SYNTHESIS OF ENCAINIDE-^{13}C HYDROCHLORIDE FROM 2-NITROBENZALDEHYDE-FORMYL-^{13}C

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SUMMARY

A facile synthesis of 2-nitrobenzaldehyde-formyl-^{13}C was developed. This compound was converted to the labelled antiarrhythmic agent, encainide-^{13}C hydrochloride, 4-methoxy-N-[2-[2-(1-methyl-2-piperidinyl)ethyl-1-^{13}C]phenyl]benzamide hydrochloride.

Key Words: Encainide-^{13}C, 2-nitrobenzaldehyde-carbonyl-^{13}C, antiarrhythmic.

INTRODUCTION

Encainide hydrochloride is a new antiarrhythmic drug (1) currently under clinical investigation (2-5). In order to study the metabolism and bioavailability of encainide hydrochloride, 4-methoxy-N-[2-[2-(1-methyl-2-piperidinyl)ethyl]phenyl]benzamide hydrochloride (8), we desired to make this compound labelled with a heavy isotope. A ^{13}C-label on the 1-position of the ethylene chain was chosen as the most economical alternative.

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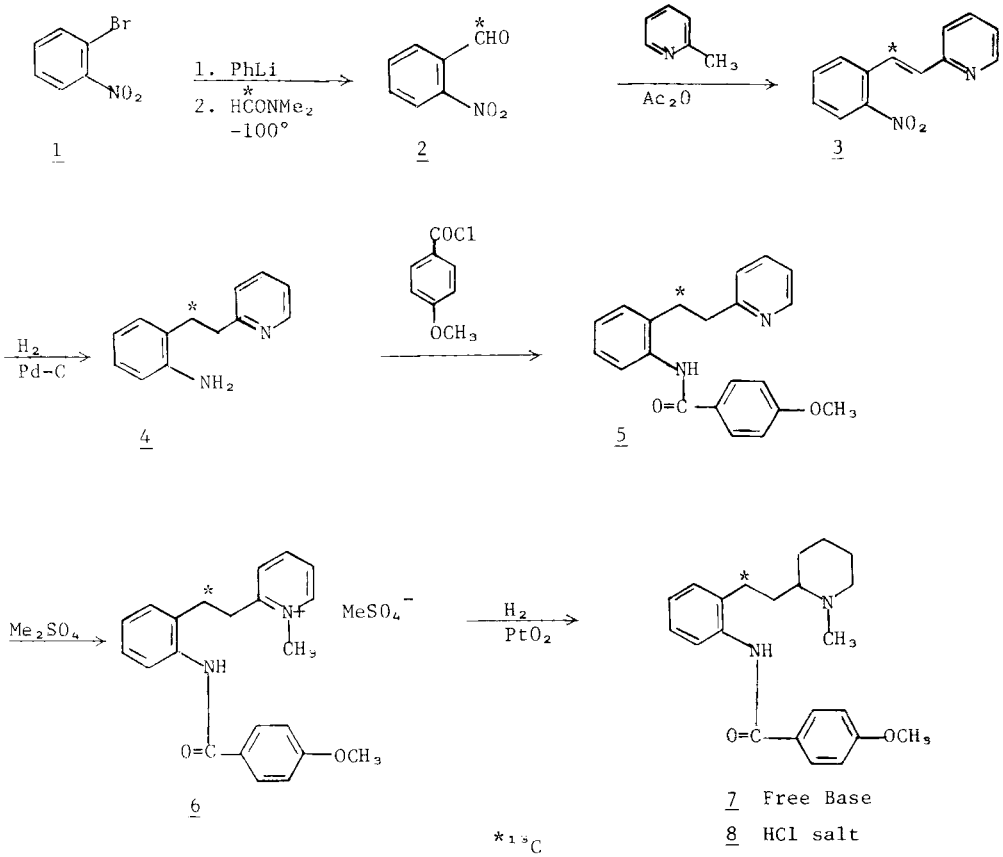
DISCUSSION

Since encainide hydrochloride had been previously prepared (6,7) from 2-nitrobenzaldehyde, the immediate goal was the synthesis of 2-nitrobenzaldehyde-formyl-^{13}C. Adapting a procedure for the synthesis of 2-nitrobenzoic acid (8,9), we prepared this aldehyde (2) in 78% yield by lithiation of 1-bromo-2-nitrobenzene with phenyllithium followed by formylation with N,N-dimethylformamide-carbamoyl-^{13}C. Great care must be taken to keep the reaction temperature below -90° and to exclude water. Above -90°C phenyllithium attacks the oxygen of 1-bromo-2-nitrobenzene to form phenol. Below -90°C lithium exchange is facilitated so that 2-nitrophenyllithium is formed (8). Better yields were also obtained by the use of phenyllithium prepared in ether compared to commercial phenyllithium in 1:1 benzene-ether.



