THE SYNTHESIS OF N-DEUTEROMETHYLATED DESIPRAMINE AND IMIPRAMINE

G. J. Shaw*
Chemistry Laboratory, National Heart and Lung Institute, National Institutes c
Health, Bethesda, Maryland 20014

S. P. Markey#
Laboratory of Clinical Science, National Institute of Mental Health, National
Institutes of Health, Bethesda, Maryland 20014

Received May 13, 1976
Revised July 1, 1976

SUMMARY

Desipramine-d_3 (5-[3-(methyl-d_3-amino)propyl]-10,11-dihydro-5H-dibenz[b,f]azepine), imipramine-d_3(5-[3-methylmethyl-d_3-amino) propyl]-10,11-dihydro-5H-dibenz[b,f]azepine and imipramine-d_6 (5-[3-(dimethyl-d_6-amino)propyl]-10,11-dihydro-5H-dibenz[b,f] azepine)have been synthesised for use as internal standards in mass spectrometric determinations. The mass spectra of these compounds is reported.

Key Words: Desipramine-d_3, Imipramine-d_3, Imipramine-d_6, Synthesis, Mass spectra

INTRODUCTION

Desipramine(6)(5-[3-(methylamino)propyl]-10,11-dihydro-5H-dibenz[b,f]azepine) and the corresponding tertiary amine, imipramine(10)(5-[3-(dimethylamino) propyl]-10,11-dihydro-5H-dibenz[b,f]azepine) are two of a number of tricyclic drugs possessing antidepressant activity (1).

Two recent reports (2,3) demonstrate quantitation by combined gas-chromatography-mass spectrometry (gc-ms) as an aid in studying the pharmacokinetics of these drugs. It can be argued that the most satisfactory internal

---

*Fellow of the Medical Research Council of New Zealand.
#To whom all correspondence should be addressed.

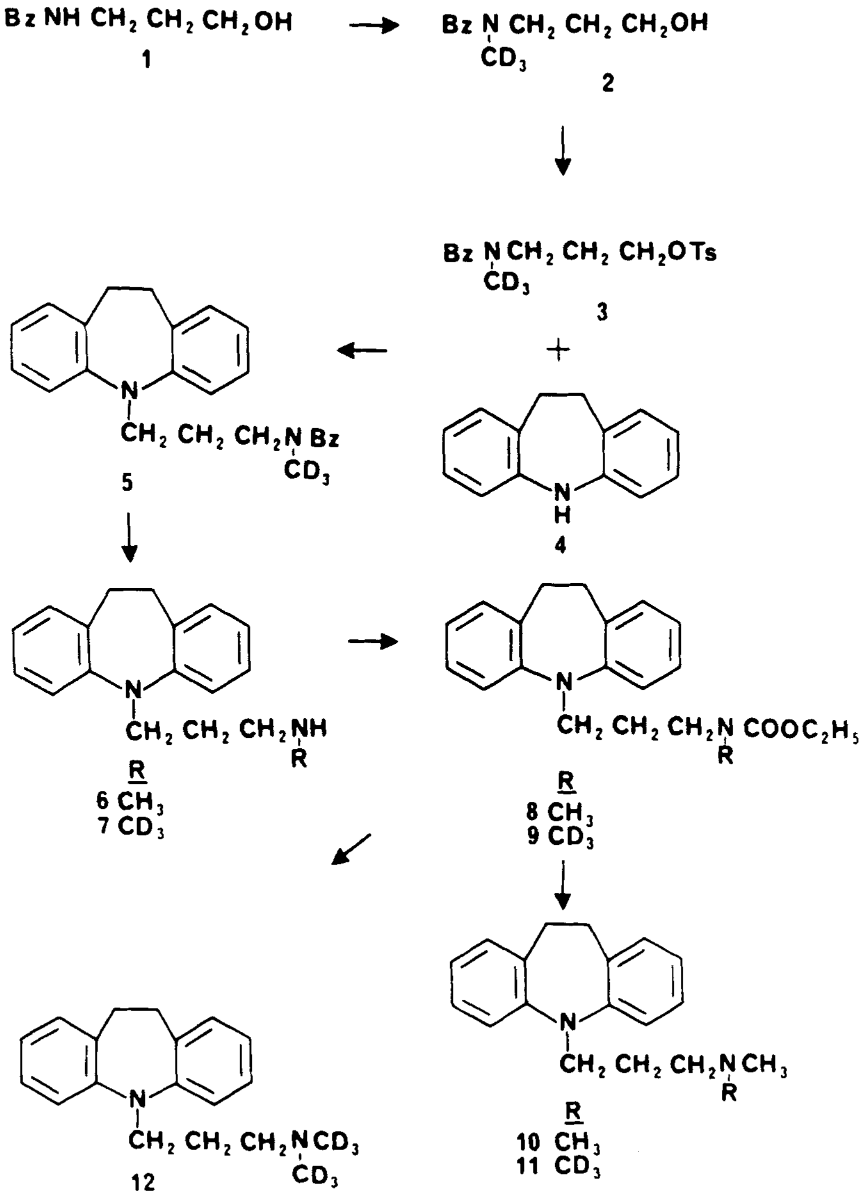

Figure 1. Synthetic scheme. Bz = $C_6H_5\cdot CH_2$-, Ts = $CH_3\cdot C_6H_4\cdot SO_2$-.

