazo[1,2-*a*]pyridines, formally 2,3-disubstituted histamines,‡ is all the more intriguing if one recalls that 3-methylhistamine (**1b**) is extremely weak as an H_1-receptor agonist.[2]

Experimental Section

Melting points were determined on an "Electrothermal" electrically heated apparatus using a thermometer corrected for stem exposure. Nmr spectra were recorded on a Varian A-60 instrument (Me_4Si). Uv spectra were recorded on a Beckman DK2 instrument. Microanalyses for elements indicated were within 0.4% of the theoretical values. Percentage yields, other than indicated, are recorded in Tables III and IV.

2-(2-Phthalimidoethyl)imidazo[1,2-*a*]pyridine (7). 1-Bromo-4-phthalimidobutan-2-one[7] (23.6 g, 0.08 mol) was added to a solution of 2-aminopyridine (7.6 g, 0.08 mol) and $NaHCO_3$ (6.8 g) in DMF (100 ml) and the mixture was heated at 100° for 1 hr, cooled, and added to H_2O. The solid was crystallized from EtOH: yield 13.4 g (64%); mp 181–181.5°. *Anal.* ($C_{17}H_{13}N_3O_2$) C, H, N.

2-(2-Aminoethyl)imidazo[1,2-*a*]pyridine Dihydrochloride (4a). A solution of 7 (15 g) in 6 *N* HCl (400 ml) was heated under reflux for 3 hr, cooled, filtered, and concentrated, and the residue was crystallized from EtOH: yield 11.6 g; uv (EtOH) λ_{max} 275 nm (log ϵ 3.85).

2-(2-Aminoethyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine Dinitrate (8a). A solution of 4a (2.2 g, 0.01 mol) in EtOH (150 ml) containing concentrated HCl (5 ml) was hydrogenated at room temperature over PtO_2 until uptake was complete (550 ml of H_2). Following filtration and concentration there was obtained a hygroscopic hydrochloride (2.0 g). Treatment with $AgNO_3$ yielded 8a as plates (1.1 g).

2-(2-Dimethylaminoethyl)imidazo[1,2-*a*]pyridine Dihydrobromide (4b). A solution of 1-bromo-4-dimethylaminobutan-2-one[8] (13.8 g, 0.05 mol) and 2-aminopyridine (4.7 g, 0.05 mol) in EtOH (50 ml) was heated under reflux for 2 hr. Cooling gave 1-methylpyrrolidin-3-one methobromide (10): 5.6 g; mp 222–227°. *Anal.* ($C_6H_{12}BrNO$) C, H; Br: calcd, 41.23; found, 41.83. Filtration, concentration, and crystallization from MeOH gave 4b: 0.45 g; uv (H_2O) λ_{max} 275 nm (log ϵ 3.90).

1-(Chloroacetyl)imidazo[1,5-*a*]pyridine (12). A solution of imidazo[1,5-*a*]pyridine[9] (100 g, 0.85 mol) in CS_2 (650 ml) was added slowly to a stirred mixture of finely powdered $AlCl_3$ (451 g, 3.38 mol) and chloroacetyl chloride (382 g, 3.38 mol) in CS_2 (750 ml). The mixture was heated at reflux for 4 hr, set aside overnight, and concentrated, ice–water was added, and the aqueous solution was neutralized with NaOH. A copious precipitate was obtained and the suspension was centrifuged. The clear supernatant was separated and extracted with $CHCl_3$ (6 × 150 ml). The solid was triturated with $CHCl_3$ (10 × 1 l.) and the extracts were dried ($MgSO_4$) and concentrated *in vacuo* at a bath temperature below

†Approximate potencies relative to histamine from submaximal responses (Table III).

‡Nomenclature used for histamine derivatives (24) is derived from the system customary for histidine[17] in which the ring-nitrogen atom adjacent to the aminoalkyl side chain is designated position 1. The other ring atoms are numbered serially in a way that assigns the smallest possible number, 3, to the second ring-nitrogen atom.

