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SYNTHESIS OF [^{14}C]IMIDAZOLE RING LABELED METIAMIDE, CIMETIDINE and IMPROMIDINE

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SUMMARY

The radiosynthesis of imidazole ring labeled [^{14}C]metiamide, [^{14}C]cimetidine and [^{14}C]impromidine are described involving the reaction of the key common intermediate 2-[[(4-methyl-1H-[2-^{14}C]imidazol-5-yl)methyl]thio]ethanamine (5) with methyl isothiocyanate, dimethyldithiocyanoiminocarbonate/methylamine and the novel dihydroimidazodiazepine (8), respectively. The ring labeled precursor (5) was prepared in five steps from potassium [^{14}C]cyanide in an overall radiochemical yield of 63%, and having a specific activity of 9.3 mCi/mmol.

Key Words: [^{14}C]impromidine, [^{14}C]metiamide, [^{14}C]cimetidine, 2-[[(4-methyl-1H-[2-^{14}C]imidazol-5-yl)-methyl]thio]ethanamine, histamine H_2-receptor antagonist, histamine H_2-receptor agonist, [^{14}C]imidazole ring labeled.

INTRODUCTION

The chemical modification of histamine in our laboratories led to the discovery of a new class of pharmacologically active agents, which were classified as H_2-receptor antagonists. Two antagonists, metiamide (1) (SK&F 92058, 6) and cimetidine (2) (SK&F 92334, 7) were first labeled in our laboratories (3) with tritium and sulfur-35 in order to facilitate the start of important metabolism studies (4,5). However, due to the lability of tritium in the 2-position of the imidazole ring to exchange in biological media, and the short half-life of sulfur-35, the development of a method to incorporate an isotope of longer half-life in a more metabolically stable position was undertaken. Thus, [^{14}C]imidazole ring labeled metiamide and cimetidine were prepared with carbon-14 in the 2-position of the imidazole ring (Scheme 1) for use in distribution, excretion and metabolism studies (6,7). Impromidine (SK&F 92676, 10) (Scheme 2), an extremely potent and specific agonist (8) for histamine-H_2-receptors, was also prepared for use in studies designed to delineate the role of histamine at the H_2-receptor sites in man (9-11).

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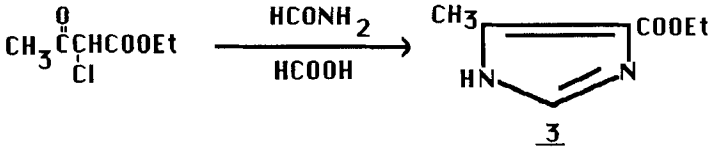
RESULTS AND DISCUSSION

Of the many synthetic approaches available for the construction of the imidazole ring system, the Bredereck reaction (12) was identified as a potential approach.



