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Facile Synthesis of (R,S)-(Z) and (R,S)-(E)-N-Methyl-(10,11-dihydro-10-hydroxy-5H-Dibenzo[a,d]cycloheptene)-$\Delta^{8,\gamma}$-propylamine. The Major Metabolites of Amitriptyline and Nortriptyline

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FACILE SYNTHESIS OF (R,S)-(Z) AND (R,S)-(E)-N-METHYL-(10,11-DIHYDRO-10-HYDROXY-5H-DIBENZO[a,d]CYCLOHEPTENE)-$\Delta^{5,\gamma}$-PROPYLAMINE THE MAJOR METABOLITES OF AMITRIPTYLINE AND NORTRIPTYLINE

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Abstract: Efficient methods for the syntheses of amines **6b** and **9b**, the major metabolites of the antidepressant drugs amitriptyline **1a** and nortriptyline **1b**, are described.

The antidepressant drug amitriptyline **1a** has been shown to be oxidized *in vivo* to (Z) and (E) geometric isomers **6b** and **9b**[1,2]. Its desmethyl analogue nortriptyline **1b** was also found to give **6b** and **9b** as major metabolites[1]. The O-glucuronide conjugates of these metabolites have recently been described[2]. Despite the great interest in the antidepressive activity of these drugs[2-5], only two reports[2,6] describe the synthesis of their hydroxylated metabolites **6b** and **9b**. The syntheses reported involved the formation of a 75: 25[2] or a 50:50[6] mixture of the geometric isomers **5a**, **8a** which are subsequently demethylated in moderate yield. To date, none of these isomers have been selectively prepared.

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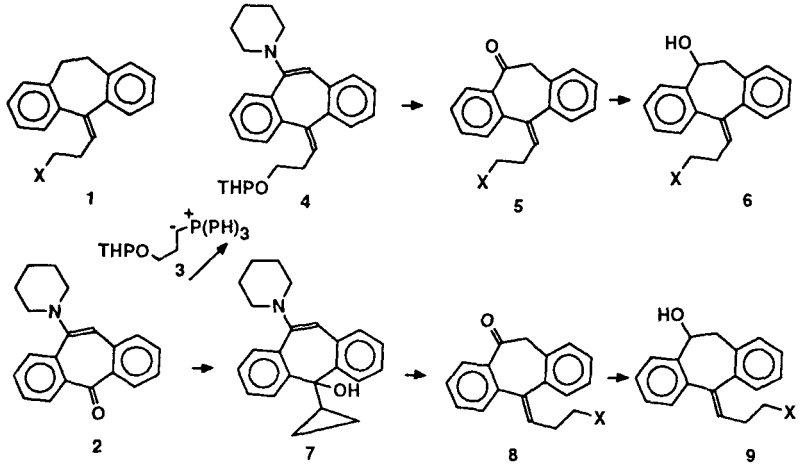

Scheme 1

Recently, the need of metabolites **6b** and **9b** prompted us to reinvestigate their synthesis. We developed a selective method for the synthesis of the Z isomer **6b** and a short synthesis for the E isomer **9b**.

The synthesis of **6b** proceeded according to Scheme 1. We were pleased to observe that the condensation of ketone **2** with tetrahydropyranyloxypropylphosphonium ylide **3**[8] afforded selectively the isomer **4** which was assigned the (Z) configuration on the basis of the ^{1}H NMR chemical shift reported for the vinylic proton of **5a**[2,6]. The tetrahydropyranyl and piperidyl groups of **4** were simultaneously removed under acidic conditions to give the ketoalcohol **5c** which was converted to the corresponding bromide **5d** under the condition described by Rabinowitz and Marcus[7]. The geometry of bromide **5d** was ascertained by X-ray crystallographic data which confirmed the (Z)

