THE SYNTHESIS OF NON-EXCHANGEABLE DEUTERATED INTERNAL STANDARDS FOR IMIPRAMINE AND ITS METABOLITES

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SUMMARY

The synthesis of 10,11-dihydro-5-(3-dimethylaminopropyl)-5H-dibenz[b,f]azepine (imipramine) and its 3-methylamino analogue (desipramine)labelled with deuterium in either the 1- or the 3-position of the side chain in high isotopic purity is described. The 3,3-d_2 compounds are obtained from the common precursor 5-(2-cyanoethyl)-10,11-dihydro-5H-dibenz[b,f]azepine by reduction and alkylation, while the 1,1-d_2 products are accessible from the 5-(3-chloropropionyl) derivative by amination and reduction. These compounds are required for use as non-exchangeable mass spectrometric stable isotope internal standards for the simultaneous determination of imipramine and desipramine in biological fluids.

Key Words: Imipramine, Desipramine, deuterium labelling

INTRODUCTION

Although the pharmacology and metabolism of the widely-used tricyclic antidepressant imipramine (10,11-dihydro-5-(3-dimethylaminopropyl)-5H-dibenz[b,f] azepine) (1a) has been widely studied,[1-3] there is little information on its pharmacokinetics, and only a few attempts have been made to follow steady state levels in man after single doses.[4] Plasma levels achieved in man and animals are rather low, and large inter-individual differences in plasma levels among subjects receiving identical dosages appear to be due to genetic factors.[5] Also the rate of demethylation of the drug to its major metabolite desipramine (10,11-dihydro-5-(3-methylaminopropyl)-5H-dibenz[b,f]azepine) (1b) appears to depend on the route of administration.[6] The simultaneous determination of both imipramine

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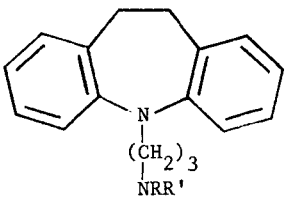
and desipramine in biological fluids demands methods combining complete specificity and sensitivity in the ng/ml region. Existing methods utilize radioactive derivatizing agents[7,8] or thin-layer chromatography with direct densitometry[9] and show reduced sensitivity and precision at low concentrations (20 ng/ml) in plasma and cerebrospinal fluid.

The combination of the techniques of gas chromatography with mass spectrometry (GC-MS) makes possible the utilization of the high resolving power of the first method and the precise identification provided by the second.[10] In addition, the technique of selected ion recording (SIR), by focusing on the mass at which the ion abundance is to be measured, can provide a sensitivity 2 or 3 magnitudes greater than that of gas chromatography alone.[10] Such a GC-MS method for the simultaneous measurement of imipramine and desipramine using promazine as internal standard has been reported.[11] However, it is well known that an ideal internal standard (added at the beginning of an extraction procedure) should have identical chemical and physical behavior to the compound being determined, and that this can best be achieved by the use of a stable isotope



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a: R = R' = CH_3

b: R = H, R' = CH_3

c: R = R' = H

labelled variant of the compound itself.[10,12] The ideal internal standard should be specifically and completely labelled in a non-exchangeable position where back-exchange cannot occur during extraction procedures at acid or alkaline pH values, and should not contain any unlabelled drug so that the labelled material may be used in large excess as a carrier in an inverse isotope dilution method for maximum recovery of trace amounts of drug or metabolite, e.g. in CSF.

