SYNTHESIS OF PYRIDYL ISOSTERES OF THIOPERAMIDE AS H_3-RECEPTOR HISTAMINE ANTAGONISTS

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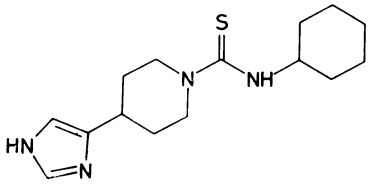
Dedicated to Dr Miroslav Protiva on the occasion of his 70th birthday.

The synthesis and evaluation as H_3-receptor histamine antagonists is described of novel isosteric analogues of thioperamide. The compounds are designed to have fewer NH groups in order to assist brain penetration. However none of the compounds is sufficiently active as an antagonist in vitro. The 2-pyridyl analogue *II* has $K_i = 13\ \mu mol\ l^{-1}$.

The actions of histamine have been characterised pharmacologically as being mediated by three subtypes of receptor, designated[1-3] H_1, H_2 and H_3. The H_3 receptor is the most recently described. It has been shown to function as a pre-synaptic autoreceptor inhibiting histamine synthesis and histamine release from neurones, especially in the central nervous system[3,4]. The presence of H_3-receptors has also been demonstrated in human brain tissue[5].

Histamine H_3-receptors were first suggested in 1983 by Arrang et al.[3] from studies using compounds which also acted at H_2 receptors. Subsequently, in 1987, they were characterised more definitively[4] using a potent selective agonist (*R*)-α-methyl-histamine and a potent and highly specific competitive antagonist, thioperamide (*I*, Table I).



I

Although thioperamide is a very potent antagonist in vitro (K_i = 4·3 nmol l^{-1}) relatively high doses are required in vivo to inhibit histamine release from the brain (in the rat). This could be due to the pharmacokinetic properties of thioperamide but is more probably a result of its poor penetration of the blood-brain-barrier.

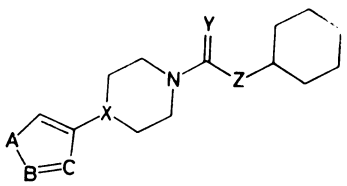
Studies with structurally analogous H_2-receptor histamine antagonists have indicated[6] that brain penetration is greatly reduced by the presence of polar hydrogen--bonding groups (acceptor or donor). Therefore we investigated the effect of replacing the 4-imidazolyl ring of thioperamide by 2-pyridyl to give compound *II* since this would substantially reduce donor hydrogen-bonding by removing an NH group, but retain a basic nitrogen atom *ortho* to the side chain. This latter is often an important chemical feature of compounds acting at histamine receptors[7].

It also seemed likely that a 2-pyridyl group would be recognised by the receptor since betahistine [N-methyl-2-(2-pyridyl)ethylamine] has some activity as an H_3--receptor antagonist[8]. Since anabasine is commercially available, this was used to also provide a 3-pyridyl isomer *III*.

As an additional modification, the piperidine ring was replaced by piperazine (compound *IV*) since this would increase the basicity of the pyridine nitrogen atom (being a 2-aminopyridine derivative). The pK_a of 2-aminopyridine is 6·71 at 25°C

TABLE I

Structures and activities of compounds tested for antagonism of histamine induced inhibition of [^3H]histamine release in slices of rat brain cortex by the method of Arrang et al.[3,4]

