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Research Article

Synthesis of triple [^{14}C]-labeled moxonidine

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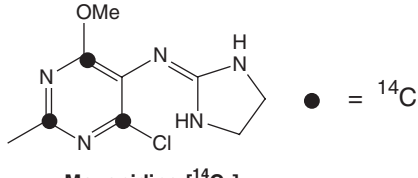
Summary

The synthesis of radiolabeled antihypertensive compound [2,4,6-$^{14}C_3$]-4-chloro-5-(imidazolidin-2-ylidenimino)-6-methoxy-2-methylpyrimidine ([$^{14}C_3$]moxonidine) was accomplished based on condensation of [1-^{14}C]acetamidine with diethyl [1,3-$^{14}C_2$]malonate to form [2,4,6-$^{14}C_3$]-4,6-dihydroxy-2-methylpyrimidine. Subsequent nitration, chlorination, and hydrogenation gave [2,4,6-$^{14}C_3$]-4,6-dichloro-2-methyl-5-aminopyrimidine. The final product was obtained after the coupling of the above aminopyrimidine with 1-acetylimidazolidin-2-one, followed by hydrolysis using sodium methoxide. Copyright © 2004 John Wiley & Sons, Ltd.

Key Words: antihypertensive; moxonidine; synthesis; ^{14}C labeled

Introduction

Moxonidine (4-chloro-5-(imidazolidin-2-ylidenimino)-6-methoxy-2-methylpyrimidine, LY 326869) is a new antihypertensive agent that acts on central nervous system imidazoline receptors to decrease sympathetic nervous system tone.[1–3] It is marketed in Europe and is generally well tolerated by hypertensive patients with fewer adverse reactions compared to the first generation α_2 agonist, clonidine.[4–6] For metabolism and pharmacokinetics studies of moxonidine in humans[7] a high specific activity radiolabeled material was required. A synthesis of moxonidine, containing three ^{14}C's in the pyrimidine fragment of the molecule, is described herein.



Moxonidine-[$^{14}C_3$]

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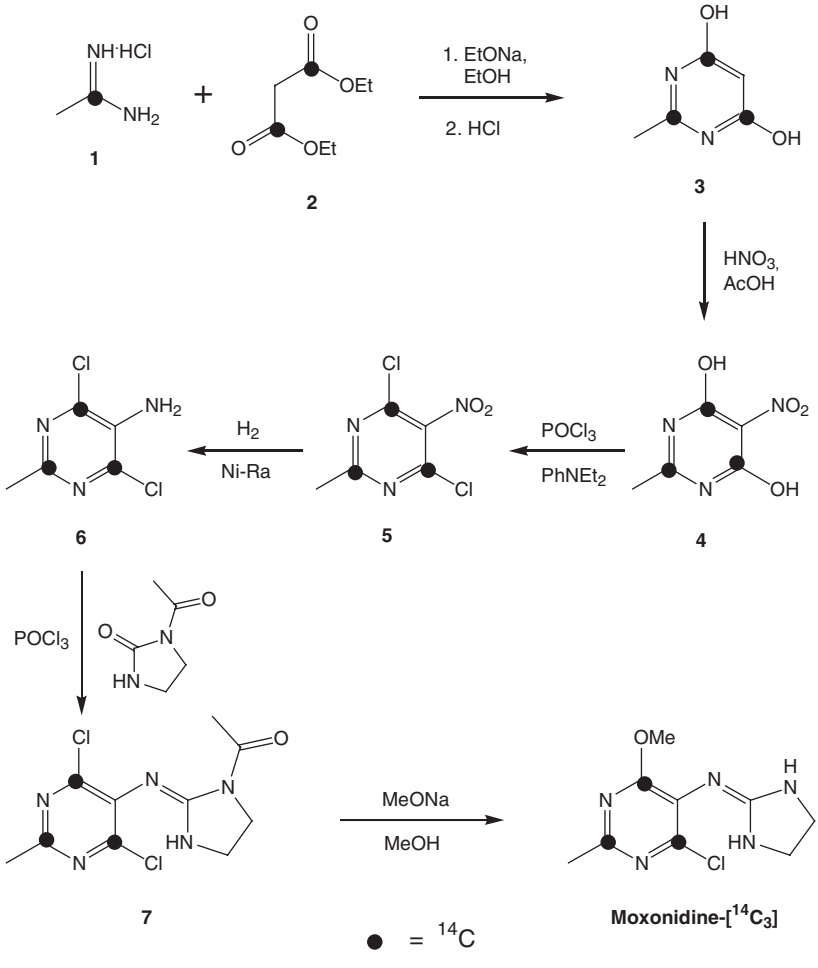
Results and discussion

