Synthesis of 3-amino-4-[3-(3-[2,6-^{14}C]-piperidinomethylphenoxy)propylamino] -1,2,5-thiadiazole hydrochloride

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SUMMARY

Synthesis of the title compound (5), an histamine H_2-receptor antagonist, is described. Treatment of 3-(3-[2,6-^{14}C]-piperidinomethylphenoxy)propylamine(1)[1] with 3-amino-4-methoxy-1,2,5-thiadiazole-1-oxide[2] produced 3-amino-4-[3-(3-[2,6-^{14}C]piperidinomethylphenoxy)propylamino]-1,2,5-thiadiazole-1-oxide(2)[3]. Hydrochloric acid extruded sulfoxide producing N-[3-(3-[2,6-^{14}C]-piperidinomethylphenoxypropyl]ethanediimidamide trihydrochloride[4]-(3). Sulfur was then inserted by the action of N,N'-thiobisphthalimide(4) and treatment with hydrochloric acid gave the title compound(5) in an overall yield of 20%.

Key Words:

3-amino-4-[3-(3-[2,6-^{14}C]piperidinomethylphenoxy)propylamino]-1,-2,5-thiadiazole hydrochloride, histamine H_2-receptor antagonist.

INTRODUCTION

Histamine H_2-receptor antagonists have shown to be effective inhibitors of gastric secretion in animals and man.[5]. Clinical evaluation of the histamine H_2-receptor antagonist Cimetidine has been shown to be an effective therapeutic agent for the treatment of peptic ulcer disease.[6] More recently, the developing of Ranitidine[7], Tiotidine[8], Etintidine[9] and Oxmetidine[10] has demonstrated the potential for an increase in potency

0362-4803/88/091035-06$05.00
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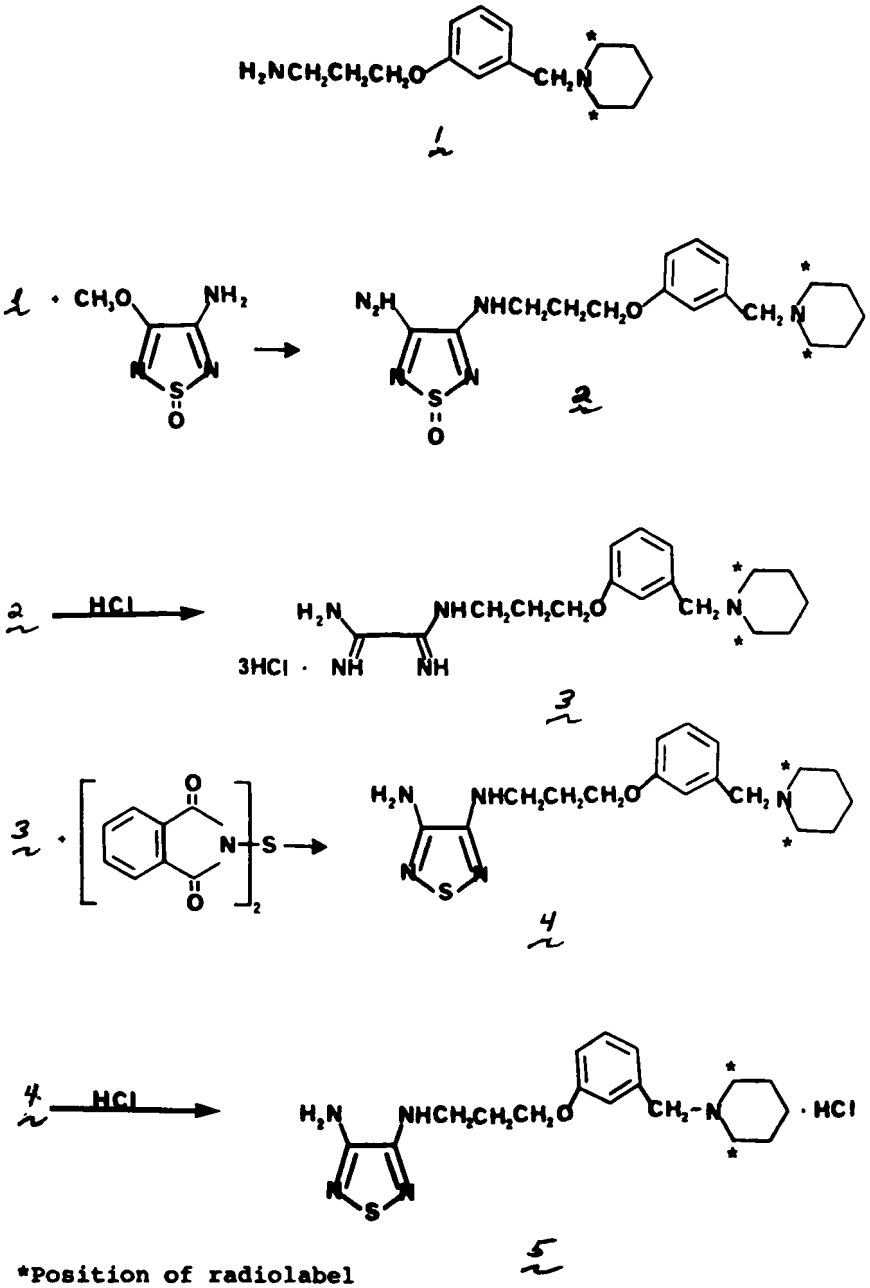
Received October 2, 1987
Revised February 2, 1988

