# DEUTERIUM LABELLING OF THE ANTIDEPRESSANT DRUG DOXEPIN FOR DISPOSITION STUDIES IN HUMAN SUBJECTS

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## SUMMARY

Two methods have been developed for the introduction of deuterium into the doxepin molecule. The key intermediate (6,11-dihydro-1,2,3,4-$^2H_4$-dibenz[b,e]oxepin-11-one, **5**) was prepared by condensation of ethyl 2-bromomethylbenzoate with [$^2H_6$]-phenol, saponification of the resulting ester, and dehydration with trifluoroacetic anhydride. Using this key intermediate, E-(1,2,3,4)-$^2H_4$-doxepin was prepared for administration to human subjects. (1,2,3,4)-$^2H_4$-N-desmethyldoxepin, (1,2,3,4,1',2',2')-$^2H_7$-doxepin, (1,2,3,4)-$^2H_4$-($N^2H_3$)$_2$-doxepin ($^2H_{10}$-doxepin) and (1,2,3,4,1',2',2')-$^2H_7$-N-desmethyldoxepin were also prepared for use as internal standards in GC/MS assays. The deuterated compounds contained less than 0.5 % protium impurity.

Key words: Deuterium, doxepin, N-desmethyldoxepin, cis-trans isomerization, stable isotopes, mass spectrometry.

## INTRODUCTION

Doxepin (Sinequan, Adapin) **1**, a mixture containing 15 % Z- and 85 % E-isomers of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin, has gained widespread use in the treatment of depression (1). In most pharmacological tests the Z-isomer is more potent than the E-isomer (2). In comparison to most other marketed tricyclic antidepressant drugs, little is known about the factors determining its disposition (3,4). Doxepin is extensively metabolized in human subjects. Identified metabolites include: N-desmethyldoxepin **2**, doxepin N-oxide and a hydroxylated metabolite and its conjugate(s) (5,6). It is known that the N-desmethyl metabolite also possesses activity although the relative potency of the Z- and E- isomers has not been determined. Considerable (10 to 80-fold) inter-subject variability exists in the plasma concentrations of both doxepin and N-desmethyldoxepin following administration of a standard doxepin dose (3,7,8). Further, it has been reported that the steady-state Z/E ratio of N-desmethyldoxepin is different

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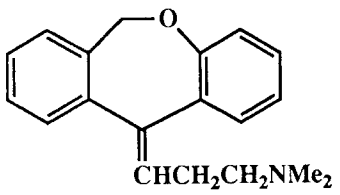
from the administered dose of doxepin (9,10). This could arise as a consequence of isomerization of the doxepin or may be a reflection of different disposition of the two doxepin isomers. The purpose of the present study was to develop methodology that would allow the mechanism of this apparent inversion to be examined.

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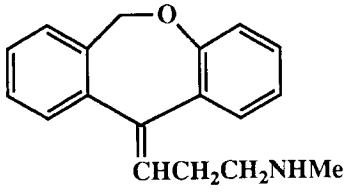



