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Two Novel Syntheses of the Histamine H_3 Antagonist Thioperamide

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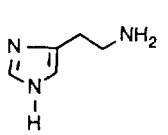
Abstract: The previously described route for the synthesis of the histamine H_3 antagonist thioperamide **3** has been improved considerably. Furthermore, two straightforward novel synthetic routes towards **3** are described herein. The last synthetic route (Scheme 3) is preferable as it is very suitable for the production of multigram quantities of thioperamide **3**.

Introduction

The neurotransmitter histamine **1** has multiple functions in cell to cell communication, mediated by various receptors. In addition to the two postsynaptic histamine receptor types, known since thirty years (H_1, H_2), a third, presynaptic, histamine receptor (H_3) was discovered more recently by the group of Schwartz[1]. Crucial for further research into the role of the histamine H_3 receptor in physiological and pathological conditions was the description of both a selective agonist (R)-α-methylhistamine[2] **2** and a selective antagonist thioperamide[2] **3**.



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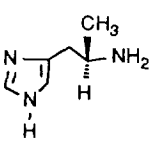

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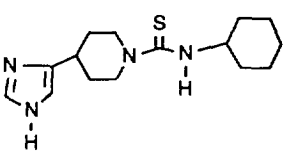


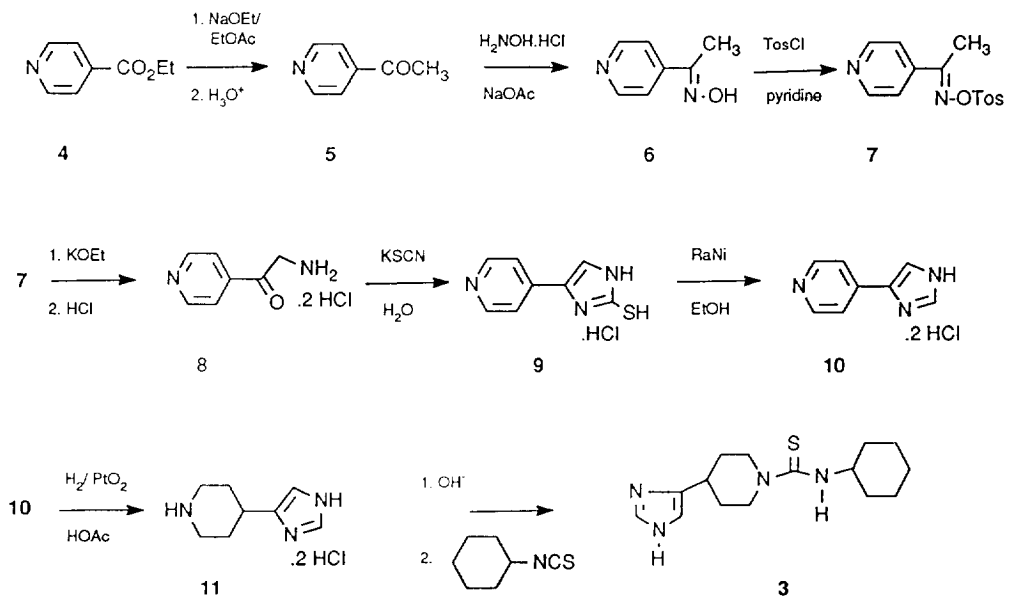
3

In order to explore in depth the potential of a selective histamine H_3 antagonist in various pharmacological models, thioperamide **3** was needed in gram quantities. Thioperamide[3] **3** can be prepared in nine steps from ethyl isonicotinate **4** as is depicted in Scheme 1. We started with the optimisation of this route. Two laborious reaction steps

were improved in our laboratory. As we were not entirely satisfied with the outcome of this improved route, more straightforward routes towards thioperamide **3** were developed.