1 2 3

4 5

6

7 Free Base

8 HCl salt

*^{13}C

The aldehyde (2) was condensed with 2-methylpyridine according to the procedure of Dykstra and Minielli (6,7) to give the nitrostyrylpyridine (3), which was hydrogenated to amine (4). Acylation of amine (4) with anisoyl chloride furnished amide (5), which was converted to quaternary ammonium compound (6). Hydrogenation of (6) gave encainide-^{13}C hydrochloride (8) with 88% ^{13}C enrichment.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded with a Perkin Elmer R32 spectrometer for ^{1}H NMR and with a Varian FT-80A spectrometer for ^{13}C NMR. Chemical shifts are reported in parts per million downfield from tetramethylsilane. Infrared (IR) spectra were determined on a Beckman IR-9 spectrophotometer using KBr pellets. Mass spectra were determined on a Finnigan 4021 GC/EI-CI mass spectrometer system. Column chromatography was performed using E. Merck Silica Gel 60 (70-230 mesh).

N,N-Dimethylformamide-carbamoyl-^{13}C (90% ^{13}C) was purchased from Prochem, B.O.C., Ltd. and from KOR ISOTOPES. Fisher certified tetrahydrofuran was used directly from the bottle as were most other solvents and reagents. An ethereal solution of phenyllithium was prepared (10) using bromobenzene and lithium wire. Its concentration was determined by the method of Krofan (11).

2-Nitrobenzaldehyde-formyl-^{13}C (2).

To a solution of 1-bromo-2-nitrobenzene (5.79 g, 28.6 mmol) in 133 mL tetrahydrofuran was added 1.02 N phenyllithium (27.0 mL, 27.5 mmol) in ether over 20 min at such a rate that the temperature remained below -100°C using a cold bath of liquid nitrogen and 1-chlorobutane. The temperature was maintained at -100°C for an additional 1.5 h. To the reaction was added N,N-dimethylformamide-carbamoyl-^{13}C (2.0 g, 27 mmol), and the reaction mixture was stirred 30 min more at -100°C. The reaction mixture was then stirred 1.5 h at

-78°C using a Dry Ice-acetone bath. Water was added and the mixture was extracted with ether. The ethereal solution was dried over $MgSO_4$ and then concentrated in vacuo to give a red oil which was chromatographed using 6:1 hexane-ethyl acetate to give 3.2 g (78%) of an orange solid which was pure by TLC.

2-[2-(2-Nitrophenyl)ethenyl-2-^{13}C]pyridine (3).

A mixture of 2-nitrobenzaldehyde-formyl-^{13}C (14.6 g, 96 mmol) and 2-methylpyridine (8.99 g, 96 mmol) in acetic anhydride (18.6 mL, 190 mmol) was heated at 140-145°C for 46 h. After cooling, the reaction mixture was poured into ice water to give a dark solid. The solid was dissolved in ether, dried over $MgSO_4$, concentrated in vacuo, dissolved in ethyl acetate, treated with charcoal, and concentrated to a thick slurry. The product was collected by filtration to give 13.9 g (64%) of a solid, mp 91-93°C [cf ref (6), mp 98-99°C].

2-[2-(2-Aminophenyl)ethyl-2-^{13}C]pyridine (4).

A solution of 2-[2-(2-nitrophenyl)ethenyl-2-^{13}C]pyridine (13.9 g, 61 mmol) in 120 mL ethanol was hydrogenated over 1.5 g 10% Pd-C. The resulting oil was purified by chromatography eluting with 25:1 chloroform-methanol to give 11.4 g (95%) of a solid.

2-[2-[2-(4-Methoxybenzamido)phenyl]ethyl-2-^{13}C]-1-methylpyridinium methyl sulfate (6).