The synthetic approach to the moxonidine molecule relies on the phosphorus oxychloride mediated coupling of a 5-aminopyrimidine[8–10] with a protected cyclic urea.[11] The introduction of the radiocarbons in the pyrimidine moiety was achieved by the base induced condensation[8] of [1-^{14}C]acetamidine hydrochloride (**1**) with diethyl [1,3-$^{14}C_2$]malonate (**2**) to give [2,4,6-$^{14}C_3$]-4,6-dihydroxy-2-methylpyrimidine (**3**). Nitration of **3** with a mixture of nitric and acetic acids[8,9] afforded [2,4,6-$^{14}C_3$]-4,6-dihydroxy-2-methyl-5-nitropyrimidine (**4**). A minimal volume of the nitration solution was used in order to achieve a good yield of the nitro product. It was then treated with phosphorus oxychloride in the presence of *N,N*-diethylaniline[9,10] to form [2,4,6-$^{14}C_3$]-4,6-dichloro-2-methyl-5-nitropyrimidine (**5**). Reduction of the nitro group by hydrogenation over Raney nickel smoothly gave [2,4,6-$^{14}C_3$]-4,6-dichloro-2-methyl-5-aminopyrimidine (**6**), without hydrogenolysis of the aromatic



chloride. Coupling of amine **6** with 1-acetylimidazolidin-2-one and phosphorus oxychloride[11] led to [2,4,6-$^{14}C_3$]-4,6-dichloro-5-(1-acetylimidazolidin-2-ylidenimino)-2-methylpyrimidine (**7**). Finally, simultaneous hydrolysis of acetamide and nucleophilic substitution, using sodium methoxide in methanol, gave the desired product, [$^{14}C_3$]moxonidine. After crystallization from ethanol the desired product had radiochemical purity 99.1%, and specific activity 632 μCi/mg.

Experimental

The acetamidine-[1-^{14}C] hydrochloride and the diethyl malonate-[1,3-$^{14}C_2$] were purchased from NEN Life Science Products and Amersham Life Science, respectively. Flash chromatography was performed on silica gel 60 (230–400 mesh). TLC was conducted on pre-coated plates of silica gel 60 F_{254}. The ^{1}H-NMR spectra were obtained on a General Electric QE-300. The chemical shifts are reported in ppm downfield from tetramethylsilane. The radiochemical purity of the final material was determined by radio-HPLC on a Hitachi L-7000 instrument using Nucleosil-C8 column (4.6 × 250 mm); eluting with mobile phase consisting of 0.02 M 1-pentanesulfonic acid sodium salt adjusted to pH 3.5 with phosphoric acid, and acetonitrile. All ^{14}C-compounds were identified by TLC and/or HPLC comparison with the corresponding non-radiolabeled isotopomers prepared according to reference methods.[8–11]

[2,4,6-$^{14}C_3$]-4,6-Dihydroxy-2-methylpyrimidine, 3

To a stirred solution of sodium ethoxide, prepared from sodium (210 mg, 9.13 mmol) and ethanol (4 ml), was added [1-^{14}C]acetamidine hydrochloride (**1**) (150 mCi, 48.92 mCi/mmol, 3.066 mmol) in one portion (rinsed with ethanol, 0.5 ml). After 5 min diethyl [1,3-$^{14}C_2$]malonate (**2**) (300 mCi, 111 mCi/mmol, 2.7 mmol) was added into the above suspension (rinsed with ethanol, 1 ml). The reaction mixture was refluxed (85°C bath) for 3 h, allowed to cool to room temperature, and diluted with water (4 ml). After all the precipitate was dissolved, concentrated hydrochloric acid (0.6 ml) was added dropwise. The precipitate was collected, washed with water (2 ml), ethanol (2 ml), ether (2 ml), and dried under vacuum to give 246 mg (69%) of [2,4,6-$^{14}C_3$]-4,6-dihydroxy-2-methylpyrimidine (**3**) as a white solid. For the non-radioactive compound (prepared in a model experiment): ^{1}H-NMR (DMSO-D_6, δ): 2.20 (s, 3 H), 3.33 (s, 2 H), 4.94 (s, 1 H).