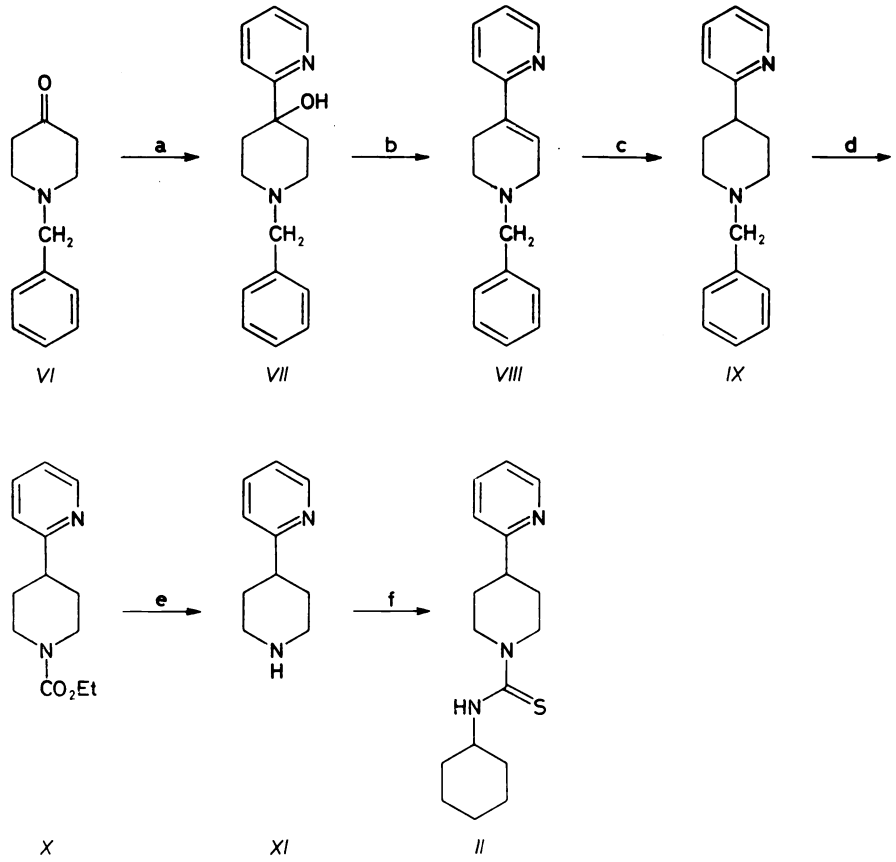


Compound	A	B	C	X	Y	Z	Activity K_i, μmol l^{-1}
I[a]	NH	CH	N	CH	S	NH	0·0043
II	CH=CH	CH	N	CH	S	NH	13 ± 1
III	CH=CH	N	CH	[b]	S	NH	>10
IV	CH=CH	CH	N	N	S	NH	>10
V	CH=CH	CH	N	N	O	CH_2	>10
VII	CH=CH	CH	N	C—OH	H_2	[c]	>100

[a] Thioperamide; [b] 2-piperidyl isomer, X = CH_2 derived from anabasine; [c] see Scheme 1.

(ref.[9]) which is close to that of imidazole 6·99 at 25°C (ref.[10]) making it resemble more closely the pK_a of the imidazole ring of thioperamide.

Finally, a further modification replaced the cyclohexylthiocarbamoyl moiety by cyclohexylacetyl (compound *V*) since this isosteric replacement of NH by CH_2 removes another donor NH group. Acetamide derivatives of histamine have since been shown to have antagonist activity at H_3-receptors[11].



VI *VII* *VIII* *IX*

X *XI* *II*

a) 2-bromopyridine, n-BuLi; b) $SOCl_2$; c) Pd-C, H_2; d) $ClCO_2Et$; e) HBr, AcOH; f) $C_6H_{11}NCS$

SCHEME 1

EXPERIMENTAL

Melting points were taken in open capillaries and are uncorrected. ^1H NMR spectra were recorded on a JEOL PMX60SI (60 MHz), Varian XL-200 (200 MHz) or VXR-400 (400 MHz) spectro-

meter, and are reported in δ ppm relative to tetramethylsilane as internal standard. The following abbreviations are used: Py pyridyl; Pip piperidyl. Mass spectra (MS) were recorded on a VG 7070H double focussing spectrometer with a Finnigan Incos data system using electron-impact (EI) at 70 eV or fast atom bombardment (FAB) in a glycerol/thioglycerol matrix.

Analytical thin-layer chromatography (TLC) was done on Merck Kieselgel 60 F-254 plates using NH_4OH, MeOH, EtOAc (1 : 1 : 5) as solvent mixture unless otherwise indicated; plates were visualized at 254 nm, and then with either iodine vapour or potassium iodoplatinate.

N-Cyclohexyl-4-(2-pyridyl)-1-piperidine Carbothioamide Trifluoroacetate (*II*)