The present paper reports the synthesis of imipramine, desipramine, and the primary amine metabolite (10,11-dihydro-5-(3-aminopropyl)-5H-dibenz[b,f]

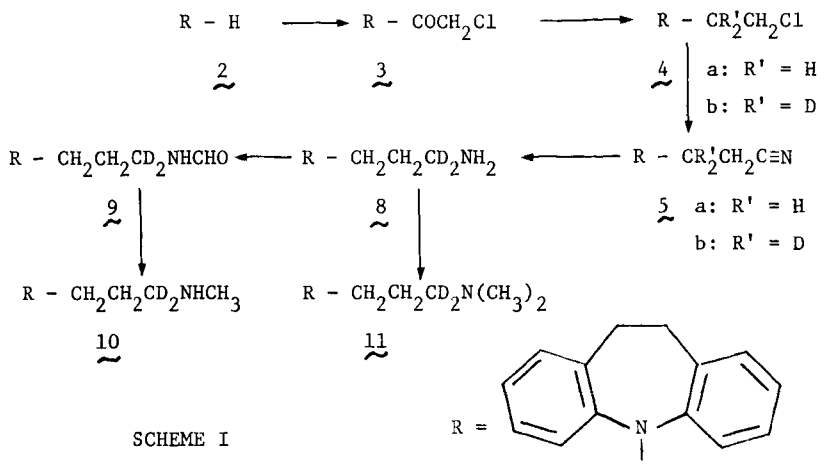
azepine) (1c), isolated as a urinary metabolite in man and animals,[13] containing two deuterium atoms at the 1- or 3-position of the sidechain.

DISCUSSION

A recent publication [14] reports the preparation of d_4-imipramine and d_4-desipramine by introduction of label into the 2,4,6 and 8-positions of the aromatic system using a multiple acid-catalyzed exchange. Isotopic distributions (by cims) were approximately d_4 55%, d_3 35% and d_2 7%. However there remains a risk of back-exchange during acid or alkaline work-up conditions if the label is in the 2, 4, 6, 8, 10 or 11 positions, i.e. the aromatic moiety or at a benzylic position. For these reasons our synthesis aimed at carbons 1 or 3 of the sidechain as the ideal sites for a non-exchangeable label.

A key intermediate is the primary amine 1c, obtainable from 10,11-dihydro-5-(2—cyanoethyl)-10,11-dihydro-5H-dibenz[b,f]azepine (5). This compound has been reported previously by a multistep synthesis [15] which gave a low yield in our hands. Attempted condensation of acrylonitrile, 3-chloro-, or 3-bromopropionitrile with iminodibenzyl (2) itself or with its alkali-metal or thallium derivatives gave only acrylonitrile polymer. The route finally devised to 5 is shown in Scheme I. Conversion of iminodibenzyl to the 5-chloroacetyl derivative 3, followed by reduction with diborane, gave the 5-(2-chloroethyl) compound (4a). Attempted conversion of this to the cyanide 5a in a variety of polar aprotic solvents resulted in a reverse Michael addition to give 2 and polyacrylonitrile, and the same products were obtained using the crown ether 18-crown-6 in the presence of potassium cyanide.[16] The cyanide 5 was successfully prepared from 4 with ethanolic potassium cyanide in the presence of a catalytic amount of potassium iodide at 60° under which conditions the product 5a crystallized out as the reaction proceeded. Reduction with lithium aluminum deuteride gave the desired primary amine 8. Selective methylation of 8, via the N-formyl derivative 9 and subsequent reduction (lithium aluminum hydride or diborane) afforded the secondary amine 10. Attempted Eschweiler-Clarke methylation[17] of 8 produced only polyacrylonitrile, while reduction of 8 with sodium cyanoborohydride in presence of formaldehyde gave the desired tertiary product 11. In every case,

analytical and spectrographic data confirmed the identity of the product, and mass spectrometry showed 8, 10 and 11 to contain 98% d_2 and 2% d_1.