Results and discussion

Thioperamide **3** has previously[3] been prepared in nine steps from ethyl isonicotinate **4** as is outlined in Scheme 1. In the first step, ester **4** was converted via a condensation reaction and subsequent decarboxylation into 4-acetylpyridine **5**[4] in 75 % yield. The methyl ketone **5** was converted[5] into the oxim **6** and subsequently reacted with p-tosyl choride in pyridine to afford[6] the corresponding tosylate **7**. Neber rearrangement[6,7] of the tosyloxim **7** gave the α-amino ketone **8** in quantitative yield. Reaction of the latter amine with potassium isothiocyanate provided[8] the imidazolyl thiol **9** in a moderate yield. The mercapto group was removed[8] in aqueous nitric acid to give the 4-imidazolyl derivative **10** in only 30 % yield. The yield of this laborious reaction could not be improved in our hands by slight modifications of the reaction conditions. However, this conversion was improved considerably by refluxing the thiol **9** in the presence of Raney Nickel in ethanol for two hours which smoothly gave **10** in 90 % yield. The original reductive procedure[8] of the pyridyl moiety in **10** was replaced by a reduction in a mixture of acetic acid and water with PtO_2 as the catalyst at 50 psi at room temperature, which afforded the corresponding 4-substituted piperidine **11** in high yield. The final step consisted of the addition of cyclohexyl isothiocyanate to **11** to afford thioperamide **3** in 62 % yield.

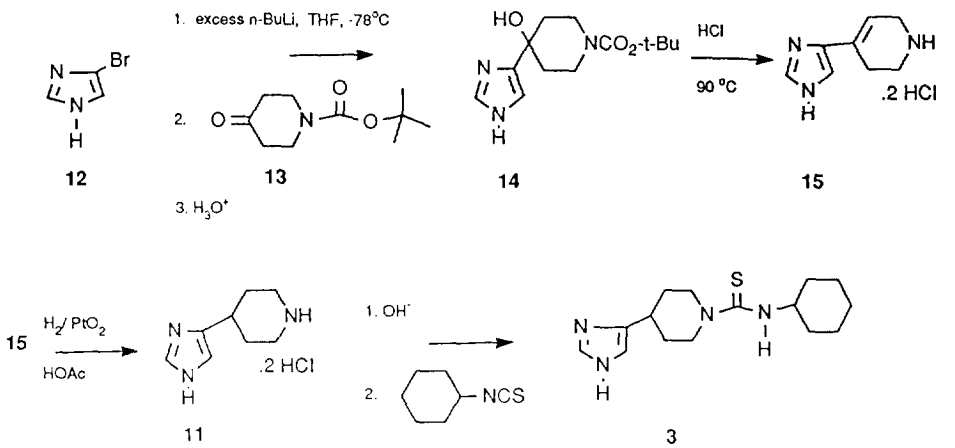


Scheme 1

However, we were not entirely satisfied with the outcome of this improved route, as it still contains some laborious steps. Therefore, a novel and more straightforward route towards thioperamide **3** was developed which consists of five steps as is depicted in Scheme 2.

Lithiation of 4-bromo-(1H)-imidazole[9] **12**, followed by the reaction with 1-t-Boc-4-piperidone[10] **13** afforded the protected piperidine **14** in 20 % yield. Attempts to optimise the yield of this reaction were not successful. For example, replacement of n-BuLi by t-BuLi gave even lower yields (8-10 %). Although the conversion of **12** into **14** has a low yield, it is very straightforward as no protection of the imidazole moiety (and a subsequent deprotective step in a later stage of the synthetic route) is required.

Removal of the t-Boc group and concomitant acid-catalyzed dehydratation of the 4-hydroxy piperidine derivative **14** gave the corresponding tetrahydropyridine **15** in 97 % yield. Hydrogenation of the double bond was performed in the presence of a catalytic amount of PtO_2 at a pressure of 50 psi, to give the 4-piperidinyl-4-imidazole **11** in 83 % yield. The dihydrogen chloride salt **11** was converted into its free base form and eventually into the thioperamide **3** as described above.



