Synthesis of 1-Amino-2- β-(3- [2,6-^{14}C] piperidinomethylphenoxy) propylamino] -1-cyclobutene-3,4-dione Hydrochloride.

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SUMMARY

The synthesis of the title compound (6) is described. The condensation of 3-aminopropanol with phthalic anhydride and subsequent treatment with phosphorous tribromide produced N-[3-bromopropyl] phthalimide. Acylation with 3-hydroxybenzaldehyde, reduction with hydrogen over Raney nickel and subsequent treatment with thionyl chloride gave N-[3-(3-chloromethylphenoxy) propyl] phthalimide (2). Treatment with [2, 6 -^{14}C] piperidine introduced the radiolabel (3). Deprotection of the amino group with hydrazine and treatment with 3-methoxy-4-amino-3-cyclobutene-1,2-dione produced 1-amino-2- [3-(3-[2,6-^{14}C] piperidinomethylphenoxy) propylamino]-1-cyclobutene-3, 4-dione (5). Treatment with hydrochloric acid yielded the title compound (6) in an overall chemical yield of 22%.

Key Words:

1-Amino-2- [3-(3-[2,6-^{14}C] piperidinomethylphenoxy) propylamino] -1-cyclobutene-3,4-dione hydrochloride, [2, 6-^{14}C] piperidine, H_2-receptor antagonists.

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INTRODUCTION

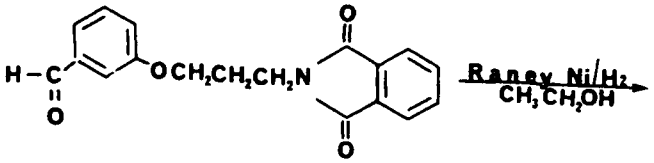
Histamine H_2-receptor antagonists have been shown to be effective inhibitors of gastric secretion in animals and man[1]. Clinical evaluation of the histamine H_2-receptor antagonist cimetidine has been shown to be an effective therapeutic agent in the treatment of peptic ulcer disease[2]. 1-Amino-2-[3-(3-piperidinomethylphenoxy)propylamino]-1-cyclobutene-3,4-dione hydrochloride has been compared with cimetidine in animals and has been found to be more potent both as a histamine H_2-receptor antagonist and as an inhibitor of gastric acid secretion.[3]

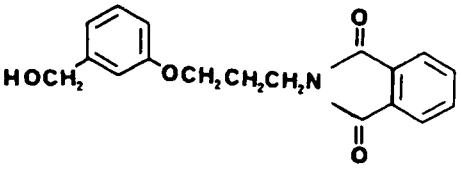
In this report, we describe the synthesis of 1-amino-2-[3-(3-[2, 6-^{14}C]-piperidinomethylphenoxy) propylamino]-1-cyclobutene-3,4-dione hydrochloride (6) for metabolism and pharmacokinetic studies utilizing both published and unpublished chemistry.[3,4,5,6] (See Synthetic Pathway scheme).

DISCUSSION AND RESULTS

[2,6 - ^{14}C] Piperidine was synthesized by Amersham Corporation by the reduction of [2,6 - ^{14}C] pyridine. The [2,6 - ^{14}C] piperidine underwent radiolysis very rapidly producing various decomposition products either as the undiluted compound or in solution. In contrast, the hydrochloride salt was stable both as a solid and in solution. The [2,6 - ^{14}C] piperidine was used directly upon receipt from Amersham Corporation. It was immediately diluted with a specific amount of non-radioactive piperidine and reacted with N-[3-(3-chloromethylphenoxy) propyl] phthalimide[5] under anhydrous conditions in acetonitrile. After column chromatography utilizing silica gel and elution with 5% methanol in methylene chloride, a light brown oil was isolated in a yield of 55%. This material was stable as an oil and in methanol and was reacted with anhdyrous hydrazine in anhydrous ethanol to remove the phthaloyl protecting group. Column chromatography using silica gel in 5% ammonium hydroxide in methanol produced a light yellow oil. A unique observation of ours

Synthetic Pathway





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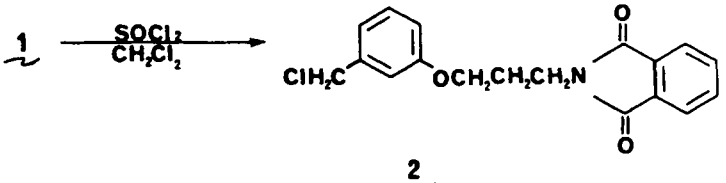