25°. Initially a dark brown solid (25.6 g) was obtained and further concentration yielded crude **12** as an off-white solid (59 g, 36%).§

1-(Phthalimidoacetyl)imidazo[1,5-*a*]pyridine (13). A solution of **12** (18.1 g, 0.093 mol) in DMF (150 ml) was added dropwise to a stirred suspension of potassium phthalimide (17.2 g, 0.093 mol) in DMF at 50°. The mixture was subsequently heated on the steam bath for 3 hr, concentrated, and triturated with dilute HCl and the solid (29 g, mp 220–224°) collected. Crystallization of part of this material (24.6 g) from $CHCl_3$–petroleum ether with filtration through silica afforded **13** (21.5 g, 90%), mp 235–238°. An analytically pure sample, mp 239–242°, was obtained after several recrystallizations from $CHCl_3$–petroleum ether. *Anal.* ($C_{17}H_{11}N_3O_3$) C, H, N.

1-(Aminoacetyl)imidazo[1,5-*a*]pyridine Hydrochloride (14a). A solution of **13** (18.1 g, 0.093 mol) in 5 *N* HCl was heated on the steam bath for 5 hr, diluted with H_2O (600 ml), filtered, and concentrated. The residue was extracted with *i*-PrOH (2 × 25 ml). Insoluble solid (3.1 g, mp >350°) was crystallized twice from MeOH–EtOH–Et_2O yielding **14a** (2.21 g). Recrystallization of a sample (0.65 g) twice from *i*-PrOH–MeOH–EtOAc yielded pure **14a**: 0.35 g; uv (H_2O) λ_{max} 359 nm (log ϵ 4.20), 345 (4.29), 262.5 (3.39), 245 (3.40).

1-(Dimethylaminoacetyl)imidazo[1,5-*a*]pyridine (14b). **12** (3.6 g, 0.019 mol) was added slowly to a cooled solution of 25% Me_2NH (8 ml, 0.044 mol) in *i*-PrOH (40 ml) and stirred for 20 min at 5°, 1.5 hr at 30°, and 0.5 hr at 50°. Aqueous Me_2NH (10 ml) was added and the solution heated for 20 min at 50° and then concentrated to low bulk. The residue was triturated with H_2O and the solid recrystallized twice to afford pure **14b** (2.01 g).

1-(Azidoacetyl)imidazo[1,5-*a*]pyridine (17). NaN_3 (6.50 g) in H_2O (10 ml) was gradually added to a solution of **13** (9.73 g) in AcOH (6 ml) at 5° and the solution left at 5° for 6 days. The clear orange solution was added to H_2O (1 l.) to give **17** as an almost colorless solid: 6.1 g (65%); mp 228–229° (Et_2O–petroleum ether); uv (50% EtOH) λ_{max} 346 nm (log ϵ 4.17), 307 (3.93), 263 (3.48), 255 (3.46), 228 (4.17), 224 (4.18). *Anal.* ($C_9H_7N_5O$) C, H, N.

1-(2-Aminoethyl)imidazo[1,5-*a*]pyridine Hydrochloride (5a). (i) $NaBH_4$ (2.72 g, 0.072 mol) was added gradually to a stirred suspension of **14a** (5.0 g, 0.024 mol) in dry "diglyme" (50 ml). A solution of BF_3–Et_2O (10.09 g, 0.071 mol) in dry "diglyme" (37 ml) was then added slowly to the cold solution. The reaction mixture was allowed to attain room temperature, stirred for 3 hr, and left overnight. After concentrating *in vacuo*, the residue was dissolved in MeOH, heated at reflux for 0.5 hr, concentrated, washed with Et_2O, and extracted several times with absolute EtOH. Concentration and crystallization from MeOH–Et_2O gave a white solid, followed by a green spongy material. The latter was treated successively with methanolic NaOH and HCl in *i*-PrOH (to pH 7) to yield a solid (1.2 g) which was twice recrystallized from EtOH–Et_2O. The almost colorless monohydrochloride of **5a** was obtained in two crops: 0.57 g (mp 215–218°) and 0.28 g (mp 210–215°) (18%); uv (H_2O) λ_{max} 331 nm (log ϵ 3.43), 285 (3.74), 274 (3.79).

(ii) 1-(Azidoacetyl)imidazo[1,5-*a*]pyridine (1.06 g, 0.005 mol) was reduced with diborane generated internally from $NaBH_4$ (0.85 g, 0.0225 mol) and BF_3–Et_2O (4.47 g, 0.03 mol) under conditions similar to those in method i to give **5a** (0.15 g, 15%), identical with that previously described.