2

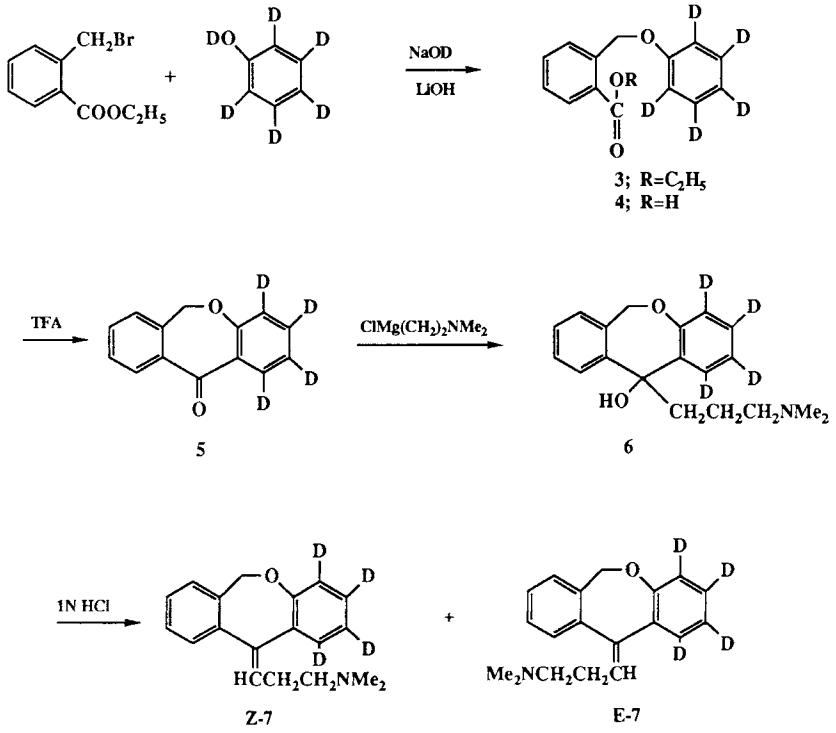
A number of analytical approaches, including gas chromatography (GC) (9-13), GC/mass spectrometry (MS) (14,15), radioimmunoassay (16) and high performance liquid chromatography (HPLC) (12, 17-21) have been used to quantify doxepin and its N-desmethyl metabolite. After reviewing these methods, it was considered that GC/MS in conjunction with stable isotope dilution techniques would be the most suitable for elucidating the mechanism of Z-E isomerization. This required the preparation of a dosage form of doxepin where one isomer was labelled with deuterium and the other was not. Such methodology has been used previously for kinetic and metabolic studies of drug enantiomers (22). We report the preparation of E-$^2H_4$-doxepin with the label in a site that is not lost during N-dealkylation for administration to human subjects. We also report the preparation of $^2H_4$-N-desmethyldoxepin, $^2H_7$-doxepin, $^2H_{10}$-doxepin and $^2H_7$-N-desmethyldoxepin (as mixtures of E and Z isomers) for use as internal standards in GC/MS studies.

## RESULTS AND DISCUSSION

Tetradeuterated doxepin was synthesized from readily available o-toluic acid (Scheme-1). o-Toluic acid was converted to ethyl o-bromomethylbenzoate using standard procedures. Condensation of the ester with sodium $^2H_6$-phenoxide using the reported method (23) gave a very poor yield of phenoxymethyl benzoyl ester. This may have been due to the insolubility of ethyl bromomethylbenzoate in water. The use of benzyltrimethylammonium hydroxide as a phase transfer catalyst and toluene as solvent provided the ether **3** in quantitative yield. Saponification of **3** with LiOH in dimethoxyethane (DME), provided the acid **4** in excellent yield. Treatment of **4** with

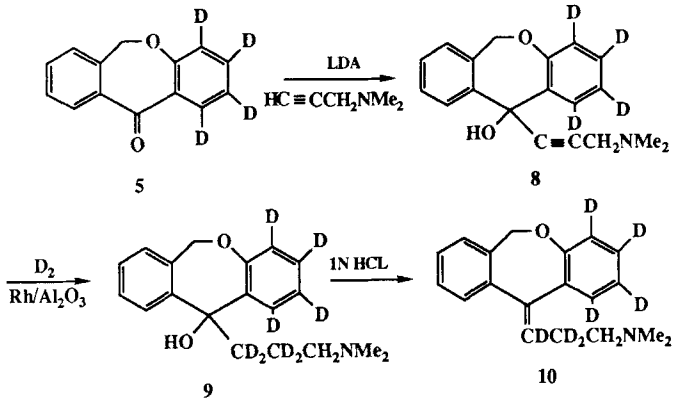
anhydrous trifluoroacetic anhydride provided the key tetradeuterated dibenzoxepin intermediate **5**.

Condensation of dibenzoxepin **5** with the Grignard reagent prepared from 3-dimethylaminopropyl chloride followed by dehydration of the resulting alcohol **6** with dilute HCl gave the $^2H_4$-doxepin **7** as a mixture of Z- and E- isomers in a ratio of 15:85. The $^2H_0$-content as determined by positive chemical ionization (PCI) MS was < 0.3 %. The geometric isomers were separated and purified by reversed-phase HPLC.




Scheme-1.