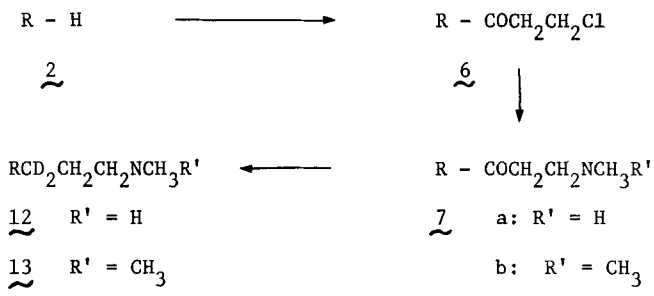


SCHEME I

Reduction of the chloroacetyl compound 3 with borane-d_3 gave 4b, converted to the cyanide 5b. The presence of the label in the 1-position of the cyanoethyl group in 5b caused the anticipated shift of two mass units (208 → 210) in the base peak of the mass spectrum. (This synthetic approach offered the possibility of introducing up to four deuterium atoms in the final product.)

An alternate pathway (Scheme II) utilized reaction of 2 with 3-chloropropionyl chloride to give the N-(3-chloropropionyl) derivative 6,[18] which could be converted with methyl- or dimethylamine to the amides 7a and 7b respectively.[18] Borane-d_3 reduction proceeded smoothly to the desired target substances 12 and 13. The isotopic composition of the products 4b, 5b, 12 and 13 was 90% d_2 and 10% d_1, in agreement with the isotopic purity of 95% d_3 of the borane-d_3 used.

The availability of stable-isotope-labelled imipramine and desipramine permits their use as non-exchangeable internal standards for the simultaneous determination of the unlabelled species in biological fluids, and these results will be reported in a separate communication.



SCHEME II

EXPERIMENTAL

Melting points, determined with a Thomas-Hoover Uni-Melt melting point apparatus, are uncorrected. Nmr spectra at 60 MHz were determined with a Varian A-60A instrument unless otherwise stated, and 100 MHz nmr spectra were recorded on a Varian XL-100-15 instrument operating in the Fourier transform mode using an internal deuterium lock. Nmr chemical shift values are expressed in δ units (parts per million) relative to TMS in organic solvents and sodium 3-trimethylsilylpropanesulfate (TMSP) in D_2O. For the presentation of nmr spectra, the following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, compm = complex multiplet. Infrared (ir) spectra were recorded on a Perkin-Elmer 337 spectrometer. The electron impact mass spectra (eims) were obtained on an AEI MS-12 instrument at 70 eV, and the chemical ionization mass spectra (cims) on an AEI MS-902 instrument modified for chemical ionization using isobutane as the reagent gas. Glc analyses were performed on a Varian Aerograph Model 2100 gas chromatography with a 6 ft. U-shaped Pyrex column packed with 3% SE-30 on Chromosorb W. Microanalyses were done by the Microanalytical Laboratory, University of California, Berkeley. Thin layer chromatography (tlc) was carried out on pre-coated silica gel sheets.

10,11-Dihydro-5-(chloroacetyl)-5H-dibenz[b,f]azepine (3). To a stirred solution of 10,11-dihydro-5H-dibenz[b,f]azepine 2 (10 g, 51.2 mmol) in 50 ml of dry benzene was added chloroacetyl chloride (5.78 g, 52.2 mmol) in 10 ml of dry benzene over a period of 10 min, followed by stirring under reflux for an additional 4.5 hr

or until the evolution of HCl subsided. The benzene was removed by vacuum distillation and the resulting oil was heated at 50° at 0.1 mm for 1 hr to remove unreacted chloroacetyl chloride and chloroacetic acid. Crystallization was effected by adding 25 ml of anhydrous Et_2O. The residue which separated was recrystallized from absolute EtOH. The total yield was 13 g (47.8 mmol, 93%), mp 96-97.5° (lit.[15] 91.5-93.0°); tlc (I_2) R_f (benzene) 0.41; nmr ($CDCl_3$) δ 2.99 (m, 4H, $-CH_2-CH_2-$), 4.00 (s, 2H, $OCCH_2-Cl$), 7.15 (m, 8H, aromatic H).

Anal. Calcd for $C_{16}H_{14}NOCl$: C, 70.71; H, 5.19; N, 5.15. Found: C, 70.47; H, 5.17; N, 5.10.