4-(2-Pyridyl)piperidine (*XI*) (0·114 g, 0·70 mmol) and cyclohexylisothiocyanate (0·1 C0 g 0·70 mmol) were heated together in absolute ethanol (30 ml) under reflux for 51 h. Solvent was removed under vacuum to give the product as a brown oil which was purified by semipreparative HPLC (Lichrosorb RP Select B 250 × 10 mm column, using 1 ml/min flow of solvent gradient A/B = 95/5 to 60/40 over 20 min (where A is water with 0·1% trifluoroacetic acid (TFA) and B is acetonitrile with 5% water) with UV detection at 254 nm. On removal of solvent under vacuum, the product was obtained as a brown oil (0·145 g, 46% overall yield). The latter was dissolved in iso-PrOH at room temperature and filtered through a sinter (to remove any traces of silica), then concentrated under vacuum to give the product *II* as trifluoroacetate, an off-white solid: m.p. 110–112°C. TLC: R_F 0·84. ^{1}H NMR (400 MHz, $CDCl_3$): 8·84 d, 1 H (Py-6, J = 5·33); 8·30 t, 1 H (Py-5, J = 7·86); 7·74 t, 1 H (Py-4, J = 5·89; 6·52); 7·68 d, 1 H (Py-3, J = 7·68); 5·54 s br, 1 H (NH); 4·82 d br, 2 H (CHNCH, eq, J = 13·54); 4·34 s br, 1 H (CHNH); 3·60 tt, 1 H (CH-Py, J = 12·81; 3·54); 3·18 t, 2 H (CHNCH, ax, J = 11·93); 2·13 m, 4 H ((Py--CH(CH_2); 1·87–1·63, 1·47–1·37, 1·22–1·13 m, 10 H, (C_6H_{10}); 1·22 d, 0·9 H (2 CH_3 of iso-PrOH, J = 6·14). Mass spectrum (EI): 303 (M^+). For $C_{17}H_{25}N_3S.1{\cdot}2\ CF_3CO_2H.0{\cdot}15$ iso--PrOH calculated: 53·1% C, 6·15% H, 9·4% N, 7·1% S; found: 53·3% C, 6·30% H, 9·6% N, 7·3% S.

N-Cyclohexyl-2-(3-pyridyl)-1-piperidine Carbothioamide Trifluoroacetate (*III*)

2(3-Pyridyl)piperidine [(±)-anabasine] (0·200 g, 1·23 mmol, 89% purity by HPLC) obtained from Sigma and cyclohexylisothiourea (0·174 g, 1·23 mmol) were heated in EtOH under reflux (30 ml) for 10 days. Solvent was removed under vacuum, and the residue dried (0·1 torr/20°C/4 h) to give the product (0·332 g, 89% overall yield). Part of this (223 mg) was purified by semi-preparative HPLC (Lichrosorb RP Select B 250 × 10 mm column, UV 220 nm detector, using 4 ml/min flow of solvent gradient A/B = 95/5 to 60/40 over 20 min and 40/60 at 30 to 37 min, where A is water with 0·1% TFA and B is acetonitrile with 0·1% TFA and 5% water) to give the product as a yellow oil (110 mg). This was dried, dissolved in iso-PrOH, filtered and redried in vacuo for 24 h to give the oily trifluoroacetate product (85 mg, yield 38%). TLC: R_F 0·86 with trace at 0·62. ^{1}H NMR (400 MHz, CD_3OD): 8·71 d, 1 H (Py-6, J = 5·53); 8·65 s, 1 H (Py-2); 8·39 d, 1 H (Py-4, J = 8·22); 8·00–7·96 m, 1 H (Py-5); 6·85 s br, 1 H (NH); 4·40 to 4·35 m, 1 H (CHNH); 4·17 d br, 1 H (CHN, J = 14·69); 3·92 septet, 0·5 H (CH from iso-PrOH, J = 6·15); 2·90 ddd, 1 H (CHN, ax, J = 10·86; 10·47; 3·79); 2·48 dd, 1 H (CHN, eq, J = 14·67; 3·29); 2·08–1·99 m, 4 H ($CH_2CH_2NCHCH_2$); 1·81–1·17 m, 12 H (C_6H_{10}, $CH_2(CH_2)_2N$); 1·15 d, 3 H (2 CH_3 from iso-PrOH, J = 6·12). Mass spectrum (FAB): 304 $(M + H)^+$. For $C_{17}H_{25}N_3S.1{\cdot}5\ CF_3CO_2H.0{\cdot}5$ iso-PrOH calculated: 51·2% C, 6·09% H, 8·3% N, 6·4% S; found: 51·2% C, 6·21% H, 8·1% N, 6·2% S.

N-Cyclohexyl-4-(2-pyridyl)-1-piperazine Carbothioamide (*IV*)

1-(2-Pyridyl)piperazine (3·0 g, 18 mmol) and cyclohexylisothiocyanate (2·76 g, 20 mmol) were heated together in toluene (200 ml) under reflux for 3 h and then left to cool, to afford colourless crystals (4·0 g). Partial concentration afforded a second crop (1·2 g). Total yield 93%. Recrystallisation from aqueous methanol (1 : 10) gave the product, m.p. 174–176°C. TLC: R_F 0·91. ^{1}H NMR (60 MHz, $CDCl_3$): 8·25 m, 1 H (Py-6); 7·7–6·4 m, 4 H (Py, NH); 3·9 s, 9 H (NCH_2, NCH); 2·4–0·8 m, 10 H (C_6H_{10}). Mass spectrum (EI): 304. For $C_{16}H_{24}N_4S$ calculated: 63·1% C, 7·95% H, 18·4% N, 10·5% S; found: 62·8% C, 8·07% H, 18·3% N, 10·8% S.