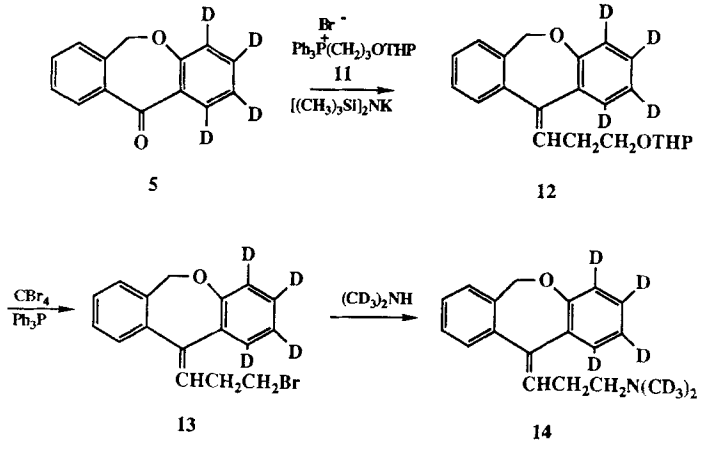
Heptadeuterated doxepin was prepared from dibenzoxepin **5** as shown in Scheme-2. Condensation of **5** with 1-dimethylamino-2-propyne in the presence of lithium diisopropylamide (LDA) gave acetylenic alcohol **8**, which was hydrogenated with deuterium gas to provide $^2H_8$-alcohol **9**. It was found that when Pd/C was used as a catalyst the reduction failed to go to completion. However, both $Rh/Al_2O_3$ and $PtO_2$ gave excellent yields of the desired tertiary alcohol **9**. Dehydration with DCl or HCl yielded the required $^2H_7$-doxepin **10** as a mixture of Z- and E- isomers in the ratio 15:85.




5 8 9 10

Scheme-2

The introduction of deuterium into the N-methyl groups of doxepin was carried out as shown in Scheme-3. Phosphonium salt **11** (24) was converted to an ylide by reaction with potassium bis(trimethylsilyl)amide in THF. Ketone **5** was then treated with this ylide and converted to the propylidene derivative **12**. The mixture of Z- and E- isomers were in a ratio of 7:3. Conversion of THP ether **12** to bromide **13** (25) followed by the reaction with excess $^2H_6$-dimethylamine yielded $^2H_{10}$-doxepin **14** as a mixture of Z- and E- isomers (7:3). The $^2H_0$-content was < 0.3 % as determined by PCI MS.

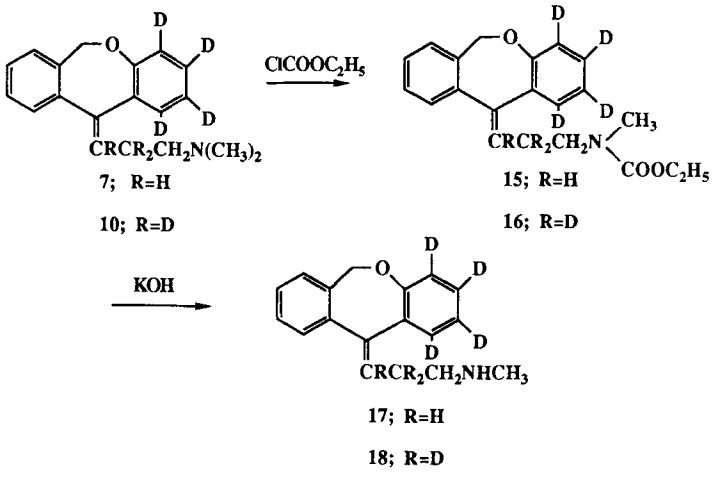



5 12 13 14

Scheme-3

Treatment of the deuterated doxepin derivatives **7** and **10** with a 4 molar excess of ethyl chloroformate (26) gave the carbamates **15** and **16**. The carbamates were hydrolyzed with alcoholic KOH to give the desired deuterated N-desmethyldoxepin derivatives **17**, **18**

as a mixture of Z- and E- isomers (15:85) (Scheme-4). The $^2H_0$-content of **17** was 0.38 % and of **18** was < 0.3 % as determined by PCI MS.