10,11-Dihydro-5-(2-chloroethyl)-5H-dibenz[b,f]azepine (4a). A 100 ml flask was dried in an oven and cooled in a dry N_2 atmosphere. The flask was equipped with a rubber septum cap, a magnetic stirring bar, and a reflux condenser which was connected to a N_2 bubbler. The flask was immersed in an ice bath at 5° and 20 ml (20 mmol) of 1 M BH_3-THF was introduced into the reaction vessel. Then 2.72 g (10 mmol) of the amide 3 in 10 ml of THF was introduced. The progress of the reaction was monitored via tlc. At the end of 4.5 hr, the reaction mixture was cooled to 5° and 10 ml of conc HCl in 5 ml of THF was added carefully. The temperature was allowed to come to 27° and the whole subjected to vacuum distillation. The residue was placed in a Soxhlet extractor and extracted with Et_2O. The Et_2O was dried, evaporated, and the residue recrystallized from absolute EtOH. The yield of 4a was 2.05 g (8 mmol, 82%), mp 83.5-85° (lit.[19] 84.5-85.5°); tlc. (I_2) R_f (benzene) 0.54; nmr ($CDCl_3$) δ 3.16 (s, 4H, $-CH_2-CH_2-$), 3.5 (t, 2H, J=6Hz, $N-CH_2-$), 4.1 (t, 2H, J=6Hz, $-CH_2-Cl$), 7.04 (m, 8H, aromatic H).

Anal. Calcd for $C_{16}H_{16}NCl$: C, 74.55; H, 6.26; N, 5.43. Found: C, 74.68; H, 6.16; N, 5.21.

10,11-Dihydro-5-(2-cyanoethyl)-5H-dibenz[b,f]azepine (5a). To a solution of 1 g (15.7 mmol) potassium cyanide and 0.1 g (0.6 mmol) potassium iodide in 150 ml of 95% EtOH was added 1 g (3.8 mmol) of the chloro compound 4a in 50 ml of EtOH (95%). The mixture was stirred at 65° for 4 days with the progress of the reaction monitored via tlc. The solvent was removed under vacuum and the

residue was taken up in cold water and filtered. The product was washed with 100 ml of cold water and recrystallized from EtOH, then benzene to yield 0.8 g (3.22 mmol, 85%), of 5a, mp 149-150° (lit.[19] 150°); ir (KBr): 2250 cm^{-1} (C≡N); tlc (I_2) R_f (benzene) 0.31; nmr ($CDCl_3$) δ 2.49 (t, 2H, J=6Hz, $-CH_2-C\equiv N$), 3.16 (s, 4H, $-CH_2-CH_2$), 3.97 (t, 2H, J=6Hz, $N-CH_2$), 7.09 (m, 8H, aromatic H); eims: 248 (42.4), 208 (100), 193 (46.0).

Anal. Calcd for $C_{17}H_{16}N_2$: C, 82.22; H, 6.45; N, 11.30. Found: C, 81.96; H, 6.45; N, 11.07.

10,11-Dihydro-5-(2-chloroethyl-1,1-d_2)-5H-dibenz[b,f]azepine (4b). Using the method described above for 4a, 20 ml (20 mmol) of 1 M borane-d_3 solution in THF and 2.72 g (10 mmol) of the amide 3 gave 2.00 g of 4b (8 mmol, 81%), mp 83.5-85° (lit.[3] 84.5-85.5°). A mixed melting point with the authentic undeuterated sample was not depressed; tlc (I_2) R_f (benzene) 0.54; nmr ($CDCl_3$) δ 3.1 (s, 4H, $-CH_2-CH_2-$), 4.25 (s, 2H, $-CH_2-Cl$) 7.06 (m, 8H, aromatic H).