1-Cyclohexylacetyl-4-(2-pyridyl)piperazine (*V*)

Freshly distilled cyclohexylacetylchloride (0·74 g, 4·6 mmol, b.p. 107° at 0·2 mm Hg; prepared from cyclohexylacetic acid and thionyl chloride) in 10 ml dry toluene was added to 1-(2-pyridyl)-piperazine (0·75 g, 4·6 mmol) in 10 ml dry toluene at 0°C with stirring and left overnight at 20°C. Water (20 ml) was added, the mixture was basified (aq. NaOH), and the organic layer was separated, dried ($MgSO_4$) and concentrated. The resulting residue was crystallized from 10 : 1 ethyl acetate: light petroleum (b.p. 60–80°C) to afford the white crystalline product, m.p. 76–77°C (0·98 g, 73% yield). TLC: R_F 0·84. ^{1}H NMR (60 MHz, $CDCl_3$): 8·1 m, 1 H (Py-6); 7·6–6·4 m, 3 H (Py); 3·5 s, 8 H (NCH_2); 2·2 m, 2 H ($COCH_2$); 2·0–0·5 m, 11 H (C_6H_{11}). Mass spectrum (EI): 287 (M^+). For $C_{17}H_{25}N_3O$ calculated: 71·0% C, 8·77% H, 14·6% N; found: 71·0% C, 8·85% H, 14·7% N.

1-Benzyl-4-(2-pyridyl)piperidin-4-ol Hydrochloride (*VII*)

A round bottom 3-necked flask fitted with a septum, pressure equalizing dropping funnel and condenser was flushed with dry N_2. Dry ether was added, and BuLi (45 mmol, 18 ml of 2·5M in hexane solution) was injected. The vessel was cooled to −40°C and a solution of 2-bromopyridine (6·32 g, 40 mmol) in dry ether (50 ml) was added over 5 min to the stirred mixture (ref.[12]). Then 1-benzyl-4-piperidinone (*VI*) (9·46 g, 50 mmol) in dry ether (50 ml) was added over 5 min. The temperature rose from −40 to −18°C over 30 min. The reaction mixture was hydrolyzed with ice cold NH_4Cl (0·045 mol, 2·4 g in 80 ml H_2O) and the clear yellow ether layer was separated and extracted with 10% aqueous HCl (40 ml). The acid extract was neutrallized with solid $NaHCO_3$ (7·72 g) to pH 7 to give a dark red oil. The latter was extracted into Et_2O (220 ml), dried ($MgSO_4$), and the solvent removed under vacuum to give unchanged 1-benzyl-4-piperidinone (5·6 g). The remaining mixture was then extracted with $CHCl_3$ (75 ml). The latter was dried ($MgSO_4$) and concentrated to give a red oil (11·0 g) which was passed through a silica gel column ($CHCl_3$–MeOH, 3 : 1 as eluant), to afford the oily base (reported[13] m.p. 58–60°C). This was converted into dihydrochloride (1·44 g) as a white cystalline solid: m.p. 254–255°C (EtOH). TLC ($CHCl_3$, MeOH, 3 : 1): R_F 0·81. One component by HPLC at 4·33 min detected at 254 nm (Lichrosorb RP Select B, 250 × 4 mm, using 1·0 ml/min of 10% aqueous methanol containing 0·1% triethylamine and 0·5% orthophosphoric acid). ^{1}H NMR (200 MHz, D_2O): 8·6 d, 1 H (Py-6, J = 7·0); 8·4 t, 1 H (Py-5, J = 8·0); 8·1 d, 1 H (Py-3, J = 9·0); 7·8 t, 1 H (Py-4, J = 8·0); 7·3 s, 5 H (Ph); 4·0 s, 2 H (CH_2); 2·7–3·2 m, 4 H ($(CH_2)_2N$); 1·3 to 2·0 m, 4 H ($(CH_2)_2C$). Mass spectrum (EI): 268 (M^+). For $C_{17}H_{20}N_2O.2$ HCl calculated: 59·8% C, 6·50% H, 8·2% N; found: 59·9% C, 6·47% H, 8·2% N.

