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NOTE

SYNTHESIS OF [N-TRIDEUTEROMETHYL] LABELLED E-DOXEPIN

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SUMMARY

A deuterium analog of doxepin was synthesized by the reduction of an N-doxepin carbamate with lithium aluminum deuteride.

Key words: Deuterium, Doxepin, Reduction

INTRODUCTION

Doxepin is a tricyclic antidepressant drug which is effective in the treatment of clinical depression.[1] The concentration of tricyclic antidepressant drugs in patients' plasma must be routinely monitored because high plasma levels have been associated with central nervous system disorders, toxicity, seizures and death, moreover, there is interpatient variation in plasma concentration for patients receiving the same dose.[2] Currently we are developing a fluorescence polarization immunoassay for the quantification of doxepin in plasma.[3] In order to correlate our immunoassay with GC/MS, we needed a suitable deuterated internal standard that would have similar chemical and physical properties as doxepin. Therefore the synthesis of the previously unknown title compound, N-trideuteromethyl E-doxepin, was developed and is presented herein.

RESULTS

The starting material for the synthesis of N-trideuteromethyl E-doxepin was the readily available carbamate **1**[4] which was reduced with lithium aluminum deuteride (LAD, 98% D) to give the desired compound **2** as an oil. The free base was transformed to the salt **3** by refluxing **2** with maleic

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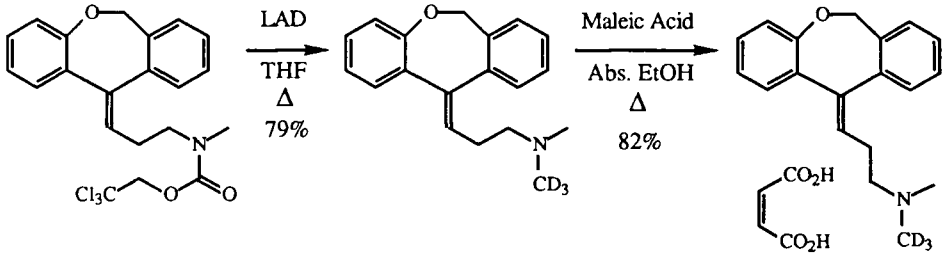
acid in absolute ethanol to afford the desired product in 65% overall yield from the carbamate **1**. We are currently using the salt **3** as an internal standard for the calibration of our doxepin immunoassay.



1 **2** **3**

EXPERIMENTAL

Proton (300 MHz) and carbon (75 MHz) spectra were recorded on a GE-300 NMR spectrometer and mass spectra were recorded on a Nermag 3010 spectrometer. All solvents were HPLC grade and used as is except for tetrahydrofuran (THF) which was distilled from sodium benzophenone ketyl immediately prior to use. Silica gel (EM grade 60, 230-400 mesh) was purchased from Aldrich.

N-Trideuteromethyl E-Doxepin Maleate Salt **3**- A solution of *N*-[2,2,2-trichloroethoxycarbonyl]-doxepin[4] (**1**, 750 mg, 1.70 mmol) and 5 mL THF was added to a suspension of lithium aluminum deuteride (LAD, 143 mg, 3.40 mmol), heated at reflux for 3 hours and quenched with water (0.15 mL), 2N NaOH (0.15 mL), and water (0.45 mL).[5] The mixture was filtered through Celite and solvent removed *in vacuo* to give 760 mg as a yellow oil. Purification by flash chromatography [methanol/methylene chloride/triethylamine (7:93:0.3), v/v] afforded 377 mg (79%) of the free base **2** as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.38-7.20 (m, 5H), 7.11 (dt, J = 7.63, 1.84 Hz, 1H), 6.86 (dt, J = 7.45, 1.10 Hz, 1H), 6.74 (dd, J = 8.28, 1.10 Hz, 1H), 6.01 (t, J = 7.17 Hz, 1H), 5.19 (v br s, 2H), 2.50-2.32 (m, 4H), 2.21 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.10, 141.17, 140.23, 134.29, 130.11, 129.51, 128.97, 128.52, 128.13, 127.81, 127.76, 127.29, 120.94, 119.13, 70.06, 59.08, 45.03, 27.50; HRMS: m/z $(M+H)^+$ calcd 544.2308, obsd 544.2308.

Maleic acid (147 mg, 1.27 mmol) was added to a solution of free base **2** (340 mg, 1.21 mmol) in 6 mL absolute ethanol, heated at reflux for 20 min and left at room temperature overnight to afford off-white crystals. This material was recrystallized from 5 mL of absolute ethanol, set overnight to give colorless crystals and dried under high vacuum (0.5 torr, 25°C) to afford 392 mg (82%) of the

desired N-trideuteromethyl E-doxepin maleate salt, **3**. m.p. 173-174°C; ^{1}H NMR ($CDCl_3$) δ 7.45-7.24 (m, 5H), 7.12 (dt, J = 7.72, 1.84 Hz, 1H), 6.87 (dt, J = 7.47, 1.10 Hz, 1H), 6.72 (dd, J = 8.09, 1.10 Hz, 1H), 6.34 (s, 2H), 5.96 (t, J = 7.35 Hz, 1H), 4.88 (v br s, 2H), 3.22 (t, J = 7.72 Hz, 2H), 2.76 (s, 3H), 2.64 (app q, J = 7.60 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 169.14(2C), 154.71, 143.11, 139.39, 134.85(2C), 133.85, 129.30, 129.08, 128.29, 128.13(2C), 126.96, 125.76, 123.47, 120.69, 118.78, 69.34, 56.22, 41.69, 24.26. Anal. Calcd. for $C_{23}H_{22}{}^2H_3N_1O_5$: C, 69.33; H, 6.37. Found: C, 69.35; H, 6.32.

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