Scheme-4

## EXPERIMENTAL SECTION

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. $^1$H-NMR Spectra were recorded in $CDCl_3$ on a Bruker/IBM NR 300. Chemical shifts ($\delta$ ppm) are reported relative to $Me_4Si$ as an internal standard. Mass spectra were obtained on a Finnigan Incos 50B quadrupole instrument interfaced to a Hewlett-Packard 5890 gas chromatograph under electron impact (EI) or PCI conditions. Injections were made in the splitless mode on a SPB-1 fused silica capillary column (0.32 mm i.d., 0.25 $\mu$m coating thickness; Supelco, Bellefonte, PA). Under standard GC conditions, the column was temperature programmed from 100 °C to 300 °C at 20 °C/min with helium as carrier gas at a flow rate of 1 ml/min. Methane was used as the reagent gas for PCI at an analyzer pressure of 5 x $10^{-5}$ Torr.

Flash chromatography was carried out on S/P silica gel 60 A°. Thin layer chromatography (TLC) was performed on Analtech silica gel GF uniplates. THF was distilled from sodium benzophenone ketyl immediately prior to use. All other solvents were reagent grade and were used directly. Reactions were carried out under a dry nitrogen atmosphere.

The HPLC system consisted of a Waters (Milford, MA, USA) Model 510 gradient delivery system, a Lambda Max Model 481 spectrophotometer set at 254 nm, a Shimadzu

C-R3A integrator and a Valco injector. An Ultrasphere semi-preparative column was used (250 mm x 10 mm, 5$\mu$m; Altex) with diisopropyl ether/methylene chloride/ methanol/perchloric acid (76:12:11:0.5) as mobile phase at a flow rate of 3 ml/min.

Ethyl o-1,2,3,4,5-($^2H_5$)-phenoxymethylbenzoate **3.** To a magnetically stirred solution of benzyltrimethylammonium hydroxide (1.5 ml, 20% solution in methanol) and ethyl o-bromomethylbenzoate (16.0 g, 0.066 mol) (21) in toluene (100 ml) was added a solution of $^2H_6$-phenol (5.0 g, 0.05 mol) in NaOD (25.5 ml, 2.5 N). The reaction mixture was stirred vigorously at 80 °C for 3 h. It was then cooled to room temperature and the organic product was extracted with ethyl acetate (3x50 ml). The organic extracts were washed successively with 10% aqueous $Na_2CO_3$ solution, saturated brine and dried ($MgSO_4$). Evaporation of the solvent followed by purification of the residue on a silica gel column using hexane/ethyl acetate (95:5) as solvent gave pure ester **3** as a colorless oil {11.8 g, 91%; protium analog was an oil (23)}. NMR ($\delta$) 7.95 (d, 1H, aromatic), 7.60 (d, 1H, aromatic), 7.46 (t, 1H, aromatic), 7.34 (t, 1H, aromatic), 5.04 (s, 2H, benzyloxy), 4.42 (q, 2H, O$\underline{CH_2}CH_3$) and 1.38 (t, 3H, OCH$_2\underline{CH_3}$). EI mass spectrum (m/z) 261 (molecular ion, $M^{+\cdot}$), 216 ($M^{+\cdot}$-$OC_2H_5$), 163 ($M^{+\cdot}$-$OC_6D_5$), 135 ($M^{+\cdot}$-$OC_6D_5$-$C_2H_5$+H) and 118 ($M^{+\cdot}$-$OC_6D_5$-$OC_2H_5$). It showed the following isotope distribution: $^2H_0$, < 0.3%; $^2H_1$, 0.44%; $^2H_2$, 0.01%; $^2H_3$, 0.77%; $^2H_4$, 10.97%; $^2H_5$, 100%.

o-1,2,3,4,5-($^2H_5$)-Phenoxymethylbenzoic acid **4.** Ester **3** (12.5 g, 0.048 mol) was dissolved in DME (100 ml) and LiOH (100 ml, 3 N) was added. The reaction mixture was stirred at 60 °C for 2 h, cooled to room temperature and then poured into ice cold water (50 ml). After acidification with HCl (4 N) the precipitate was filtered, washed with water and dried over $P_2O_5$ for 16 h. The yield was 9.2 g (82%). A small sample crystallized from methanol as prismatic needles, m.p. 121-123 °C {protium analog m.p. 118-122 °C (23)}.