1-(2-Dimethylaminoethyl)imidazo[1,5-*a*]pyridine Dihydrochloride (5b). Reduction of **14b** (4.5 g) by method i used for **14a** gave **5b** as the dihydrochloride: 4.47 g; uv (H_2O) λ_{max} 318 nm (log ϵ 3.44), 284 (3.76), 274 (3.80).

1-(2-Amino-1-hydroxyethyl)imidazo[1,5-*a*]pyridine Dihydrochloride (18). A suspension of **14a** (5.3 g, 0.025 mol) in H_2O (15 ml) was added slowly to a stirred solution of $NaBH_4$ (2.0 g, 0.05 mol) in H_2O (15 ml), stirred for 5 hr at room temperature, and left overnight. A few drops of dilute HCl were added, followed by excess picric acid in H_2O. The picrate obtained (9.43 g, mp 165–170° dec) was suspended in H_2O and cooled during the addition of 1 *N* HCl (90 ml). Filtration and concentration gave **18** (3.6 g) which was recrystallized to give buff needles: 2.47 g; uv (50% EtOH) λ_{max} 328 nm (log ϵ 3.47), 284 (3.77), 273 (3.81).

1-(2-Dimethylaminoethyl)-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridine Dihydrochloride (19b). Hydrogenation of **14b** (1.0 g, 0.0038 mol) in HAc (100 ml) at atmospheric pressure over 5% Pd/C was complete within 0.5 hr (uptake of H_2, 205 ml) and uv of the solution (no absorption, 250 nm) indicated the complete reduction of the imidazo[1,5-*a*]pyridine ring. Filtration, concentration, and crystallization gave **19b** (0.9 g).

1-(2-Aminoethyl)-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridine Dihydrochloride (19a). Hydrogenation of **14a** (1.55 g) by the method used for **14b** followed by acidification with HCl gave **19a** as the dihydrochloride (1.25 g).

5,6,7,8-Tetrahydroimidazo[1,5-*a*]pyridine Picrate (19c). Hydrogenation of imidazo[1,5-*a*]pyridine[9] (2.0 g, 0.017 mol) with Pd/C gave **19c** (1.94 g, 94%), characterized as the picrate, mp 149–150° (MeOH). *Anal.* ($C_7H_{10}N_2 \cdot C_6H_3N_3O_7$) C, H, N.

2-(2-Phthalimidopropionamidomethyl)pyridine Hydrochloride (22). A solution of 2-phthalimidopropionyl chloride (11.9 g, 0.05 mol) in C_6H_6 (200 ml) was added rapidly to a solution of 2-picolylamine (5.4 g, 0.05 mol) in C_6H_6 (100 ml), stirred for 2 hr, and left overnight. Crystallization from EtOH gave the hydrochloride of **22** as needles: 8.3 g (48%); mp 216–220°. *Anal.* ($C_{17}H_{15}N_3O_3 \cdot HCl$) C, H, N.

3-(2-Phthalimidoethyl)imidazo[1,5-*a*]pyridine (20). A mixture of **22** (base, 3.1 g, 0.01 mol) and $POCl_3$ (35 ml) was heated at reflux for 2 hr, concentrated, dissolved in H_2O, and neutralized with $NaHCO_3$ to afford **20** as a yellow solid which was recrystallized from EtOH–Et_2O as yellow plates (2.5 g, 85%), mp 158–161°. *Anal.* ($C_{17}H_{13}N_3O_2$) C, H, N.

3-(2-Aminoethyl)imidazo[1,5-*a*]pyridine Dihydrochloride (21). Hydrolysis of **20** (7.5 g, 0.025 mol) with 6 *N* HCl and recrystallization gave **21** as pale blue needles: 1.0 g; uv (EtOH) λ_{max} 310 nm (log ϵ 3.49), 282 (3.85), 272 (3.88). From a similar hydrolysis, 2-picolylamine hydrochloride, mp 211–216° (lit.[10] mp 209–212°), was isolated.

§ This chloro ketone is a powerful skin irritant and lachrymator.

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