standard for quantitation is the use of a stable isotopically enriched form of a compound, and one of these investigations reports such a procedure (3). In that study, the internal standards (desipramine-d_4 and imipramine-d_4) were prepared by isotopic exchange giving a mixture of isotopically enriched species of which the tetradeuterated derivatives constituted only 55-56% of the mixture in each case.

For further metabolic studies, a method for preparing specifically deuterated, non-exchangeable, internal standards was considered. This paper details the synthesis of desipramine-d_3(7), imipramine-d_3(11) and imipramine-d_6(12).

RESULTS AND DISCUSSION

The synthetic approach considered was dictated by a desire to obtain a simple and efficient synthesis leading, initially, to desipramine-d_3. A suitably derivatised sidechain was prepared from 3-benzylamino-1-propanol(1) by N-methylation with iodomethane-d_3, giving 3-(benzyl-d_3-amino)-1-propanol(2) and subsequent tosylation with p-toluenesulfonyl chloride to give 3-(benzylmethyl-d_3-amino)propyl p-toluenesulfonate(3). Condensation with 10,11-dihydro-5H-dibenz [b,f]azepine(4), in the presence of sodium amide, gave 5-[3-(benzylmethyl-d_3-amino)propyl]-10,11-dihydro-5H-dibenz[b,f]azepine(5) in 57% yield. The desired product, desipramine-d_3, was readily prepared by debenzylation with palladium on charcoal in ethanol-acetic acid (4).

Imipramine-d_6 was then prepared, in good yield, by sequential reaction of desipramine-d_3 with ethyl chloroformate (5) giving 5-[3-(N-methyl-d_3-ethoxycarbamoyl)propyl]-10,11-dihydro-5H-dibenz[b,f]azepine(9) and reduction with lithium aluminum deuteride in tetrahydrofuran. Imipramine-d_3 was prepared in an analogous manner from commercial desipramine. The synthetic scheme is summarized in Figure 1.

The precise isotopic enrichment for each compound was calculated using a computer program developed by C.F. Hammer (6). Data were obtained by selected ion recording of ions in the molecular ion regions, formed by electron ionization of the deuterated and non-deuterated compounds. The isotopic distributions were: desipramine-d_3:d_3 = 100%; imipramine-d_3:d_3 = 93.8%, d_2 = 6.2% and imipramine-d_6: d_6 = 94.1%, d_5 = 5.9%. Electron ionization mass spectra of the three deuterated analogs and the undeuterated standards are shown in Figure 2. Comparison of these spectra reveals that desipramine-d_3, imipramine-d_3 and imipramine-d_6 are