1-Benzyl-4-(2-pyridyl)-1,2,5,6-tetrahydropyridine Dihydrochloride (*VIII*)

1-Benzyl-4-(2-pyridyl)piperidin-4-ol dihydrochloride (*VII*) (5·44 g) was added in small portion

to $SOCl_2$ (50 ml), stirred magnetically and cooled in an ice-water bath. The colourless solution was left at room temperature for 2 days (moisture excluded), then concentrated under reduced pressure; the residue was taken into Et_2O, concentrated and dried at 70°C/0·33 torr to give a hygroscopic off-white solid: m.p. 153°C (with prior softening from 135°C) (4·94 g, 98% yield). TLC ($CHCl_3$, MeOH, 3 : 1): R_F 0·89. ^{1}H NMR (400 MHz, $(CD_3)_2SO$): 8·60 d, 1 H (Py-6); 7·95 m, 1 H (Py-5); 7·36—7·78 m, 7 H (Py-3, 4, Ph); 6·74 s br, 1 H (C=CH); 4·43 m, 2 H (CH_2Ph); 3·7—4·3 v br s (H_2O); 2·60—3·85 m, 6 H ($CH_2CH_2NCH_2$). Mass spectrum (EI): 250 (M^+). For $C_{17}H_{18}N_2.2$ HCl calculated: 63·2% C, 6·24% H, 8·7% N; found: 62·9% C, 6·42% H, 8·4% N.

1-Benzyl-4-(2-pyridyl)piperidine (*IX*)

1-Benzyl-4-(2-pyridyl)-1,2,5,6-tetrahydropyridine dihydrochloride (*VIII*) (2·47 g, 7·24 mmol) in EtOH (50 ml) was shaken in a Parr apparatus at room temperature, with Pd/C (10%, 1·047 g) and H_2 (413·7 kPa) for 70 h. During this time, the catalyst was replaced and acetic acid added twice (0·5 g, 2 ml and 0·3 g, 3 ml, respectively). The reaction mixture was filtrered, evaporated to dryness under reduced pressure, stirred with Et_2O and decanted several times, to give the dihydrochloride as a solid (1·57 g, 64%). This was dissolved in water (5 ml), basified with $NaHCO_3$ and extracted with CH_2Cl_2 (10 × 5 ml). The combined extracts were dried ($MgSO_4$), and evaporated to give the base (0·922 g) as a solid. TLC ($CHCl_3$, MeOH, NH_4OH, 5 : 1 : trace): R_F 0·61. ^{1}H NMR (200 MHz, $CDCl_3$): 8·51 br s, 1 H (Py-6); 7·63 t, 1 H (Py-5, J = 7·0); 7·50—7·05 m, 7 H (Py-3, 4, Ph); 3·76 s, 2 H (CH_2Ph); 3·17 br d, 2 H (Pip-2 CH eq, Pip-6 CH eq, J = 14·0); 2·82 br m, 1 H (Py-CH); 2·37 br m, 2 H (Pip-2-CH ax, Pip-6-CH ax); 2·04 br s, 4 H (Pip-3-CH_2, Pip-5-CH_2). Mass spectrum (EI): 252 (M^+).

1-Ethoxycarbonyl-4-(2-pyridyl)piperidine (*X*)

1-Benzyl-4-(2-pyridyl)piperidine (*IX*) (0·363 g, 1·44 mmol) was suspended in Na dried benzene (10 ml). Ethyl chloroformate (0·44 g, 4·08 mmol) was added together with MeOH (1 ml) to dissolve *IX*, and the mixture was heated under reflux following the general procedure[14], for 20 h; the reaction mixture was then evaporated to dryness under reduced pressure, $ClCO_2Et$ (10 ml) was added and the mixture heated for 40 h. The reaction mixture was evaporated to dryness under reduced pressure; glacial acetic acid was then added and the mixture concentrated to dryness; the procedure was then repeated with ether to afford a brown solid (0·30 g). ^{1}H NMR (200 MHz, CD_3OD) indicated presence of a pyridine ring at δ 7—9, absence of benzyl, and peaks due to the Et group at δ 1·25 and 1·96. Mass spectrum (EI): 234 (M^+).