Scheme 2

The crucial step in our synthetic route is the addition reaction between the dilithiated form of **12** and the piperidone building block **13**. There are two complicating factors which account for the low yield that was found. Firstly, it is known[11] that imidazolyl anions are readily generated on C_2, but generation of the thermodynamically less stable C_4 anions, in the absence of C_2 protecting groups[12,13] is much more difficult. Many researchers have dealt with this problem by using either unprotected 4-bromo-(1H)-imidazole[14] **12** or protected imidazoles[15]. It was reported[14] that reaction of 4-bromo-(1H)-imidazole with lithium naphtalenide, followed by quenching the lithiated intermediate with benzophenone gave (1H)-imidazol-4-yldiphenylmethanol. However, attempts to quench the intermediate with other electrophiles, such as DMF, triethyl orthoformate, methyl iodide or dimethyl sulfide, failed[13].

Secondly, piperidone derivatives, such as **13** and 1-benzyl-4-piperidone, contain enolisable hydrogen atoms at C_3 and C_5. Therefore, the electrophilicity of the carbonyl group must be high enough to avoid competing side reactions, for

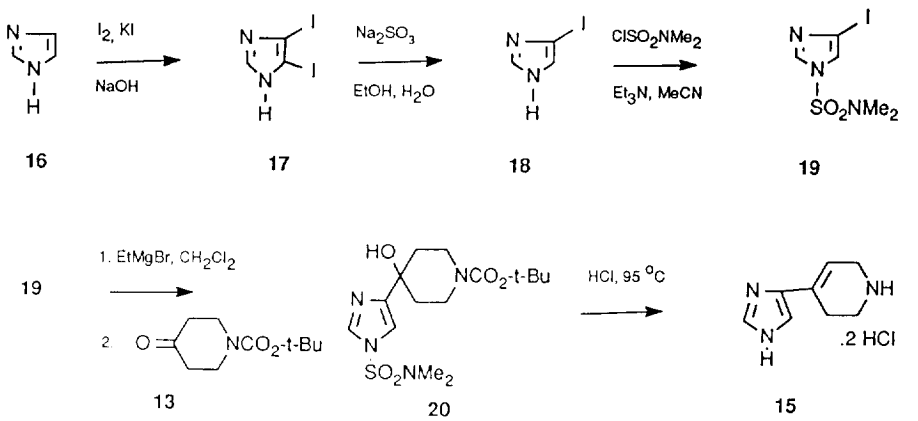
example, the occurrence of hydrogen-lithium exchange between the dilithiated intermediate and the (enolised) electrophilic substrate.

In the case where 1-benzyl-4-piperidone was used as the electrophile, a mixture of products was formed, which contained 1-benzyl-4-piperidone, imidazole and some other unidentified products.

These results prompted to use N-protected piperidones that possess a more reactive carbonyl moiety than is the case in 1-benzyl-4-piperidone. This formed the rationale for applying the tert-butoxycarbonyl (t-Boc) group (which has the additional advantage of being easily removable under acidic conditions) as N-protecting group in **13**.

Interestingly, Schwartz et al[16] reacted 2-bromopyridine with n-BuLi and quenched the resulting 2-lithiopyridine with 1-benzyl-4-piperidone to give 1-benzyl-4-(2-pyridyl)piperidin-4-ol in a modest yield. The use of 1-tert-butoxycarbonyl-4-piperidone **13** instead of 1-benzyl-4-piperidone, might give a higher yield in this reaction, too.

Obviously, the synthetic route in Scheme 2 is more straightforward than the original route. However, attempts to upscale the key step in this route, viz. the coupling of the imidazole building block **12** with the t-Boc protected piperidone **13** were unsatisfactory. This prompted the development of the route which is depicted in Scheme 3. In this route, the key step is a Grignard-type coupling[17] of dimethylsulfamoyl-protected iodoimidazole derivative **19** with piperidone **13**.