6,11-Dihydro-1,2,3,4-$^2H_4$-dibenz[b,e]oxepin-11-one **5.** A solution of trifluoroacetic anhydride (30 ml) was added to 2-phenoxymethylbenzoic acid **4** (9.0 g, 0.038 mol) in small portions over 30 min. The reaction mixture was stirred for an additional 3 h and then poured into ice cold water (100 ml). Aqueous NaOH (50%) was added to the suspension until the pH was 12 and the organic layer was extracted with ethyl acetate (3x50 ml). The combined ethyl acetate extracts were washed with water and dried ($MgSO_4$). Concentration of the solvent and the purification of the residue on a silica column using ethyl acetate/hexane (5:95) as solvent yielded the pure ketone **5** (6.1 g, 73.8%), m.p. 73-75

°C {protium analog m.p. 70.5-71.5 °C (23)}. NMR 7.88 (d, 1H, aromatic), 7.53 (m, 1H, aromatic), 7.43 (m, 1H, aromatic), 7.32 (d, 1H, aromatic) and 5.12 (s, 2H, benzyloxy). EI mass spectrum (m/z) 214 ($M^{+\cdot}$), 185 ($M^{+\cdot}$-CO-H) It showed the following isotope distribution: $^2H_0$, 0.12%; $^2H_1$, 1.0%; $^2H_2$, 9.63%; $^2H_3$, 71.87%; $^2H_4$, 100%.

11-(3-Dimethylaminopropyl)-6,11-dihydro-1,2,3,4-$^2H_4$-dibenz[b,e]oxepin-11-ol **6.** To a stirred suspension of magnesium turnings (920 mg, 0.038 mol) in ether (5 ml), a crystal of iodine and few drops of methyl iodide were added slowly with gentle heating. A solution of freshly distilled dimethylaminopropyl chloride (4.6 g, 0.038 mol) in ether (75 ml) was then added slowly. After all the alkyl halide had been added, the suspension was heated at reflux for 2 h. A solution of ketone **5** (4.0 g, 0.019 mol) in ether (40 ml) was added dropwise over a period of 1.5 h to the refluxing Grignard reagent. The reaction mixture was heated under reflux for an additional 12 h. The reaction was cooled to room temperature and aqueous $NH_4Cl$ (20 ml, 10%) followed by ice water (20 ml) were added. The organic layer was separated and the aqueous solution was extracted with ether (2x25 ml). The combined organic extracts were washed with water (2x25 ml) and dried ($MgSO_4$). The solvent was evaporated and the residue was purified on a silica gel column using 2% $CH_3OH$ in $CH_2Cl_2$ as solvent to yield pure alcohol **6** (4.12 g, 73%), m.p. 118-120 °C {protium analog m.p. 121-123 (23)}. NMR ($\delta$) 8.16 (d, 1H, aromatic), 7.32 (m, 1H, aromatic), 7.24 (m, 1H, aromatic), 6.97 (d, 1H, aromatic), 5.55 (d, 1H, benzyloxy), 5.13 (d, 1H, benzyloxy), 3.21 (m, 1H, H-1'), 2.36 (m, 8H, H-3' and $N(CH_3)_2$), 2.15 (m, 1H, H-1') and 1.51 (m, 2H, H-2'). PCI mass spectrum (m/z) 302 ($MH^+$), 284 (M-OH). It showed the following isotope distribution: $^2H_0$, <0.3 %; $^2H_1$, <0.3%; $^2H_2$, 3.94%; $^2H_3$, 40.28%; $^2H_4$, 100%.