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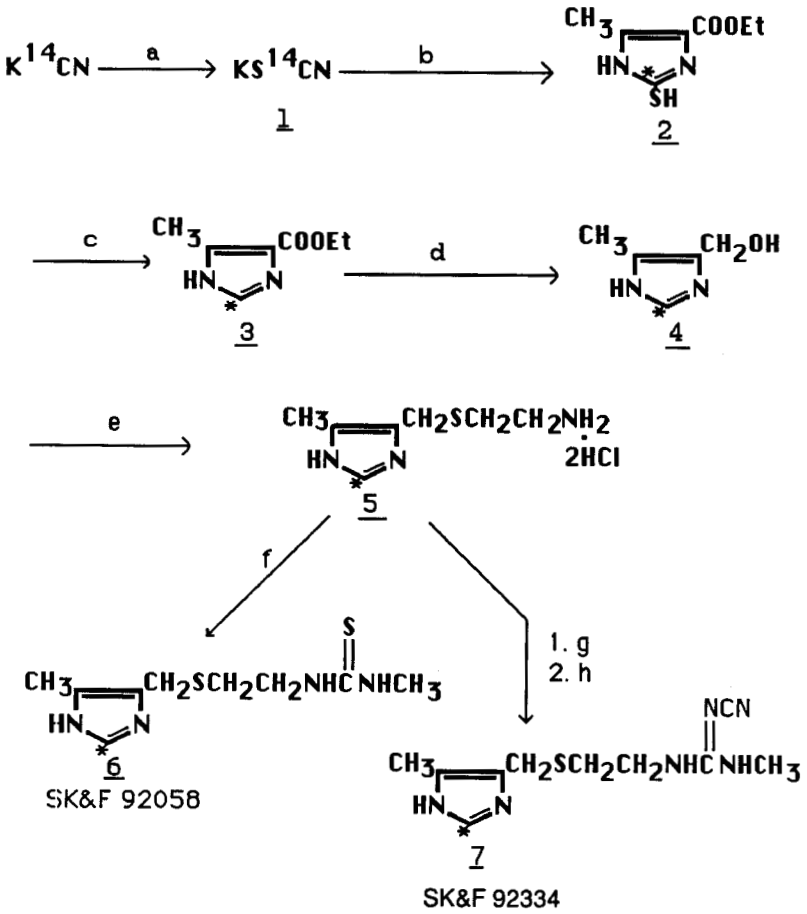
The adaptation of the Bredereck reaction to the isotopic synthesis of 3 proved to be problematical giving consistantly low yields (33%) of 3, under a wide variety of reaction conditions. Furthermore, the use of this approach would require ethyl [2 or 3-^{14}C]chloroacetoacetate. Since large amounts of labeled 3 were required, purchase of ethyl [2 or 3-^{14}C]chloroacetoacetate was not a viable option, and the literature procedures for its synthesis gave variable and largely unacceptable results. Unable to adapt the Bredereck reaction satisfactorily to the preparation of isotopically labeled 3, an alternative approach was developed (Scheme 1) from which the key intermediate (5) was obtained in high radiochemical yield and purity. Thus, the condensation of potassium [^{14}C]thiocyanate (13) with ethyl 2-aminoacetoacetate hydrochloride (14,15) gave the thiol (2) (16) in excellent yield. The desulfurization of 2 was initially carried out with activated Raney nickel affording 3 in 68% yield. The low yield was attributed to difficulties associated with the isolation of 3 from the catalyst surface. A more efficient desulfurization procedure proved to be reaction with non-pyrophoric Raney alloy in refuxing formic acid (17). This procedure gave 3 in 96% radiochemical yield. Subsequent reduction of 3 with lithium aluminumhydride, followed by reaction with 2-aminoethanethiol hydrochloride gave the desired product 5 in 63% overall radiochemical yield with a radiochemical purity and specific activity of 97% and 9.3 mCi/mmol, respectively.

The H_2-agonist [^{14}C]impromidine 10 was prepared as shown in Scheme 2 (18). The free base of 5 was treated with diazepin (8) in refluxing ethanol for 20 hours, and gave 9 in 78% radiochemical yield after HPLC purification. The hydrolysis of 9 in concentrated hydrochloric acid at reflux for 24 hours gave (10). Recrystallization gave 4.5 mCi of 10 (45% overall radiochemical yield).