4(2-Pyridyl)piperidine (*XI*)

A mixture of 1-ethoxycarbonyl-4-(2-pyridyl)piperidine (*X*) (0·30 g, 1·36 mmol), aqueous HBr (48%, 3 × weight equivalent) and glacial acetic acid (11 × weight equivalent) was heated under reflux for 3 h following the general procedure[14]. The mixture was cooled, then ice was added and the mixture made alkaline to pH 14 with dilute NaOH and extracted with CH_2Cl_2 (5 × 20 ml). The combined extracts were dried ($MgSO_4$) and evaporated to yield the base as a brown oil, (0·2 g, 94% yield). Silica gel column chromatography of the product, using $CHCl_3$–MeOH (5 : 1) as eluant removed starting material while the product remained at the top of the column. The top band was extracted with hot 1 : 1 $CHCl_3$–MeOH (250 ml), and the white solid (30 mg) obtained extracted with iso-PrOH (2 × 30 ml) to give a colourless oil (11 mg), identified by TLC and ^{1}H NMR. More product was extracted from the column using MeOH with 2% NH_4OH (250 mg) to give a brown oil (23 mg). Combined yield from the column 34 mg, (16%). The

product (23 mg, 0·14 mmol) was treated with oxalic acid (0·028 g, 0·312 mmol) in EtOH (2 ml). Addition of Et_2O, and trituration with several decantations of solvent resulted in the dioxalate (42 mg, 40%) which, after recrystallization from iso-PrOH–EtOH (1 : 1), yielded a solid: m.p. 191–192°C. TLC: R_F 0·23. ^{1}H NMR (400 MHz, CD_3OD): 8·53 m, 1 H (Py-6); 7·84 t, 1 H (Py-5, J = 7·73); 7·41 d, 1 H (Py-3, J = 7·89); 7·33 m, 1 H (Py-4); 3·55–2·45 m, 3 H (Py-CH, Pip-2-CH eq, Pip-6-CH eq); 3·19–3·10 m, 3 H (NH, Pip-2-CH ax, Pip-6-CH ax); 2·15–2·03 m, 4 H (Pip-3-CH_2, Pip-5-CH_2); 1·2 (iso-PrOH and EtOH). Mass spectrum (EI): 162 (M^+).

RESULTS

The synthesis of compound *II* is outlined in Scheme 1. 1-Benzylpiperidin-4-one (*VI*, Aldrich) was treated with 2-pyridyl lithium according to the procedure described by Gilman and Spatz[12] to give the pyridyl piperidin-4-ol (*VII*) isolated as dihydrochloride[13].

Dehydration of the carbinol *VII* proved to be difficult; thus, treatment with *p*-toluene sulphonyl chloride in dry pyridine at 4°C for 12 days, or treatment with anhydrous $KHSO_4$ or HBr/AcOH, left the starting material unchanged.

Treatment of *VII* with thionyl chloride under reflux for 1 h gave a tar, but when the carbinol was stirred with an excess of thionyl chloride at 20°C for 2 days it was quantitatively converted into 1-benzyl-4-(2-pyridyl)-1,2,5,6-tetrahydropyridine dihydrochloride (*VIII*).

Attempts to reduce the double bond with concomitant hydrogenolysis of the benzyl protecting group failed, and hydrogen with Pd/C catalyst only reduced the double bond to afford 1-benzyl-4-(2-pyridyl)piperidine (*IX*). More prolonged treatment with H_2 and Pd/C, or use of Raney Ni, or sodium in NH_3, led to reduction of the pyridine ring.

The benzyl group in *IX* was removed by treatment with chloroethyl formate[14] to give the ethoxycarbonyl piperidine *X*. This was hydrolysed in HBr/AcOH under reflux to give 4-(2-pyridyl)piperidine (*XI*) isolated as dioxalate. Compound *XI* as base has been reported in ref.[15]. Treatment of the corresponding base with cyclohexylisothiocyanate then afforded product *II*.

Compounds *III* and *IV* were synthesized directly from cyclohexylisothiocyanate and commercially available anabasine or 1-(2-pyridyl)piperazine respectively. Compound *V* was made from cyclohexylacetyl chloride and 1-(2-pyridyl)piperazine.

Products *II*–*V* and *VII* were tested for their effect on histamine inhibition of the K^+ induced release of [^3H]histamine from slices of rat cerebral cortex which had been preincubated with [^3H]histidine according to the described procedure[3,4].

Only *II* showed activity, having a K_i of 13 μmol l^{-1}, i.e. some 3 000 times weaker than thioperamide (*I*). It thus appears that the presence of an imidazole ring in this type of structure is probably critical for activity as an antagonist of histamine at H_3 receptors.

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