To a solution of 2-[2-(2-aminophenyl)ethyl-2-^{13}C]pyridine (11.49 g, 57 mmol) in 50 mL pyridine was added 4-methoxybenzoyl chloride (11.26 g, 60 mmol) dropwise with stirring. The mixture was heated 3 h at 70°C and then concentrated in vacuo. The resulting oil was suspended in 50 mL 20% NaOH solution and stirred for 1 h. The mixture was extracted with dichloromethane, washed with water, dried over $MgSO_4$, and concentrated to give 17.9 g (69%) of a red oil (5). This oil was dissolved in warm acetonitrile, treated with dimethyl sulfate (8.0 g, 63 mmol), and heated to 70°C to 2.5 h. The crystalline salt which resulted from standing overnight was collected by

filtration, washed with acetone, and dried to a constant weight of 19.6 g (68%), mp 159-160°C. IR 3215, 1655, 1635, 1610, 1510, 1450, 1292, 1280, 1255, 1220, 1015, 770, cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.32 (m,1H,$J_{H,C}$=132 Hz), 3.80 (m,1H,$J_{H,C}$=132 Hz), 3.35 (s,3H), 3.35 (m,2H), 3.84 (s,3H), 7.05 (m,2H), 7.27 (m,4H), 7.92 (m,4H), 8.41 (t,1H,J=8.0 Hz), 8.89 (d,1H,J=6.1 Hz), 9.86 (br s,1H). CI mass spectrometry indicated 86% ^{13}C. Anal. Calcd for $C_{22}H_{23}N_2O_2 \cdot CH_3O_4S$: C, 60.25; H, 5.72; N, 6.11. Found: C, 60.13; H, 5.83; N, 6.09.

4-Methoxy-N-[2-[2-(1-methyl-2-piperidinyl)ethyl-1-^{13}C]phenyl]benzamide (7).

A solution of 2-[2-[2-(4-methoxybenzamido)phenyl]ethyl-2-^{13}C]-1-methylpyridinium methyl sulfate (19.6 g, 42 mmol) in 120 mL ethanol was hydrogenated using 85% platinum oxide (1.0 g). Filtration and concentration gave a white solid which was dissolved in 1N HCl, washed with ether, and basified with 50% sodium hydroxide solution. The free base was extracted with dichloromethane, washed with water, dried over $MgSO_4$, and concentrated to give a white solid which was recrystallized from 2-propanol to afford 13.1 g (84%) of a white solid, mp 129-130°C [cf ref (6), mp 131.5-132.5°]. IR 3285, 2930, 1641, 1637, 1603, 1505, 1500, 1290, 1250, 1022, 763, cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (m,6H), 1.82 (m,5H), 2.00 (m,1H,$J_{H,C}$=127 Hz), 3.40 (m,1H,$J_{H,C}$=127 Hz), 2.23 (s,3H), 3.83 (s,3H), 6.91 (m,2H), 8.14 (m,1H), 10.59 (br s,1H); ^{13}C NMR ($CDCl_3$) δ 21.1, 24.6, 26.2 (^{13}C label), 26.7, 34.9 ($J_{C,C}$=38.0 Hz), 37.1, 55.1, 55.4, 58.8, 113.4, 123.9, 124.7, 126.5, 128.9, 129.3, 129.8, 133.6 ($J_{C,C}$=41.0 Hz), 137.4, 162.0, 166.8. CI mass spectrometry (isobutane) indicated 88% ^{13}C. Anal. Calcd for $C_{22}H_{28}N_2O_2$: C, 74.97; H, 8.01; N, 7.95. Found: C, 74.71; H, 7.96; N, 7.65.

4-Methoxy-N-[2-[2-(1-methyl-2-piperidinyl)ethyl-1-^{13}C]phenyl]benzamide hydrochloride (8).

A warm solution of 12.0 g (34 mmol) of encainide-^{13}C (7) in 30 mL ethyl acetate was treated with 4.7 mL of 8.7 N hydrogen chloride in

2-propanol. An additional 10 mL of 2-propanol was added to form a clear solution. Cooling overnight gave a white solid, 11.6 g (88%), mp 186-187°C. IR 3180, 2955, 2940, 2620, 1650, 1605, 1505, 1450, 1255, 1020, 769, cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.70 (m,9H), 2.62 (br d,3H), 3.01 (m,4H), 3.83 (s,3H), 7.05 (m,2H), 7.26 (m,4H), 8.06 (m,2H), 9.95 (br s, 1H), 10.80 (br s,1H). CI mass spectrometry (isobutane) indicated 88% ^{13}C. Anal. Calcd for $C_{22}H_{28}N_2O_2 \cdot HCl$: C, 68.01; H, 7.50; N, 7.19. Found: C, 68.09; H, 7.62; N, 7.28.

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