SCHEME I



* Denotes position of carbon-14

[a] S/acetone

[b] $CH_3COCH(NH_2)COOC_2H_5$/aqueous ethanol

[c] Raney alloy/formic acid

[d] $LiAlH_4$/tetrahydrofuran

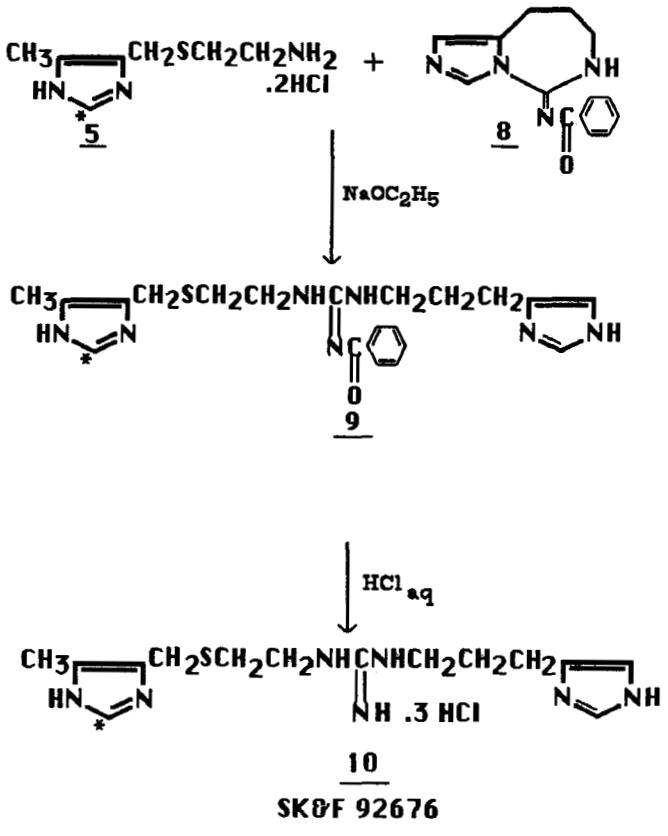
[e] $HSCH_2CH_2NH_2.HCl$/acetic acid

[f] methyl isothiocyanate

[g] $NaOC_2H_5/(CH_3S)_2C{=}NCN$

[h] CH_3NH_2

SCHEME II



*Denotes position of carbon-14

EXPERIMENTAL

Potassium [^{14}C] cyanide at 60 mCi/mmol was purchased from Amersham Corporation, and was diluted to 10 mCi/mmol prior to use. Raney alloy was purchased from W. R. Grace & Co.; sold under the trade name Raney Catalyst Powder. Radiochemical purities were determined by TLC-Scanning on the Berthold radioscanner/integrater (model 6000-10), by autoradiography and by segmentation of TLC plates followed by liquid scintillation counting. Radiochromatograms were obtained using Analtech silica gel GF and Merck Kieselgel/Kieselguhr F254 plates. Radioactivity measurements were carried out using a Beckman LS 6800, Packard Tri-Carb 3003 and Nuclear Enterprise NE 8212 liquid scintillation counters.

Potassium [^{14}C] thiocyanate (1)

A mixture of 250 mCi of potassium [^{14}C] cyanide (1.63 g, 25 mmol), elemental sulfur (0.8 g, 25 mmol) and acetone (50 mL) was heated at reflux for 2 hours. The reaction mixture was cooled, filtered and concentrated in vacuo. The crude product was obtained as a tan solid, which was further dried at 50 °C under vacuum. This procedure gave a quantitative yield of 1 (2.4 g) which was used directly in the next step.

Ethyl 4-methyl-2-mercapto-1H-[2-^{14}C]imidazole-5-carboxylate (2)

A solution of ethyl 2-aminoacetoacetate hydrochloride (5.45 g, 30 mmol) in a mixture of water (110 mL), absolute ethanol (15 mL) and concentrated hydrochloric acid (1.2 mL, 15 mmol) was added to a solution of 2.4 g (250 mCi, 25 mmol) potassium [^{14}C] thiocyanate in 12.5 mL of water. The reaction mixture was refluxed for 2 hours, cooled in an ice bath and the pure white solid collected by filtration. The solid was washed with water, then dried at 50 °C under aspirator vacuum to give 3.9 g of 2 (209 mCi, 21 mmol) with a radiochromatographic purity of >99% by TLC (silica gel GF: chloroform/methanol/ammonium hydroxide; 90:10:0.5, by volume). The radiochemical yield was 84% based on potassium [^{14}C] cyanide.