10,11-Dihydro-5-(2-cyanoethyl-1,1-d_2)-5H-dibenz[b,f]azepine (5b). Prepared from 4b by the method described above for 5a, the product 5b had mp 145-150° (lit.[19] 150°). A mixed melting point with the authentic undeuterated sample was not depressed; ir (KBr): 2250 cm^{-1} (C≡N); tlc: (I_2) R_f (benzene) 0.31; nmr ($CDCl_3$) δ 2.49 (broad s, 2H, $-CH_2-C\equiv N$), 3.16 (s, 4H, $-CH_2-CH_2-$), 7.10 (8H, aromatic H); eims: 250 (42.8), 249 (7.6), 248 (1.9), 210 (100), 193 (54.2).

10,11-Dihydro-5-(3-aminopropyl-3,3-d_2)-5H-dibenz[b,f]azepine Hydrochloride (8.HCl). The cyanide 5a (100 mg, 0.427 mmol) was placed in a predried, flamed 25 ml Soxhlet extractor and lithium tetradeuteridoaluminate (99% d_4) (100 mg, 2,43 mmol) in 50 ml of anhydrous Et_2O was placed in a predried, flamed 50 ml flask cooled in a stream of N_2. The reaction mixture was refluxed for 86 hr. The excess deuteride was destroyed by the addition of 2 ml D_2O. To the cloudy solution was added 1 g of NaOH in 5 ml of water and the whole extracted with Et_2O. The ether layers were combined, washed with sat NaCl and dried over Na_2SO_4. The drying agent was removed and ethereal HCl was added until further addition produced no precipitation. The solution was cooled overnight and the filtrate recrystallized from EtOH to yield 8.HCl (100 mg, 0.35 mmol, 81%),

(100 mg, 0.35 mmol, 81%), mp 275-276° (lit.[15] 275°). A mixed melting point with the authentic undeuterated sample was not depressed; tlc (I_2) R_f (15 AcOH: 65 BuOH: 20 H_2O) 0.80; nmr ($CDCl_3$) δ 1.26 (s, 2H, $-NH_2$), 1.62 (broad t, $-CH_2-CH_2-CD_2$), 3.08 (s, 4H, $-CH_2-CH_2-$), 3.70 (t, 2H, J=6Hz, $N-CH_2$), 6.99 (m, 8H, aromatic H); eims: 254 (33.8), 253 (0.6), 237 (38.2), 208 (100), 194 (37.7), 193 (67).

10,11-Dihydro-5-(3-formamidopropyl-3,3-d_2)-5H-dibenz[b,f]azepine (9). To a solution of the amine 8 (50 mg, 0.1968 mmol) in 30 ml of dry benzene was added 2 ml of 98% formic acid all at once. The flask was equipped with a Dean-Stark separator for the removal of water. The reaction was refluxed for 6 hr, 2 ml of 98% formic acid were added and the mixture was refluxed overnight. After 24 hr of refluxing, the Dean-Stark apparatus was replaced with a Soxhlet extractor containing molecular sieve (3A) and refluxing continued for 24 hr. The solvent was removed under vacuum to leave a brown residue which was dissolved in Et_2O and washed with 50 ml of 10% HCl. The ether was dried over $MgSO_4$, filtered, and evaporated leaving a tan solid which recrystallized from acetonitrile to yield 39 mg (0.1 mmol, 70%) of 9 mp 142-143°, nmr ($CDCl_3$) δ 2.04 (broad t, 2H, $-CH_2-CH_2-CD_2-$), 3.1 (s, 4H, $-CH_2-CH_2-$), 3.81 (t, 2H, $N-CH_2-$), 6.40 (broad s, 1H, N-H), 7.05 (m, 8H, aromatic H), 8.10 (d, 1H, NOC-H); eims: 282 (42.3), 281 (1.5), 208 (100), 193 (43.1); cims: exact mass 282.1696 (calcd for $C_{18}H_{18}N_2OD_2$ 282.172).