11-(3-Dimethylaminopropylidene)-6,11-dihydro-1,2,3,4-$^2H_4$-dibenz[b,e]oxepin **7.** A suspension of alcohol **6** (4.1 g, 13.6 mmol) in HCl (100 ml, 1 N) was heated at 100 °C for 1 h. Aqueous NaOH (6 N) was added until the pH reached 11. The liberated product was extracted with ethyl acetate (2x50 ml) and the combined extracts were washed with water and dried over $MgSO_4$. Evaporation of the solvent and purification of the residue on a silica gel column using $CH_2Cl_2/CH_3OH/(C_2H_5)_3N$ (97:2:1) as solvent yielded $^2H_4$-doxepin **7** (3.6 g, 93%) as a mixture of Z- and E- isomers (15:85), m.p. 181-182 °C. NMR ($\delta$) 7.26 (m, 4H, aromatic), 6.01 (t, 0.85H, E =CH), 5.68 (t, 0.15H, Z =CH), 4.82 to 5.35 (bs, 2H, benzyloxy), 2.38 (m, 4H, H-2' and H-3') and 2.13 (s, 6H, $N(CH_3)_2$). PCI mass spectrum (m/z) 284 ($MH^+$). It showed the following isotope distribution: $^2H_0$, < 0.3%; $^2H_1$, <0.3%;

$^2H_2$, 27.22%; $^2H_3$, 5.18%; $^2H_4$, 100%. The isomers were separated and purified on semi-preparative HPLC. The pure isomers were then converted to hydrochloride salts by mixing an acetone solution of the free base with 1N HCl and evaporating the resultant solution.

11-(3-Dimethylaminoprop-1-ynyl)-6,11-dihydro-1,2,3,4-$^2H_4$-dibenz[b,e]oxepin-11-ol **8.** To a magnetically stirred solution of 1-dimethylamino-2-propyne (250 mg, 2.80 mmol) in THF (3.5 ml) was added dropwise a solution of LDA (2.8 ml, 2.80 mmol, 1 M) at -78 °C. The reaction mixture was stirred for 15 min and then ketone **5** (500 mg, 2.34 mmol) in THF (2ml) was added in one portion. The reaction mixture was slowly warmed to 25 °C and allowed to stir for an additional 10 h. Ether (50 ml) was added, followed by saturated $NH_4Cl$ solution (5 ml). The organic layer was separated and the aqueous solution was further extracted with ether (2x20 ml). The combined extracts were washed with water (10 ml), brine (10 ml) and dried over $MgSO_4$. The organic extracts were evaporated and the residue was purified on a silica gel column using 2% methanol in methylene chloride as solvent to give the acetylenic alcohol **8** as a white solid (620 mg, 89.3%), m.p. 134-135 °C. NMR ($\delta$) 8.02 (m, 1H, aromatic), 7.30 (m, 2H, aromatic), 7.13 (m, 1H, aromatic), 5.52 (d, 1H, benzyloxy), 5.16 (d, 1H, benzyloxy), 3.47 (s, 2H, H-3') and 2.33 (s, 6H, $N(CH_3)_2$). EI mass spectrum (m/z) 297 ($M^{+\cdot}$), 280 ($M^{+\cdot}$-OH), 253 ($M^{+\cdot}$-$N(CH_3)_2$) and 235 ($M^{+\cdot}$-$N(CH_3)_2$-$H_2O$). It showed the following isotope distribution: $^2H_0$, < 0.3%; $^2H_1$, < 0.3%; $^2H_2$, 1.32%; $^2H_3$, 10.87%; $^2H_4$, 100%.

11-(3-Dimethylamino-1,1,2,2-$^2H_4$-propyl)-6,11-dihydro-1,2,3,4-$^2H_4$-dibenz[b,e]oxepin-11-ol **9.** $Rh/Al_2O_3$ (60 mg) in ethyl acetate (5 ml) was charged with deuterium gas for 5 min. The alcohol **8** (400 mg, 1.34 mmol) in ethyl acetate (10 ml) was added and the suspension was magnetically stirred under a deuterium atmosphere until the uptake of deuterium ceased (2h, 58 ml). The catalyst was removed by filtration and washed with more ethyl acetate. Evaporation of the combined organic solvents and purification of the residue by flash chromatography (2% methanol in methylene chloride) provided octadeuterated alcohol **9** (304 mg, 74.1%) as white solid, m.p. 102-105 °C {protium analog m.p. 121-123 °C (23)}. NMR ($\delta$) 8.07 (d, 1H, aromatic), 7.23 (m, 1H, aromatic), 7.14 (m, 1H, aromatic), 6.96 (d, 1H, aromatic), 5.44 (d, 1H, benzyloxy), 5.04 (d, 1H, benzyloxy), 3.39 (s, 2H, H-3') and 2.29 (s, 6H, $N(CH_3)_2$). PCI mass spectrum (m/z) 306 ($M^{+\cdot}$), 287 ($MH^+$-$H_2O$).