Ethyl 4-methyl-1H-[2-^{14}C]imidazole-5-carboxylate (3)

The product from the previous step was dissolved in 80% formic acid (65 ml), 2.46 g of Raney alloy (50 % Ni by weight, 21 mmol Ni) was added, and the mixture was heated at reflux. The course of the reaction was monitored by hydrogen sulfide evolution. After 45 minutes the evolution of hydrogen sulfide ceased, and the reaction mixture was cooled to room temperature and filtered through Celite. The Celite was washed with 90% formic acid and the combined filtrates concentrated in vacuo. The resulting oil was dissolved in water (50 mL) and neutralized to pH 7 with concentrated ammonium hydroxide. The precipitate was filtered off, washed with water and dried at 50°C under aspirator vacuum to give 3.1g of 3 (200 mCi, 20 mmol) with a radiochemical purity of ≥99% by TLC (silica gel GF: chloroform/methanol/ammonia; 80:20:0.5, by volume). The radiochemical yield was 96%.

5-Hydroxymethyl-4-methyl-1H-[2-^{14}C]imidazole (4)

To a stirred suspension of lithium aluminumhydride (1.5 g, 39 mmol) in tetrahydrofuran (15 mL), under nitrogen and with ice bath cooling, was added a suspension of finely ground 3 (3.1g, 200 mCi, 20 mmol) in tetrahydrofuran (15 mL) over a 10 minute period. After the addition, the mixture was refluxed for 10 minutes. The reaction was then cooled to ice bath temperature and very slowly quenched by the addition of water (4 mL). The suspension was allowed to warm to room temperature, treated with methanol (50 mL) and then heated to near reflux temperature. The suspension was filtered(while hot) through a bed of Celite. The Celite was washed several times with hot methanol, and the combined filtrates acidified with a solution of 6.4 N HCl in isopropanol (6 mL, 1:1v/v). The acidic solution was concentrated in vacuo and then the semi-solid residue

triturated with 60 mL of diethyl ether/acetone (1:1 v/v).
A few drops of methanol were added to produce a crystalline solid. The solid was collected by filtration and dried at 50 °C under aspirator vacuum to give 2.5 g of 4 (168 mCi, 16.8 mmol) with a radiochromatographic purity of 98.8% by TLC (vide supra). The radiochemical yield was 84%.

2-[[(4-methyl-1H-[2-^{14}C]imidazol-5-yl)methyl]thio]ethanamine, dihydrochloride (5)

A mixture of 2.5 g (168 mCi, 16.8 mmol) 4, and 1.9 g (16.8 mmol) 2-aminoethanethiol hydrochloride in 17 mL glacial acetic acid was refluxed for 17 hours. The reaction was cooled, then stirred at room temperature for 1 hour. The resulting white solid was filtered, washed with ethanol, diethyl ether and dried at 50 °C under aspirator vacuum to give 4.2 g of 5 (156.6 mCi) with a radiochromatographic purity of 97 % by TLC (silica gel GF: ethyl acetate/methanol/ammonium hydroxide; 50:50:5, by volume). The radiochemical yield was 93.4 % and the specific activity 9.3 mCi/mmol.

N-methyl-N'-[2-[[(5-methyl-1H-[2-^{14}C]imidazol-4-yl)methyl]thio]ethyl]thiourea (6)

A mixture of 1.12 g of 5 (39.2 mCi, 4.6 mmol) (an impure lot of the previously prepared product), and 0.63 g of potassium carbonate (4.6 mmol) in 11 mL of water was stirred for 15 minutes at room temperature, then 0.4 g of methylisothiocyanate (5.5 mmol) added in one portion. The reaction mixture was refluxed for 45 minutes, and the resulting solution concentrated by distillation at atmospheric pressure, then cooled to room temperature and stirred in an ice/water bath for 30 minutes. The resulting tannish-yellow solid was filtered and washed with cold water (2 x 10 mL), acetone (2 x 10 mL), and then dried under aspirator vacuum at 50 °C to give 0.8 g of 6 (30.4 mCi, 3.27 mmol) with a radiochromatographic purity of 98.5% by TLC (silical gel GF: ethylacetate/methanol/ ammonium hydroxide; 100:10:5, by volume). The radiochemical yield was 78% and the specific activity 9.3 mCi/mmol.