Scheme 3

Iodination of imidazole **16** afforded 4,5-diiodo-(1H)-imidazole **17**, which was reduced to 4(5)-iodoimidazole **18** by the published procedure[18]. Subsequent dimethylsulfamoyl protection of the imidazole nitrogen atom smoothly afforded the monoprotected imidazole[17] **19**. Treatment of **19** with ethyl magnesium bromide, followed by the addition of t-Boc protected piperidone[10] **13** gave the addition product **20** in 50 % yield.

Concerted removal of the dimethylsulfamoyl moiety, the t-Boc group and elimination gave tetrahydropyridine **15** which was converted to thioperamide **3**, according to Scheme 2.

In conclusion, the previously described route for the synthesis of thioperamide **3** has been improved considerably. Furthermore, two straightforward novel synthetic routes towards **3** are described herein. The last

synthetic route (Scheme 3) is preferable as it is very suitable for the production of multigram quantities of thioperamide **3**.

Acknowledgements

The colleagues of the Structure Analysis Department are gratefully acknowledged for supplying the spectroscopic data.

Experimental section

All melting points were determined on a Mettler FP62 apparatus and are uncorrected. Infra red spectra were recorded on a Nicolet 60SX spectrometer with a MCT-B detector. Only characteristic absorptions are reported. The shape of the IR absorptions is given by the following abbreviations: vb = very broad, b = broad, s = sharp. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AM 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz) spectrometer, with tetramethylsilane or the sodium salt of 3-trimethylsilyl propionic acid as the internal standard. The shape/multiplicity of the NMR absorptions is given by the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Mass spectra were taken with a Kratos Concept 1S double focussing mass spectrometer or with a Finnigan 4000 quadrupole mass spectrometer. Only significant fragment ions are reported. Silica gel 60 (Merck) was used for flash column chromatography. The ratio of solvent mixtures is shown as volume/volume. Pre-coated silica gel 60 F-254 TLC plates (Merck) were used for thin layer chromatography (TLC). TLC spots were visualised with an UV lamp, iodine vapor or after spraying with Dragendorff reagent (characteristic for amines). All yields refer to isolated, purified material, and are unoptimised.

THF was dried by distillation from $LiAlH_4$. Dichloromethane was dried on molsieves (4A). Glass equipment and syringes were oven-dried.

4-(4-pyridyl)-(1H)-imidazole dihydrochloride[8] **10**

To a suspension of the thiol **9** (1.0 g, 5.64 mmol) in ethanol (50 ml) was added Raney Nickel (3.0 g). The resulting mixture was heated at reflux for two hours and filtered. (TLC analysis showed that the reaction was complete within two hours; R_f 0.3 (CH_2CL_2/EtOH/NH_4OH (25 % aq.) = 87.5/12/0.5)). The Raney Nickel precipitate was washed with ethanol (3x). The combined ethanol fractions were concentrated in vacuo to give an oily residue (0.75 g). After addition of an ethanolic hydrogen chloride solution (containing approximately 4 equivalents of HCl) and evaporation in vacuo, diethyl ether was added and the formed precipitate was filtered to give **10**[8,19] as a white solid, which was immediately converted to compound **11**.

4-(4-piperidyl)-(1H)-imidazole dihydrochloride[8,19] **11**

PtO_2 (0.3 g) was added to a solution of **10** (0.55 g) in acetic acid (12.5 ml) and water (5 ml) and the resulting mixture was hydrogenated overnight at approximately 50 psi. The catalyst was removed by filtration (hyflo). The filtrate was evaporated in vacuo to afford pure **11** (0.47 g, 83 %) as a white solid, mp 300 °C (dec.). R_f 0.1 (MeOH/NH_4OH(25 % aq.) = 100/1; I_2 vapor). ^{1}H-NMR (D_2O): δ 1.93 (m, 2H), 2.32 (m, 2H), 3.20 (m, 3H), 3.56 (m, 2H), 7.34 (s, 1H), 8.65 (s, 1H). ^{13}C-NMR (D_2O): δ 30.1 (t), 32.6 (d), 46.3 (t), 117.6 (d), 136.4 (d), 138.4 (s).