11-(3-Dimethylamino-1,2,2-$^2H_3$-propylidene)-6,11-dihydro-1,2,3,4-$^2H_4$-dibenz[b,e]oxepin **10.** Dehydration of alcohol **9** (300 mg. 0.98 mmol) with HCl (10 ml) as described for **7** yielded

$^2H_7$-doxepin **10** as a free base, which was then converted to hydrochloride salt (256 mg, 92%), m.p. 178-181 °C. PCI mass spectrum (m/z) 287 ($MH^+$). It showed isotope distribution as follows: $^2H_0$, < 0.3%; $^2H_1$, < 0.3%; $^2H_2$, 1.58%; $^2H_3$, 10.57%; $^2H_4$, 35.76%; $^2H_5$, 65.62%; $^2H_6$, 100.00; $^2H_7$, 83.62%.

11-[3-(Tetrahydro-2H-pyran-2-yl)oxypropylidene]-6,11-dihydro-1,2,3,4-$^2H_4$-dibenz[b,e]-oxepin **12.** To a magnetically stirred suspension of 3-(tetrahydro-2H-pyran-2-yl)oxypropyl triphenylphosphonium bromide **11** (4.15 g, 8.6 mmol) in dry THF (6 ml) was added dropwise a solution of potassium bis(trimethylsilyl)amide (17.2 ml, 8.6 mmol, 0.5 M in hexane) at room temperature and the mixture was stirred for 1 h when a deep orange color was obtained. It was then cooled to 0 °C and ketone **5** (500 mg, 2.34 mmol) in THF (1 ml) was added and the reaction mixture was stirred for 3 h at room temperature. After quenching with saturated solution of $NaHCO_3$ (5 ml) the product was extracted with ethyl acetate (2 x 25 ml). The combined extracts were washed with water and dried ($MgSO_4$). The solvent was evaporated and the residue was purified on a silica gel column using 5% ethyl acetate in hexane as solvent to provide pure **12** as an oil (620 mg, 78%). NMR ($\delta$) 7.26 (m, 4H, aromatic), 6.04 ( t, 0.3H, E =CH), 5.71 (t, 0.7H, Z =CH), 5.18 (bs, 2H, benzyloxy), 4.58 (m, 1H, methine of THP), 3.82 (m, 2H, H-3'), 3.49 (m, 2H, $CH_2$-CH of THP) and 1.48 to 1.72 (m, 8H, THP and H-2'). EI mass spectrum (m/z) 340 ($M^{+\cdot}$), 256 ($M^{+\cdot}$-THP+H), 240 ($M^{+\cdot}$-OTHP+H), 212 ($M^{+\cdot}$-$CH_2CH_2$OTHP+H).

11-(3-Bromopropylidene)-6,11-dihydro-1,2,3,4-$^2H_4$-dibenz[b,e]oxepin **13.** A solution of THP ether **12** (500 mg, 1.47 mmol) in $CH_2Cl_2$ (25 ml) was stirred magnetically and treated with $CBr_4$ (635 mg, 1.91 mmol). The solution was cooled (-40 °C) and treated with triphenylphosphine (500 mg, 1.91 mmol) in four portions (15 min). The mixture was then warmed slowly to 25 °C over 1.5 h. Evaporation of the solvent and purification of the residue on a silica gel column using 5% ethyl acetate/hexane as solvent yielded the required bromide **13** as an oil (345 mg, 74%). NMR ($\delta$) (7.26 m, 4H, aromatic), 6.04 (t, 0.3H, E =CH), 5.71 (t, 0.7H, Z =CH), 5.18 (bs, 2H, benzyloxy), 3.46 (m, 2H, H-3') and 1.52 (m, 2H, H-2'). PCI mass spectrum (m/z) 321/319 ($MH^{+\cdot}$), 239 ($M^{+\cdot}$-Br).