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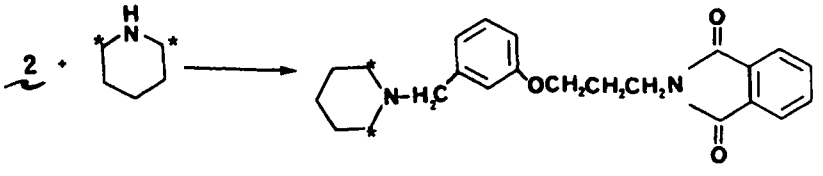

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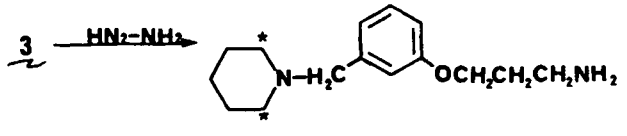

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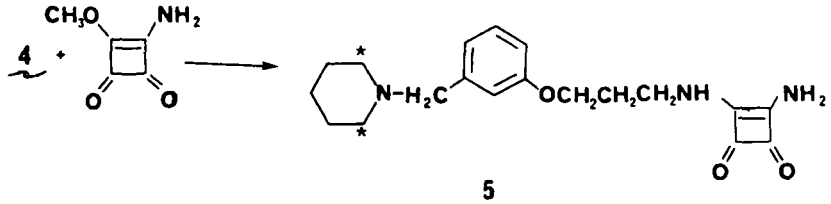
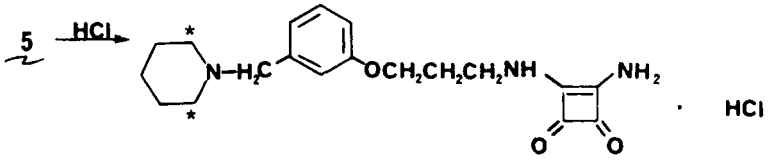
*Position of radiolabel

Synthetic Pathway

(continued)





*Position of radiolabel

was that this material underwent radiolysis very rapidly as a neat oil. In a seven day period 90% of the material degraded as evidenced by the appearance of additional components on a thin layer chromatography plate . By contrast as a solution in methanol, the material was stable for several months. Consequently, a standard solution, analyzed by high pressure liquid chromatography was established for use in subsequent reactions. A given volume of this methanol solution of 3-(3-[2,6-^{14}C] piperidinomethylphenoxy) propylamine (4) was reacted with a 20% excess of 3-methoxy-4-amino-3-cyclobutene-1,2-dione[6] producing compound (5) of sufficient purity to be used in the next reaction. Reaction with 1N hydrochloric acid in a one to three mixture of isopropyl alcohol and acetone produced crystalline desired product (6) in an overall yield of 22%. All experimental conditions were optimized using non-radioactive materials.

EXPERIMENTAL

MATERIALS

[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 thickness. Radioactivity was measured by a Beckman LS9000 liquid scintillation counter. All the high pressure liquid chromatography was carried out on Water Associates instrumentation. Nuclear magnetic resonance was measured on a Bruker 360. Weighings were carried out on a Satorius 200 balance and a Mettler Microanalytical M5AS balance.

N-3- [3-(N- [2,6 - ^{14}-C] Piperidinomethylphenoxy) propyl] phthalimide (3)

[2, 6 -^{14}C]Piperidine (469 mg, 180 mCi) in acetonitrile (52 ml) was transferred into a 100 ml round bottom flask. Non-radioactive piperidine (296 mg) was added producing a total of 8.99 mmoles of piperdine. To this was added N-[3-(3-chloromethylphenoxy) propyl] phthalimide[5] (2.29g, 7.5 mmoles) followed by powdered 4A molecular sieves (1.28 g) and stirred at room temperature for 48 hrs. The reaction mixture was filtered to remove the molecular sieves and the filtrate concentrated under reduced pressure to a light brown oil, which was dissolved in methylene chloride (50 ml) and layered with water (50 ml). The aqueous layer was adjusted to pH 12 with aqueous sodium carbonate. The layers were separated and the aqueous layer again extracted with methylene chloride (1 x 50 ml). The methylene chloride extracts were combined, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to an oil. A chromatography column was prepared using silica gel (100 g, 63-200 mesh, Woelm) in 5% methanol/methylene chloride. Application of the oil, elution and collection of desired product yielded compound (3) 1.56 g. with a yield of 55%.