10,11-Dihydro-5-(3-methylaminopropyl-3,3-d_2)-5H-dibenz[b,f]azepine (10.HCl) A 50 ml flask was dried in an oven, flamed and cooled in a dry N_2 atmosphere. The flask was equipped with a rubber septum, a magnetic stirring bar, and a reflux condenser which was connected to a N_2 bubbler. The flask was immersed in an ice bath and 5 ml (5 mmol) of 1 M borane solution in THF was introduced into the reaction flask. Then 0.0425 g (0.15 mmol) of the amide 9 in 12 ml of THF was introduced. The reaction was refluxed 6 hr, cooled to 5° and 5 ml of conc HCl in 5 ml of THF added carefully. The whole mixture was subjected to vacuum distillation. The residue was washed with Et_2O, treated with 0.1 N NaOH and extracted with Et_2O. The basic ether extract was washed with 10% $NaHCO_3$ and sat NaCl, dried over Na_2SO_4 and filtered. Freshly prepared ethereal

HCl was added to the filtrate until further addition produced no cloudiness. The solution was cooled overnight and the precipitate recrystallized from EtOH to yield 0.0334 g (0.11 mmol, 75%) of the hydrochloride of 10, mp 210-212° (lit.[15] 212-214°). A mixed melting point with the authentic undeuterated sample was not depressed. tlc (I_2) R_f (15 AcOH: 65 BuOH: 20 H_2O) 0.75; nmr ($CDCl_3/D_2O$) δ 2.02 (broad t, 2H, CH_2-CH_2-CD_2), 2.75 (s, 3H, N-CH_3), 3.10 (s, 4H, -CH_2-CH_2-), 3.8 (t, 2H, N-CH_2-), 7.00 (m, 8H, aromatic H); eims: 268 (38), 267 (3), 237 (100), 236 (80), 208 (65), 195 (60), 193 (66), 46 (80).

10,11-Dihydro-5-(3-dimethylaminopropyl-3,3-d_2)-5H-dibenz[b,f]azepine (11.HCl). To a stirred solution of 500 mg (2 mmol) of the amine 8 and 2 ml (25 mmol) of 37% aqueous formaldehyde in 15 ml of acetonitrile was added 500 mg (8 mmol) of sodium cyanoborohydride. A vigorous exothermic reaction ensued, and a dark residue separated. The reaction mixture was stirred for 15 min, and then 0.3 ml glacial HOAc was added dropwise over a priod of 7 min. Stirring was continued for 2 hr, and an additional 0.3 ml of glacial HOAc added. After stirring for an additional 30 min, the solution was diluted with 100 ml of Et_2O, washed with 20 ml of 0.5 N NaOH, and then extracted with three 10 ml portions of 1 N HCl. The acid extracts were combined, neutralized with solid NaOH, extracted with Et_2O, and the combined ether extracts dried (Na_2SO_4) and filtered. Ethereal HCl was added to the filtrate and the solid which separated was recrystallized from EtOh to yield 545 mg (1.7 mmol, 86%) of the hydrochloride of 11 mp 171-173° (lit.[20] mp 173-174°). A mixed melting point with the authentic undeuterated sample was not depressed; tlc (I_2) R_f (15 AcOH: 65 BuOH: 20 H_2O) 0.70; nmr ($CDCl_3$): δ 2.10 (broad t, 2H, -CH_2-CD_2-N), 2.68 (s, 6H, -N-(CH_3)$_2$), 3.15 (s, 4H, -CH_2-CH_2-), 3.75 (t, 2H, N-CH_2), 6.94 (m, 8H, aromatic H); eims: 283 (5), 282 (23.4), 281 (0.9), 237 (80.4), 236 (57), 208 (26.3), 86 (58), 60 (100), 36 (25).