11-(3-$^2H_6$-Dimethylaminopropylidene)-6,11-dihydro-1,2,3,4-$^2H_4$-dibenz[b,e]oxepin **14.** To a solution of bromide **13** (32 mg, 0.1 mmol) in absolute ethanol (1.0 ml) was added an excess of $^2H_6$-dimethylamine (30% solution in ethanol) and the reaction mixture was stirred at room temperature overnight. The solvent was evaporated and the residue purified on a

silica gel column using $CH_3OH/CH_2Cl_2$ (5:95) as solvent to give pure $^2H_{10}$-doxepin **14** (27 mg, 90%), m.p. 180-82 °C (HCl salt). PCI mass spectrum (m/z) 290 ($MH^+$). It showed the following isotope distribution: $^2H_0$, <0.3%; $^2H_1$, <0.3%; $^2H_2$, <0.3%; $^2H_3$, <0.3%; $^2H_4$, <0.3%; $^2H_5$, <0.3%; $^2H_6$, 0.71%; $^2H_7$, 23.07%; $^2H_8$, 14.83%; $^2H_9$, 0.66%; $^2H_{10}$, 100%.

11-(3-Methylaminopropylidene)-6,11-dihydro-1,2,3,4-$^2H_4$-dibenz[b,e]oxepin **17.** To a refluxing solution of ethyl chloroformate (270 mg, 2.5 mmol) in toluene (1 ml) was added **7** (170 mg, 0.6 mmol) in toluene (1 ml). The reaction mixture was heated under reflux for a further 10 h. Evaporation of the solvents and purification of the residue on a silica gel column using 25% ethyl acetate in hexane as solvent yielded carbamate derivative **15** (180 mg, 87.8%). PCI mass spectrum (m/z) 342 ($MH^+$), 296 ($MH^+$-$C_2H_5OH$) and 239 ($MH^+$-$N(CH_3)COOC_2H_5$-H).

Carbamate derivative **15** (180 mg, 0.53 mmol) was dissolved in ethanol (1.0 ml, 95%). Powdered KOH (180 mg) was added and the reaction mixture was heated under reflux for 12 h. After cooling to room temperature, water (3 ml) was added and the product was extracted with ethyl acetate (3x10 ml). The combined extracts were washed with water, brine and concentrated. Purification of the residue on a silica gel column using 5% MeOH in $CH_2Cl_2$ as solvent provided the pure $^2H_4$-N-desmethyldoxepin **17** (102 mg, 71.7%) as an oil. It was converted to the hydrochloride salt, m.p. 218-226 °C (decomp.). NMR ($\delta$) 7.26 (m, 4H, aromatic), 6.01 (t, 0.85H, E =CH), 5.68 (t, 0.15H, Z =CH), 4.82 to 5.35 (bs, 2H, benzyloxy), 2.38 (m, 4H, H-2' and H-3') and 2.23 (s, 3H, $NCH_3$). PCI mass spectrum (m/z) 270 ($MH^+$) and 239 (M-$NHCH_3$). It showed the following isotope distribution: $^2H_0$, 0.38%; $^2H_1$, 4.98%; $^2H_2$, 14.80%; $^2H_3$, 18.77%; $^2H_4$, 100%.

11-(3-Methylamino-1,2,2-$^2H_3$-propylidene)-6,11-dihydro-1,2,3,4-$^2H_4$-dibenz[b,e]oxepin **18.** Treatment of **10** with ethyl chloroformate gave the carbamate **16.** Base hydrolysis as described for **15** afforded pure heptadeuterated N-desmethyldoxepin **18** as a viscous oil {m.p. 210-218 °C (decomp.) HCl salt}. PCI mass spectrum (m/z) 273 ($MH^+$). It showed the following isotope distribution: $^2H_0$, <0.3%; $^2H_1$, 1.58%; $^2H_2$, 10.57%; $^2H_3$, 35.76%; $^2H_4$, 63.85%; $^2H_5$, 97.44%; $^2H_6$, 100%; $^2H_7$, 79.16%.

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