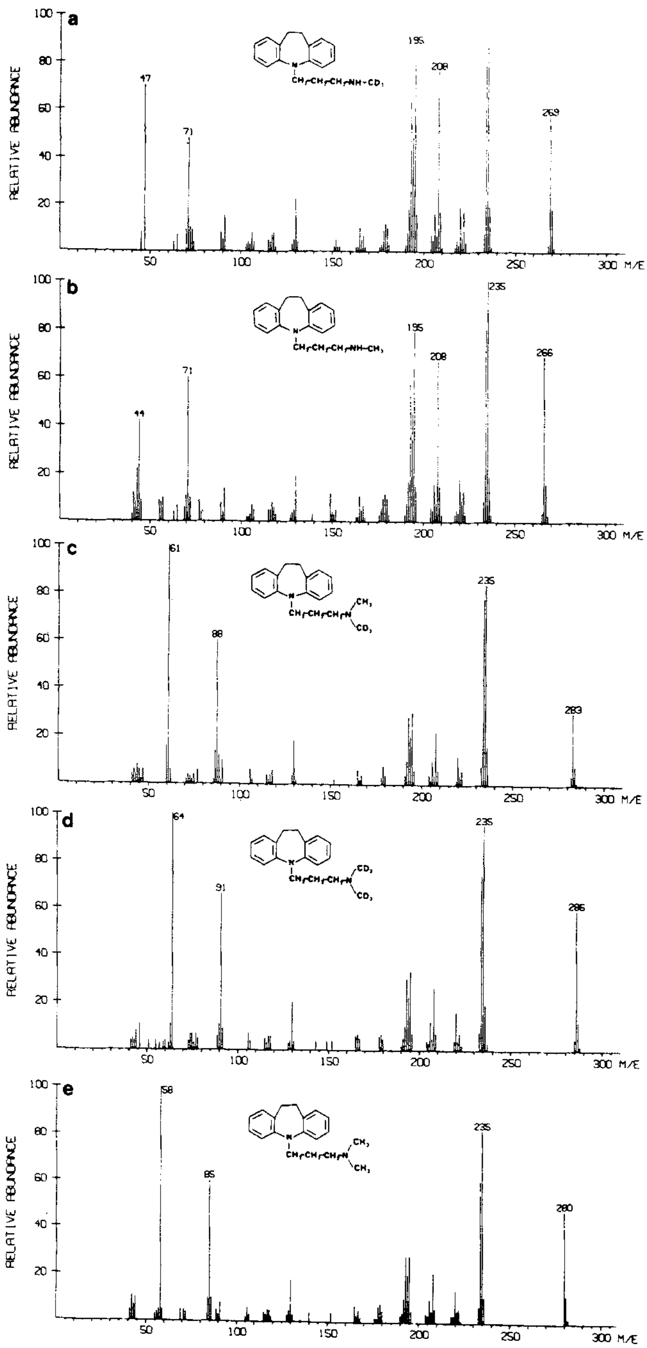

Figure 2. Mass spectra of deuterated and non-deuterated desipramine (a, b) and imipramine (c, d, e).

well suited for use as internal standards in gc-ms assays. In each case, the molecular ion is clearly separated from the corresponding ion in the undeuterated analogs.

Our mass spectral results confirm the fragmentation pathway proposed by Belvedere et al. (2). Major ions at m/e 44 and 58 in desipramine and imipramine are shifted 3 or 6 amu in the deuterated analogs. Losses of methylamine and dimethylamine give rise to fragments at m/e 234 and 235 unshifted in the spectra of the deuterated compounds.

EXPERIMENTAL SECTION

All melting points were determined on a Kofler hotstage microscope and are uncorrected. Low resolution electron ionization mass spectra were recorded with an LKB 9000 mass spectrometer and the high resolution electron ionization mass spectrum on an AEI MS9 mass spectrometer.

3-(Benzylmethyl-d_3-amino)-1-propanol(2)--To a cooled (5°) solution of 3-benzylamino-1-propanol(1, 5 g, 30.3 mmol) in sodium hydroxide (2 g) and water-methanol (50%, 17 ml) was added iodomethane-d_3 (7) (2.2 ml, 34.5 mmol, > 99% D). The reaction was capped and left at room temperature for 12 hr with stirring. The product was extracted with chloroform, washed with water before drying over anhydrous sodium sulfate. The solvent was removed giving an oil which was completely dried by azeotropic distillation with benzene. Yield 5.1 g (93%). bp 138-140° (10 mm). Lit (8) 143-144° (10 mm). Mass spectrum: 182(4)(M^+), 137(35), 120(9), 92(9), 91(100), 65(10), 61(6), 47(6), 45(9), 39(6).

3-(Benzylmethyl-d_3-amino)propyl p-toluenesulfonate(3)--To a solution of 3-(benzylmethyl-d_3-amino)-1-propanol (2, 5 g, 27.4 mmol) in pyridine (30 ml) at 0° was added p-toluenesulfonyl chloride (10.4 g, 54.4 mmol). After solution was complete the reaction was left at 2° for 20 hr. The mixture was poured onto ice (200 g) and stirred for 15 min. The resulting oil was extracted with chloroform (200 ml) and washed with water, dilute hydrochloric acid, dilute sodium hydroxide and again with water before drying over sodium sulfate. The solvent was removed and the resulting oil was completely dried by azeotropic distillation with benzene. M/e, 336.1581 (calc. for $C_{18}H_{20}D_3NO_3S$, 336.1587). Mass spectrum:

336(2)(M^+), 319(6), 318(24), 274(8), 146(10), 137(36), 118(14), 92(12), 91(100), 65(8).