Thin Layer Chromatography: 5% methanol in methylene chloride, Analtech silica gel plates, visualization with iodine vapors. Product at Rf = 0.20.

High Pressure Liquid Chromatography was carried out in Waters Associates instrumentation with the following parameters: Eluent - 40% aqueous solution of heptanesulfonic acid (0.005M) adjusted to pH 3.5 with glacial acetic acid and 60% methanol. Flow Rate - 2 ml/min. Detector - Ultraviolet at 254 nm. Temperature - 22.5°C. Column - Waters Associates analytical C-18. Retention Time - 5.92 min.

3-(3- [2,6 - ^{14}-C] Piperidinomethylphenoxy) propylamine (4)

N-3- [3-(N- [2,6 - ^{14}C] piperidinomethylphenoxy) propyl] phthalimide (3), (1.56 g, 4.12 mmoles) was dissolved in anhydrous ethanol (70 ml). To this was added anhydrous hydrazine (0.61 ml, 19 mmoles), and the mixture was stirred at room temperature for 16 hrs., followed by concentration under reduced pressure and trituration with diethyl ether (75 ml). The insoluble material was removed by filtration and washed with diethyl ether (50 ml). The filtrate was extracted with 20% sodium hydroxide solution (125 ml), the ether layer separated, and dried over anhydrous magnesium sulfate and concentrated under reduced pressure to a yellow oil. This oil was purified by column chromatography utilizing silica gel (100 g, 63-200 mesh, Woelm) and an eluent of 5% ammonium hydroxide in methanol. The purified material was dissolved in methanol (50 ml). High pressure liquid chromatography determined that 18.4 mg/ml of pure desired product was present.

Thin Layer Chromatography: 5% ammonium hydroxide in methanol, Analtech silica gel plates, visualization was with iodine vapors. Product at Rf = 0.63.

High Pressure Liquid Chromatography was carried out on Waters Associates instrumentation with the following parameters: Eluent - 40% aqueous solution of heptansulfonic acid (0.005M) adjusted to pH 3.5 with glacial acetic acid and 60%

methanol. Flow Rate -2 ml/min. Detector - Ultraviolet at 254 nm. Temperature - 22.5°C. Column -Waters Associates analytical C-18. Retention Time - 23.02 min.

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

Methanol (4 ml) was added to an aliquot (2.83 ml) of the methanol solution from the previous reaction and stirred with 3A molecular sieves at room temperature for 4 hrs. The molecular sieves were removed by filtration and to the filtrate was added 3-methoxy-4-amino-3-cyclobutene-1,2-dione[6], (32 mg, 20% excess). The reaction mixture was stirred at room temperature for 16 hrs. The resulting solid was removed by filtration and washed with methanol (0.5 ml) producing compound (5) 65 mg; yield of 91%.

High Pressure Liquid Chromatography was carried out on Waters Associates instrumentation with the following parameters: Eluent - 60% aqueous solution of heptanesulfonic acid (0.01M) adjusted to pH 3.5 with glacial acetic acid and 40% methanol. Flow/Rate -2 ml/min. Detector - Ultraviolet at 254 nm. Temperature - 22.5°C. Column - Water Associates analytical C-18. Retention Time - 33.6 min.

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

1-Amino-2-[3-(3-[2,6 -^{14}C] piperidinomethylphenoxy) propylamino] -1-cyclobutene-3, 4-dione (5) (65 mg) was suspended in isopropyl alcohol (250 µl) and to this was added with stirring, 1N hydrochloric acid (200 µl). The mixture was stirred at room temperature for 15 min., filtered and to the filtrate was added acetone (730 µl). This mixture was stirred at room temperature for 3 hrs. A crystalline solid resulted. It was isolated by centrifugation and decantation. The crystalline solid was dried under high vacuum (0.1 mm) for 16 hrs producing the title compound (6) 39 mg; yield 54 %.

High Pressure Liquid Chromatography was carried out on Waters Associates instrumentation with the following parameters: Eluent - 60% aqueous solution of heptanesulfonic acid (0.01M) adjusted to pH 3.5 with glacial acetic acid and 40% methanol. Flow Rate - 2 ml/min. Detector- Ultraviolet at 254 nm. Temperature - 22.5°C. Column - Waters Associates analytical C-18. Retention Time - 34.3 min.

Specific Activity: 44.4 μCi/mg

Radiochemical purity: 97%

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