10,11-Dihydro-5-(3-chloropropionyl)-5H-dibenz[b,f]azepine (6). To a stirred solution of 19.53 g (100 mmol), 10,11-dihydro-5H-dibenz[b,f]azepine 2 in 150 ml of anhydrous benzene was added dropwise a solution of 14.0 g (110 mol) 3-chloropropionyl chloride (freshly distilled) in 50 ml of dry benzene. The mixture was stirred at reflux for 3 hr or until HCl was no longer evolved. The

benzene was removed under vacuum to give an oil. The oil was heated to 70° under vacuum (ca 0.1 mm) for 1 hr to remove excess 3-chloropropionyl chloride, then cooled to room temperature, and Et_2O was added. The white solid was recrystallized from EtOH to yield 25 g (87.5 mmol) of the amide 6, mp 103-104° (lit.[18] 105-106°); ir (KBr) 1645 cm^{-1} (amide C=O); tlc (I_2) R_f (benzene) 0.38; nmr ($CDCl_3$) δ 2.46-3.98 (m A_2B_2 + AA'BB', 8H, $-CH_2-CH_2-$, $OC-CH_2-CH_2-Cl$), 7.12 (s, 8H, aromatic H).

Anal. Calcd for $C_{17}H_{16}ClNO$: C, 71.45; H, 5.64; N, 4.90. Found: C, 71.31; H, 5.67; N, 4.67.

10,11-Dihydro-5-(3-methylaminopropionyl)-5H-dibenz[b,f]azepine (7a). A 250 ml two-necked flask was oven-dried and equipped with a dry ice condenser and a rubber septum cap. The flask was immersed in an ice bath (0°) and 100 ml of dry toluene was introduced via syringe. Gaseous methylamine was condensed into the toluene until 4 ml was collected. To this solution was added 3 g (10.5 mmol) of the chloro compound 6 in 25 ml dry toluene. The reaction was stirred with cooling for 72 hr and finally refluxed for 2 hr.

The solution was filtered to remove the $(CH_3)NH_2.HCl$ and the resulting solution was concentrated under vacuum to yield 7a as an oil. The oil was dissolved in Et_2O and Et_2O-HCl was added until further addition produced no cloudiness. The hydrochloride salt of 7a was hygroscopic and could not be crystallized; it was dissolved in H_2O and treated with aqueous lithium picrate to yield the picrate of 7a. Recrystallization from EtOH afforded an analytical sample, mp 140-141° (dec). Nmr ($CDCl_3$) δ 2.5-3.6 (compm, 12H, methylenes H and $-NCH_3$), 7.3 (m, 8H, aromatic H), 8.8 (s, 2H, picric acid H).

Anal. Calcd for $C_{24}H_{23}N_5O_8$: C, 56.58; H, 4.55; N, 13.75. Found: C, 56.31; H, 4.56; N, 13.63.

10,11-Dihydro-5-(3-methylaminopropyl-1,1-d_2)-5H-dibenz[b,f]azepine (12.HCl). A 100 ml flask was dried in an oven, flash flamed and cooled down in a dry N_2 atmosphere. The flask was equipped with a rubber septum cap and a magnetic stirring bar, and a reflux condenser connected to an N_2 source. The flask was immersed in an ice bath (ca 5°) and 11.4 ml (10 mmol) of 0.88 M BD_3-THF was

introduced into the reaction flask. Then 2.7 g (10 mmol) of the amide 7a in 8.6 ml of THF was introduced over a period of 0.5 hr. After the addition was completed, the resulting mixture was refluxed for 3 hr. The reaction flask was cooled and 10 ml of 6 N HCl was added slowly. The THF was removed under vacuum as hydrogen was evolved. The aqueous phase was basified with solid NaOH and extracted with Et_2O. After drying over sodium sulfate, the ether was acidified with ethereal HCl. The hydrochloride of 12 was recrystallized from absolute EtOH to give 2.4 g (8 mmol, 80%), mp 210-212° (lit.[20] 212-214°). A mixed melting point with the authentic undeuterated sample was not depressed; tlc (I_2) R_f (15 AcOH: 65 BuOH: 20 H_2O) 0.75; Nmr ($CDCl_3$) δ 2.00 (broad t, 2H, $-CD_2-C\underline{H}_2-CH_2-$), 2.42 (m, 3H, $-NCH_3$), 2.85 (broad t, 2H, $-C\underline{H}_2-CH_2-N$), 3.15 (s, 4H, $-C\underline{H}_2-C\underline{H}_2-$), 7.09 (m, 8H, aromatic H); eims 268 (35.7), 267 (4.5), 266 (0.4), 235 (76.7), 195 (100), 193 (79.1), 44 (93.0).