5-[3-(Benzylmethyl-d_3-amino)propyl]-10,11-5H-dibenz[b,f]azepine(5)--To a stirred suspension of sodium amide (0.4 g, 10.2 mmol) in dry benzene was added 10,11-dihydro-5H-dibenz[b,f]azepine (4, 1.25 g, 6.4 mmol) over 5 min and the mixture refluxed for 2 hr. The reaction was cooled and a solution of 3-(benzylmethyl-d_3-amino)propyl p-toluenesulfonate (3, 2.45 g, 7.29 mmol) in benzene (20 ml) was added over 5 min. The mixture was refluxed for an additional 15 hr. The excess sodium amide was cautiously destroyed with water and the product extracted with ethyl acetate (100 ml), washed with dilute sodium hydroxide and water. The extract was dried over sodium sulfate and the solvent evaporated in vacuo to give an oil. Yield 1.3 g (57%). bp 208-215° (0.05 mm). Lit (9) 195-201° (0.04 mm). Mass spectrum: 359(6)(M^+), 236(10), 235(52), 234(24), 222(20), 208(14), 196(16), 195(100), 194(83), 193(30), 192(12), 180(27), 164(15), 163(10), 137(14), 118(17), 97(15), 91(58), 84(10), 47(11).

5-[3-(Methyl-d_3-amino)propyl]-10,11-dihydro-5H-dibenz[b,f]azepine(7)--To a solution of 5-[3-(benzylmethyl-d_3-amino)propyl]-10,11-5H-dibenz[b,f]azepine(5, 837 mg, 2.3 mmol) in ethanol (20 ml) and acetic acid (0.5 ml) was added 10% palladium on charcoal (500 mg). The mixture was stirred for 6 hr under hydrogen (3 atm). At the end of this time the mixture was filtered and the solvent removed. The residue was taken up in chloroform and the product precipitated with hydrogen chloride gas giving the hydrochloride salt. Yield 639 mg (90%). mp 213-215°. Lit (10) 206-208°. Mass spectrum: Shown in Figure 2a.

5-[3-(Dimethyl-d_6-amino)propyl]-10,11-dihydro-5H-dibenz[b,f]azepine(12)--To a solution of desipramine-d_3 hydrochloride (88 mg, 0.29 mmol) in pyridine (10 ml) was added ethyl chloroformate (60 mg, 0.55 mmol). The solution was stirred for 12 hr at room temperature. Following extraction of the product with ethyl acetate, the organic phase was washed with dilute hydrochloric acid, sodium hydroxide and water and dried over sodium sulfate before evaporating to dryness. The crude carbamate (9) was dissolved in dry tetrahydrofuran and added dropwise to a stirred suspension of lithium aluminum deuteride (7) (50 mg, 1.2 mmol, > 99% D). The mixture was gently refluxed for 12 hr. The excess lithium aluminum deuteride was destroyed with water and the mixture was filtered. After washing the salts with fresh tetrahydrofuran, the combined extracts were concentrated and redissolved in chloroform, washed with dilute hydrochloric acid and water before drying. The solvent was removed *in vacuo* and the residual oil was completely dried by azeotropic distillation with benzene. A chloroform solution of the oil was treated with hydrogen chloride gas giving the product as its hydrochloride. This material was recrystallised from acetone. Yield 74 mg (79%). mp 171-173°. Lit (11) 173-175°. Mass spectrum: Shown in Figure 2d.

5-[3-(Methylmethyl-d_3-amino)propyl]-10,11-dihydro-5H-dibenz[b,f]azepine(11)--This was prepared from desipramine (10) (Ciba-Giegy) via the carbamate (8) in an analogous manner to the hexadeuterated analog. Mass spectrum: Shown in Figure 2c.

REFERENCES

1. Klerman G.L. and Cole J.O. - Pharmacol. Rev. 17: 101 (1965)
2. Belvedere G., Burti L., Frigerio A., and Pantarotto C. - J. Chromatogr. 111: 313 (1975)
3. Claeys M., Muscettola G., and Markey S.P. - Biomed. Mass Spectrom. 3, No. 3 (1976) (in press)
4. Augustine R.L. - Catalytic Hydrogenation, Marcel Dekker, Inc., New York, 1965, p. 139
5. Easton N.R., Lukach C.A., Nelson S.J., and Fish V.B. - J. Am. Chem. Soc. 80: 2519 (1958)
6. This program, LABDET, is a component of the NIH/EPA computer-based Chemical

Information System. For further details, contact C.F. Hammer, Georgetown University, Washington, D.C. 20037

7. Merck, Sharp and Dohme, Canada Ltd., Isotope Division, Pointe Claire, Quebec, Canada
8. Schlögl K. and Schlögl R. - Monatsh 95: 922 (1964)
9. Biel J.H. and Judd C.I. - Chem. Abstr. 63: P14830d (1965)
10. Kresze G. and Trede A. - Chem. Abstr. 58: 11337g (1963)
11. Schindler W. and Häfliger F. - Helv. Chim. Acta 37: 472 (1954)