[2,4,6-$^{14}C_3$]-4,6-Dihydroxy-2-methyl-5-nitropyrimidine, 4

To a mixture of nitric acid (fuming, 0.5 ml) and acetic acid (glacial, 0.25 ml) at 10–15°C was added [2,4,6-$^{14}C_3$]-4,6-dihydroxy-2-methylpyrimidine (**3**)

(246 mg, 1.86 mmol) in portions over a period of 30 min. The reaction mixture was stirred for 3 h at room temperature, then cooled to 0°C, diluted with cold water (0–5°C, 0.4 ml), stirred for 3 min more, and filtered. The solid was washed with cold water (0–5°C, 0.2 ml), ethanol (1 ml) and ether (2 ml), and dried under vacuum to give 241 mg (73%) of [2,4,6-$^{14}C_3$]-4,6-dihydroxy-2-methyl-5-nitropyrimidine (**4**) as a pink solid. For the non-radioactive compound (prepared in a model experiment): ^{1}H-NMR (DMSO-D_6, δ): 2.35 (s, 3 H), 3.60 (s, 2 H).

[2,4,6-$^{14}C_3$]-4,6-Dichloro-2-methyl-5-nitropyrimidine, 5

To a suspension of [2,4,6-$^{14}C_3$]-4,6-dihydroxy-2-methyl-5-nitropyrimidine (**4**) (241 mg, 1.36 mmol) in phosphorus oxychloride (1 ml) was added *N*,*N*-diethylaniline (0.28 ml, 1.76 mmol) dropwise. The reaction mixture was refluxed (115°C bath) for 2.5 h, and cooled to room temperature. Excess phosphorus oxychloride was evaporated under vacuum. The residue was diluted with ether and poured onto ice. The water layer was extracted with ether (3 × 5 ml). The combined organic extract was washed with saturated solutions of sodium bicarbonate and sodium chloride, dried over sodium sulfate, and evaporated under vacuum. Flash chromatography of the residue (eluting with 5% ether in hexane) gave 191 mg (66%) of [2,4,6-$^{14}C_3$]-4,6-dichloro-2-methyl-5-nitropyrimidine (**5**) as light brown crystals. For the non-radioactive compound (prepared in a model experiment): ^{1}H-NMR ($CDCl_3$, δ): 2.83 (s, 3 H).

[2,4,6-$^{14}C_3$]-4,6-Dichloro-2-methyl-5-aminopyrimidine, 6

A solution of [2,4,6-$^{14}C_3$]-4,6-dichloro-2-methyl-5-nitropyrimidine (**5**) (191 mg, 0.89 mmol) in ethanol (5 ml) was hydrogenated (1 atm of hydrogen) over Raney nickel (20 mg) at room temperature for 3 h. The solution was decanted, and the catalyst was washed with ethanol. The combined solution was evaporated under vacuum. The residue was subjected to flash chromatography (eluting with 45% ether in hexane) to give 145 mg (88.5%) of [2,4,6-$^{14}C_3$]-4,6-dichloro-2-methyl-5-aminopyrimidine (**6**) as white crystals. For the non-radioactive compound (prepared in a model experiment): ^{1}H-NMR ($CDCl_3$, δ): 2.55 (s, 3 H).