10,11-Dihydro-5-(3-dimethylaminopropionyl)-5H-dibenz[b,f]azepine (7b). A 250 ml two-necked flask was oven-dried and equipped with a dry ice condenser and a rubber septum cap. The flask was immersed in an ice bath (0°) and 100 ml of dry toluene was introduced via syringe. Gaseous dimethylamine was condensed into the toluene until 4 ml was collected. To this solution was added 3 g (10.5 mmol) of the chloro compound 6 in 25 ml dry toluene. The reaction was stirred with cooling for 72 hr and finally refluxed for 2 hr.

The solution was filtered to remove the $(CH_3)_2NH.HCl$ and the resulting solution was concentrated under vacuum to yield 2.50 g (8.4 mmol, 81%) of 7b as an oil $bp_{0.1}$ 180-182° (lit.[18] $bp_{0.2}$ 195-197°). The oil was dissolved in Et_2O and Et_2O-HCl was added until further addition produced no cloudiness. The hydrochloride salt of 7b was hygroscopic and was dissolved in H_2O and treated with aqueous lithium picrate to yield the picrate of 7b. Recrystallization from EtOH afforded an analytical sample, mp 179-181° (dec). Nmr ($CDCl_3$) δ 2.4-3.7 (compm, 14H, methylenes H, and $-N(C\underline{H}_3)_2$), 7.3 (m, 8H, aromatic H), 8.8 (s, 2H, picric acid H).

Anal. Calcd for $C_{25}H_{25}N_5O_8$: C, 57.36; H, 4.78; N, 13.38; Found: C, 57.25; H, 4.83; N, 13.29.

10,11-Dihydro-5-(3-dimethylaminopropyl-1,1-d_2)-5H-dibenz[b,f]azepine (13.HCl).

A 100 ml flask was dried in an oven, flash flamed, and cooled down in a dry N_2 atmosphere. The flask was equipped with a rubber septum cap and a magnetic stirring bar, and a reflux condenser connected to an N_2 source. The flask was immersed in an ice bath and 11.4 ml (10 mmol) of 0.88 M BD_3-THF was introduced in the reaction flask. Then 2.8 g (10 mmol) of the amide 7b in 8.6 ml of THF was introduced over a period of 0.5 hr. The reaction was then carried out as for 12 above, and the amorphous hydrochloride was dissolved in water and treated with a neutral solution of lithium picrate. The picrate of 13 crystallized from EtOH in 87% yield, mp 144-146° (dec). eims 282 (15.6), 281 (1.5), 236 (60.2), 235 (39.1), 87 (46.9), 58 (100).

The free base was liberated from the picrate by elution on a basic alumina column with chloroform. The chloroform was evaporated and ether added. Addition of Et_2O-HCl yielded the hydrochloride salt of 13, (1.8 g, 6.4 mmol, 64%), mp 171-173° (lit.[20] 173-174°). A mixed melting point with the authentic undeuterated sample was not depressed; tlc (I_2) R_f (15 AcOH: 65 BuOH: 20 H_2O) 0.70; nmr ($CDCl_3$) δ 2.08 (broad t, 2H, $-CD_2-CH_2-CH_2-$), 2.57 (s, 6H, $-N-(CH_3)_2$), 2.94 (broad t, 2H, $-CH_2-CH_2-N$), 3.10 (s, 4H, $-CH_2-CH_2-$), 7.04 (m, 8H, aromatic H); eims: 282 (19.5), 281 (2.3) 236 (72.2), 235 (42.9), 234 (15.7), 210 (16.8), 87 (45.6), 58 (100), 36 (21.4).

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