4-[4-(4-hydroxy-1-tert-butoxycarbonyl)piperidyl]-(1H)-imidazole **14**

To a solution of 4-bromo-(1H)-imidazole **12** (4.00 g, 27.2 mmol) in dry THF (40 ml) was slowly added n-BuLi (30 ml of a 2.5 M solution in hexane, 75 mmol) with a syringe at -70 °C in a nitrogen atmosphere. The resulting solution was stirred for 1.5 hour at 10-15 °C and cooled again to -70 °C. A solution of N-tert-butoxycarbonyl-4-piperidone **13** (10.83 g, 54.4 mmol) in THF (40 ml) was gradually added with a syringe and the resulting mixture was stirred overnight at room temperature. After acidification with saturated aqueous NH_4Cl, extraction with CH_2Cl_2 (3x), drying over Na_2SO_4 and concentration in vacuo, the resulting crude material was recrystallised from acetonitrile (10 ml). Subsequently, the crystalline material was washed with diethyl ether and dried to give the adduct **14** (1.45 g, 5.43 mmol, 20 %) as white crystals, mp 189.5-190 °C. R_f 0.5 (CH_2Cl_2/MeOH/NH_4OH (25 % aq.) = 85/15/1. IR (KBr): ν 3150 (vb), 1690 (b), 1680 (b), 1370 (s), 1170 (b), 635 (s) cm^{-1}. ^{1}H-NMR (DMSO/$CDCl_3$=4/1): δ 1.41 (s, 9H), 1.68 (m, 2H), 1.84 (m, 2H), 3.21 (m, 2H), 3.64 (m, 2H), 4.77 (br s, 1H), 6.86 (br s, 1H), 7.50 (d, J=1 Hz, 1H), 11.90 (br s, 1H). MS (EI): m/z 267 (M^+), 192, 166, 148, 111, 57. Found: 267.1593. $C_{13}H_{21}N_3O_3$ requires 267.1583.

4-[4-(1,2,5,6-tetrahydropyridyl)]-(1H)-imidazole dihydrochloride **15**

A solution of **14** (2.00 g, 7.49 mmol) in concentrated aqueous HCl (15 ml) was heated for 40 hours at 95 °C. The resulting reaction mixture was evaporated in vacuo and recrystallised from a mixture of acetic acid (20 ml) and water (1ml), to afford **15** (1.61 g, 7.25 mmol, 97 %) as white crystals, mp 287-288 °C. IR (KBr): ν 3145 (b), 2950 (vb), 1590 (s), 1090 (s), 795 (s), 630 (s) cm^{-1}. ^{1}H-NMR (D_2O): δ 2.78 (m, 2H), 3.53 (t, J=6 Hz, 2H), 3.94 (m, 2H), 6.35 (m, 1H), 7.54 (s, 1H), 8.75 (s, 1H). MS (EI): (m/z) 149 (M^+), 134, 119. Found: 149.0948. $C_8H_{11}N_3$ requires 149.0953.

4-(4-piperidyl)-(1H)-imidazole dihydrochloride **11**

A solution of **15** (5.65 g, 25.5 mmol) in a mixture of acetic acid (40 ml) and water (20 ml) was hydrogenated for 24 hours at 50 psi at room temperature in the presence of a catalytic amount of PtO_2. The resulting mixture was filtered and the filtrate was evaporated in vacuo. The resulting crude product was recrystallised from a mixture of ethyl acetate (50 ml) and acetic acid (50 ml) to give **11** (5.00 g, 88 %) as white crystals (mp 300 °C, dec.).