[2,4,6-$^{14}C_3$]-4,6-Dichloro-5-(1-acetylimidazolidin-2-ylidenimino)-2-methylpyrimidine, 7

To a suspension of 4,6-dichloro-2-methyl-5-aminopyrimidine-[2,4,6-$^{14}C_3$] (**6**) (145 mg, 0.788 mmol) in phosphorus oxychloride (1.45 ml) was added 1-acetylimidazolidin-2-one[12] (111 mg, 0.866 mmol). The reaction mixture was heated at 105–110°C (bath) for 2.5 h, and cooled to room temperature. Excess

phosphorus oxychloride was completely evaporated under vacuum. The residue was treated with ice water (2 ml). The mixture was made alkaline (pH > 10) with aqueous sodium hydroxide (5 N, 1.5–1.7 ml) at 0–5°C (ice bath), and extracted with dichloromethane (30 ml). The extract was washed with saturated solutions of sodium bicarbonate and sodium chloride, dried over sodium sulfate, and evaporated under vacuum. Flash chromatography of the residue (eluting with 50% ethyl acetate in hexane) gave 189 mg (81.6%) of [2,4,6-$^{14}C_3$]-4,6-dichloro-5-(1-acetylimidazolidin-2-ylidenimino)-2-methylpyrimidine (**7**) as a white solid. For the non-radioactive compound (prepared in a model experiment): ^{1}H-NMR ($CDCl_3$, δ): 2.59 (s, 3 H), 2.63 (s, 3 H), 3.59 (t, J = 7 Hz, 2 H), 4.08 (t, J = 7 Hz, 2 H), 4.85 (s, 1 H).

[2,4,6-$^{14}C_3$]-4-Chloro-5-(imidazolidin-2-ylidenimino)-6-methoxy-2-methylpyrimidine ([$^{14}C_3$]moxonidine)

A solution of sodium methoxide in methanol (0.2 M, 3.7 ml, 0.74 mmol) was added to [2,4,6-$^{14}C_3$]-4,6-dichloro-5-(1-acetylimidazolidin-2-ylidenimino)-2-methylpyrimidine (**7**) (189 mg, 0.64 mmol). The reaction mixture was refluxed (65–70°C bath) for 2 h, and cooled to room temperature. Most of the methanol was evaporated under vacuum. The precipitate was filtered off, washed with water (1.5 ml), and dried under vacuum to give 115 mg (72%) of the product. Recrystallization from ethanol (3.5 ml) gave 84 mg (53%) of [2,4,6-$^{14}C_3$]-4-chloro-5-(imidazolidin-2-ylidenimino)-6-methoxy-2-methylpyrimidine ([$^{14}C_3$]moxonidine) as a white solid with specific activity 632 μCi/mg and radiochemical purity 99.1%. For the non-radioactive compound (prepared in a model experiment): ^{1}H-NMR (DMSO-D_6, δ): 2.37 (s, 3 H), 3.28 (s, 4 H), 3.81 (s, 3 H), 6.19 (s, 2 H).

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References

1. Emsberger PR, Westbrooks KL, Christen MO, Schafer SG. *J Cardiol Pharmacol* 1992; **20** (Suppl. 4): 1–10.
2. Ernsberger P, Eliott H, Weiman H-J, Raap A, Haxhiu MA, Hofferber E, Loew-Kroeger A, Reid JL, Mest H-J. *Cardiovasc Drug Rev* 1993; **11**: 411–431.
3. Szabo B, Urban R. *Arzneim-Forsch.drug Res* 1997; **47**: 1009–1015.
4. Planitz V. *J Clin Pharmacol* 1987; **27**: 46–51.
5. Ollivier J-P, Bouchet V. *Am J Cardiol* 1992; **70**: 27C–36C.
6. Webster J, Koch H. *J Cardiovasc Pharmacol* 1996; **27**: S49–S54.
7. He MM, Abraham TL, Lindsay TJ, Schaefer HC, Pouliquen IJ, Payne C, Czeskis B, Shipley LA, Oliver SD, Mitchell MI. *Drug Metab Disp* 2003; **31**: 334–342.

8. Albert A, Brown DJ, Wood HCS. *J Chem Soc* 1954; 3832–3839.
9. Norman MH, Chen N, Chen Z, Fotsch C, Hale C, Han N, Hurt R, Jenkins T, Kincaid J, Liu L, Lu Y, Moreno O, Santora VJ, Sonnenberg JD, Karbon W. *J Med Chem* 2000; **43**: 4288–4312.
10. Baindur N, Chadha N, Player MR. *J Comb Chem* 2003; **5**: 653–659.
11. Stenzel W, Fleck W, Cohnen E, Armah B. *US Patent* 4323570, issued April 6, 1982.
12. Roberts JG. *J Chem Soc* 1964; 176–178.