SYNTHETIC PATHWAY



*Position of radiolabel

relative to Cimetidine while maintaining high H_2-receptor specificity.

In this report, we describe the synthesis of 3-amino-4-[3-(3-[2,6-^{14}C]piperidinomethylphenoxy)propylamino]-1,2,5-thiadiazole hydrochloride (5) a potent histamine H_2-receptor antagonist, for metabolism and pharmacokinetic studies.

DISCUSSION

The reaction of 3-(3-[2,6-^{14}C]piperidinomethylphenoxy)propylamine with 3-amino-4-methoxy-1,2,5-thiadiazole-1-oxide went smoothly with a 73% yield of a crystalline material after chromatographic purification. Numerous attempts utilizing both chemical and catalytic methods failed to effect the reduction of the thiadiazole sulfoxide to the thiadiazole. Treatment of 3-amino-4-[3-(3-[2,6-^{14}C]piperidinomethylphenoxy)propylamino]-1,2,5-thiadiazole-1-oxide with a 9 molar excess of ethanolic hydrogen chloride resulted in extrusion of the sulfur from the thiadiazole ring, providing the diimidamide trihydrochloride (3) in 97% yield. Sulfur could be reinserted using, N,N'-thiobisphthalimide, in 60% yield, giving the thiadiazole (4). Attempts to reform the 1,2,5-thiadiazole ring using other reagents, such as SCl_2, gave very low yields. Concentrated hydrochloric acid in isopropyl alcohol yielded the title compounds (5), having a radiochemical purity of 98% as determined by high pressure liquid chromatography utilizing fraction collection and a specific activity of 43.9 μCi/mg. All experimental conditions were optimized using non-radiolabelled materials.

EXPERIMENTAL

[2,6-^{14}C]Piperidine was purchased from Amersham Corporation. All chemicals used in the synthesis were purchased commercially and used without any further purification. All other solvents were either redistilled or of analytical reagent quality. Thin layer chromatography plates used were Analtech silica gel GF, scored 10 x 20 cm, 250 microns. Radioactivity was measured using a Beckman LS9000 liquid scintillation counter. All the high pressure liquid chromatography was carried out on Waters Associates instrumentation. Nuclear magnetic resonance was measured on a Bruker 360. Weighings were carried out on a Sartorius 200 balance and Mettler Microanalytical M5A5 balance.

3-Amino-4-[3-(3-[2,6-^{14}C]piperidinomethylphenoxy)propylamino-1,2,5-thiadiazole-1-oxide(2)

A solution of 3-(3-[2,6-^{14}C]piperidinomethylphenoxy)propylamine[1] (1) (18.4 mg/ml) in methanol was prepared. To the above solution (19 ml) was added

with stirring, 3-amino-4-methoxy-1,2,5-thiadiazole-1-oxide[2] (207 mg, 1 eq). The reaction was stirred at room temperature for 3 hr. Thin layer chromatographv indicated that the reaction was complete. The reaction mixture was concentrated under reduced pressure to an oily solid and the product purified bv column chromatography over silica gel in methanol yielding a crystalline solid (374 mg, 73% yield).

Thin Layer Chromatography: Eluent-methylene chloride (100), methanol (20) and ammonium hydroxide (1), Analtech silica gel plates, visualization with iodine vapors. Product at R_f = 0.51.

High Pressure Liquid Chromatography was carried out using the following parameters: Eluent - methylene chloride (100), methanol (2) and ammonium hydroxide (1). Flow Rate - 2 ml/min. Detector - Ultraviolet at 254 nm. Column - Waters Associates analytical μ-porasil. Temperature - 22.5°C. Retention Time - 3.25 min.