N-Cyano-N'-methyl-N"-[2-[[(5-methyl-1H-[2-^{14}C]imidazol-4-yl)methyl]thio]ethyl]guanidine (7)

Diluted 5 (0.38 g, 0.8 mCi, 1.6 mmol,) was dissolved in ethanol (35 mL) and an ethanolic solution of sodium ethoxide added (2.1 mL of 172 mg of sodium in 5 mL ethanol, 3.1 mmol). The reaction mixture was evaporated to dryness in vacuo and the residue taken up in chloroform (50 mL) and filtered. The chloroform solution was evaporated to dryness in vacuo to yield 0.27 g (1.6 mmol) of a colorless oil, which was dissolved in ethanol (10 mL). Dimethyldithiocyanoimino-carbonate (0.23 g, 1.6 mmol) was then added and the mixture stirred for 20 hours at room temperature. The reaction was 94% complete by TLC (silica: ethyl acetate/methanol/ammonia; 10:1:1, by volume). A solution of methylamine in ethanol (10 mL, 0.78 g/mL) was added and the reaction mixture was stirred for 40 hours at room temperature. The reaction mixture was evaporated to dryness in vacuo and the resulting oil crystallized from isopropanol to yield 0.59 mCi 7 (0.5 mCi/mmol) for a radiochemical yield of 74%.

N-benzoyl-N'-[3-(1H-imidazol-4-yl)propyl]-N"-[2-[[(5-methyl-1H-[2-^{14}C]imidazol-4-yl)methyl] thio]ethyl]guanidine (9)

To a stirred suspension of 298 mg 5 (10 mCi, 1.2 mmol) in 15 mL of ethanol was added 5 mL of an ethanolic, 0.5 M sodium ethoxide solution (2.5 mmol). The solution was warmed to 60 ^{o}C and stirred for 30 minutes before evaporation to dryness in vacuo. The residue was extracted with dichloromethane (3 x 10 mL) and the combined filtered extracts evaporated in vacuo to yield the free base of 5. This was dissolved in ethanol (10 mL), 299 mg of 8 (1.2 mmol) was added and the resulting mixture was refluxed for 20 hours. The ethanol was evaporated in vacuo and the residue purified by normal phase semi-preparative HPLC using the following conditions:

Column: 30 cm x 8 mm ID Whatman Partisil 10 μm (slurry packed vertically at 5000 psi)
Mobile Phase: dichloromethane/methanol/ammonia (90:10:1, by volume)
Flow Rate: 3 ml/min
Detection: UV @ 235 nm
Retention Time: 3.5 min

This procedure gave 401 mg of the purified intermediate 9 (7.8mCi, 0.94 mmol) in 78% radiochemical yield.

N-[3-(1H-imidazol-4-yl)-propyl]-N'-[2-[[(5-methyl-1H-[2-^{14}C]imidazol-4-yl)methyl]thio]ethyl] guanidine, trihydrochloride (10)

A mixture of 401 mg 9 (7.8 mCi, 0.94 mmol) in 40 mL of concentrated hydrochloric acid was refluxed for 24 hours. The resulting solution was reduced in volume to 10 mL and extracted with diethyl ether (3 x 5 ml) in order to remove the benzoic acid formed. The acidic solution was then concentrated in vacuo, and the residue azeotroped several times with ethanol. The residue was then recrystallized twice from ethanol/ethyl ether to give 4.5 mCi of (10) with a specific activity of 8.2 mCi/mmol, and a radiochemicalpurity of 97.5% by TLC and autoradiography (Merck Kieselgel: ethylacetate/methanol/ ammonia; 5:1:1, by volume) and n-propanol/ammonia; 7:3, v/v).The radiochemical yield from 5 was 45%.

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