1-(dimethylsulfamoyl)-4-[4-(4-hydroxy-1-tert-butoxycarbonyl)piperidyl]-(1H)-imidazole **20**

To a stirred solution of **19**[17] (17.14 g, 56.9 mmol) in dry dichloromethane (220 ml), ethyl magnesium bromide (20.9 ml, 62.6 mmol; 3 M solution in diethyl ether) was dropwisely added in a nitrogen atmosphere. The resulting solution was stirred for 30 minutes at room temperature and subsequently cooled to - 78 °C. After dropwise addition of a solution of N-tert-butoxycarbonyl-4-piperidone **13** (12.46 g, 62.6 mmol) in dry dichloromethane (110 ml), the resulting solution was allowed to attain room temperature and stirred overnight. The solution was washed (aqueous NH_4Cl) dried over Na_2SO_4, filtered and concentrated in vacuo to afford pure **20** (10.56 g, 50 % yield) after crystallisation (diisopropyl ether; mp 143-6 °C). ^{1}H-NMR ($CDCl_3$) δ 1.47 (s, 9H), 1.84 (m, 2H), 1.93 (dt, J=5 Hz, J=12 Hz, 2H), 2.62 (br s, 1H), 2.88 (s, 6H), 3.31 (br t, 2H), 3.90 (m, 2H), 7.10 (d, J=1 Hz, 1H), 7.85 (d, J=1 Hz, 1H). MS (EI): (m/z) 374 (M^+), 317, 299, 273, 255, 108, 57. Found: 374.1622. $C_{15}H_{26}N_4O_5S_1$ requires 374.1624.

4-(4-(1,2,5,6-tetrahydropyridyl))-(1H)-imidazole dihydrochloride **15**

To a concentrated aqueous HCl solution (90 ml) was added **20** (11.97 g, 32.0 mmol). The resulting solution was stirred for 40 hours at 95 °C, cooled to room temperature and concentrated in vacuo. The resulting solid material was recrystallised (acetic acid (80 ml)/water (4 ml)), and subsequently washed with acetic acid and diethyl ether,

respectively, to give pure **15** (4.13 g; mp 291-2 °C). Crystallisation of the mother liquor afforded another portion of **15** (1.52 g, mp 290-1 °C; 80 % total yield).

4-[4-(1-(cyclohexylaminothioxomethyl)piperidyl)]-(1H)-imidazole **3** (Thioperamide)

To a solution of NaOH (1.88 g, 47 mmol) in methanol (65 ml) was added **11** (4.80 g, 21.4 mmol) and stirred for 30 minutes. The resulting precipitate (NaCl) was removed by filtration and washed with some methanol. The filtrate was concentrated in vacuo. The residue was dissolved in dry acetonitrile (200 ml) and cyclohexylisothiocyanate (3.53 ml, 25.7 mmol) was added. The mixture was stirred for 2 hours at 50 °C followed by 40 hours at room temperature and subsequently evaporated in vacuo. The crude[20] thioperamide was crystallised from a mixture of acetonitrile (40 ml) and ethylacetate (80 ml) to give thioperamide (3.86 g, 62 %) as a white solid, mp 160-162 °C (lit[3] 170 °C). R_f 0.15 (EtOAc/MeOH/NH_4OH(25 % aq.) = 90/10/0.5). Compound **3** showed identical spectral data in comparison with a sample which was kindly supplied by Prof. dr. H. Timmerman, Vrije Universiteit, Amsterdam, The Netherlands. ^{1}H-NMR ($CDCl_3$/DMSO=4/1) δ 1.10 (m, 1H) , 1.17-1.34 (m, 4H), 1.49 (m, 2H), 1.61 (m, 1H), 1.64-1.94 (m, 6H), 2.80 (m, 1H), 3.02 (m, 2H), 4.21 (m, 1H), 4.69 (m 2H), 6.75 (s, 1H), 7.13 (d, J=7-8 Hz, 1H), 7.52 (s, 1H), 11.0-12.5 (m, 1H). MS (EI): (m/z) 292 (M^+), 258, 151, 141, 95. Found: 292.1724. $C_{15}H_{24}N_4S_1$ requires 292.1722.

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20. The crude thioperamide was contaminated by a minor amount of its sodium salt.

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