N-[3-(3-[2,6-^{14}C]piperidinomethylphenoxy)propyl]ethanediimidamide trihydrochloride (3)

3-Amino-4-[3-(3-[2,6-^{14}C]piperidinomethylphenoxy)propylamino]-1,2,5-thiadiazole-1-oxide[3] (2) (374 mg) was dissolved in methanol (7.75 ml) and to this was added concentrated hydrochloride acid (0.68 ml). The reaction was stirred at room temperature for 3 hrs. Thin layer chromatography indicated that the reaction was complete. Upon concentration under reduced pressure an oily solid resulted. To this was added isopropyl alcohol (25 ml), which was concentrated under reduced pressure to remove all water as an azeotrope. After the residue was dried under high vacuum for 16 hrs., a crystalline solid resulted. (429 mg), 97% yield.

Thin Layer Chromatography: Eluent-methylene chloride (50), methanol (50), Analtech silica gel plates, visualization with iodine vapors. Product a streak from origin to R_f = 0.15.

High Pressure Liquid Chromatography was carried out using the following parameters: Eluent - 70% aqueous solution of heptanesulfonic acid (0.005M) adjusted to pH 3.5 with glacial acetic acid and 30% acetonitrile. Flow Rate - 2 ml/min. Detector - Ultraviolet at 254 nm. Temperature - 22.5°C. Column - Waters Associates analytical C-18. Retention Time - 5.60 min.

3- Amino-4-[3-(3-[2,6-^{14}C]piperidinomethylphenoxy)propylamino-1,2,5-thiadiazole (4)

N-[3-(3-[2,6-^{14}C]piperidinomethylphenoxy)propyl]ethanediimidamide trihydrochloride[4] (3) (429 mg) was suspended in methylene chloride (6 ml). To this was added triethylamine (0.43 ml), followed by N,N'-thiobisphthalimide (400 mg) and the mixture was stirred under a nitrogen atmosphere at room temperature for 1 hr. To this was added 20% potassium hydroxide (2 ml), water (3 ml) and the layers were separated. The aqueous layer was extracted again with methylene chloride (12 ml). The methylene chloride extracts were combined, dried over magnesium sulfate and concentrated under reduced pressure to an oil. This was dried under high vacuum for 16 hr. The resulting material was purified by column chromatography using silica gel in a mixture of methylene chloride (100), isopropyl alcohol (5) and ammonium hydroxide (1). (210 mg) yield = 60%.

Thin Layer Chromatography: Eluent-methylene chloride (100), isopropyl alcohol (5) and ammonium hydroxide (1), Analtech silica gel plates, visualization with iodine vapors. Product R_f = 0.33.

High Pressure Liquid Chromatography was carried out using the following parameters: Eluent - 70% aqueous solution of heptanesulfonic acid (0.005M) adjusted to pH 3.5 with glacial acetic acid and 30% acetonitrile. Flow Rate - 2 ml/min. Detector - Ultraviolet at 313 nm. Temperature - 22.5°C. Column - Waters Associates analytical C-18. Retention Time - 4.9 min.

3-Amino-4-[3-(3-[2,6-^{14}C]piperidinomethylphenoxy)propylamino]-1,2,5-thiadiazole hydrochloride (5)

3-Amino-4-[3-(3-[2,6-^{14}C]piperidinomethylphenoxy)propylamino]-1,2,5-thiadiazole [4] (4) (210 mg) was dissolved in isopropyl alcohol (10 ml) and to this was added concentrated hydrochloric acid (50 µl). The reaction was stirred at room temperature for 10 min. and then concentrated under reduced pressure to an oily solid. Last traces of water were removed as an azeotrope with isopropyl alcohol (3 x 5 ml). To the resulting foam was added isopropyl alcohol (2 ml) and seeds of non-radiolabelled product, the mixture was stirred at room temperature for 2 hrs. The resulting crystalline solid was removed by filtration and dried under high vacuum for 16 hrs (106 mg) yield = 46%. Radiochemical purity 98% as measured by high pressure liquid chromatography and specific activity = 43.9 µCi/mg.

High Pressure Liquid Chromatography was carried out using the following parameters: Eluent - 70% aqueous solution of heptanesulfonic acid (0.005M) adjusted to pH 3.5 with glacial acetic acid and 30% acetonitrile. Flow Rate - 2 ml/min. Detector - Ultraviolet at 254 nm. Temperature - 22.5°C. Column - Waters Associates analytical C-18. Retention Time - 4.9 min.

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