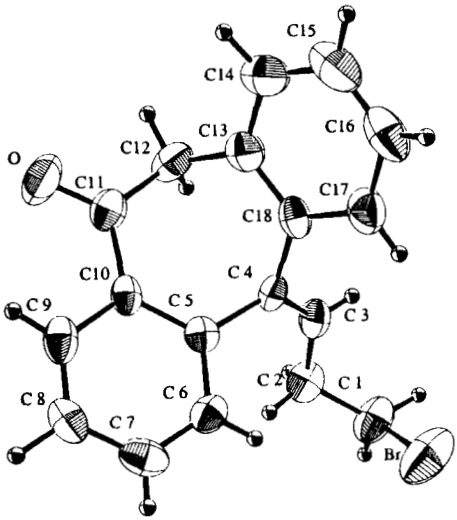

Fig 1. ORTEP view of the crystallographically determined structure for **5d**. (50% probability ellipsoid)

orientation of the bromoethyl moiety with respect to the ketone function (Fig. 1) . The latter was reduced with sodium borohydride to the bromoalcohol **6d** which was then treated with methylamine to give **6b** as an oil. Monomethylamine **6b** was crystallized as its oxalate, the ^{1}H NMR and melting point of which corresponded to literature values[2,6].

The preparation of **9b** proceeded according to an adaptation of the strategy developed by Hoffsommer *et al*[8]. Ketone **2** was treated with cyclopropylmagnesium bromide to give alcohol **7** as an unstable oil which was submitted to boiling in 48% aqueous HBr overnight to provide a 3:1 mixture of the E and Z geometric isomer **8d** and **5d**. The E isomer **8d** was easily isolated by fractional recrystallization from a 1:1 benzene/hexane mixture. The isomer ratio was assigned by the integration of the two triplets corresponding to the vinylic protons of the two isomers. A similar type of assignment was reported for the E and Z mixture of **6a** and **8a**[2,6].

The ketone function of the major isomer **8d** was reduced with sodium borohydride and its bromine displaced with methylamine to give **9b** which was recrystallized in the presence of maleic acid (1eq) to give the correponding maleate, the melting point and ^1H NMR parameters of which corresponded to literature values.

These synthetic routes are short and involve the use of inexpensive reagents. The major advantage of the first method is that it offers a unique and easy way to selectively access the minor Z isomer. Although the second method involve a mixture of isomers, the alkylbromides **5d** and **8d** are easily separated under the conditions described.

EXPERIMENTAL

Melting points were measured on a Gallenkamp block and are uncorrected. Thin-layer and flash chromatography were performed on silica gel 60 F_{254} aluminum plates and Merck Silica Gel 60 (230-400 mesh) respectively. ^1H NMR spectra were recorded on a Varian XL-200 at 200 MHz. All ^1H NMR spectra were run in $CDCl_3$ or in DMSO-d_6 and chemical shifts are reported downfield from TMS. All coupling constants are in Hz. Mass spectra were recorded on a Kratos MS25RFA instrument. All compounds were shown to be homogeneous by TLC and high-field NMR, or to have a purity of > 95% by elemental analysis. Unless otherwise stated, all reaction extracts were dried over magnesium sulphate.

5-(γ-Hydroxypropylidene)-(10,11-dihydro-10-oxo-5H-dibenzo[a,d])-cycloheptene (5c). n-Butyllithium (1,6M in hexane, 4.5 mL) was added dropwise at -80° C to a solution of tetrahydropyranyloxypropylphosphonium bromide **3** (2.6 g, 5.4 mmol) in THF (100 mL). . The temperature was slowly brought to room temperature and the mixture was stirred

until the color changed from pale yellow to brown. The temperature was brought down to 0° and ketone **2** (1.5 g, 1eq) in THF (10 mL) was introduced dropwise. The resulting mixture was stirred for 4 hrs at room temperature and the solvent evaporated under vacuum. Water was added and the solution extracted with methylene dichloride. The organic layer was removed, dried and evaporated, leaving a brown oily residue which was purified on a silica gel column (Hexane:ethyl acetate: 90:10) to give **4** (1.6 g, 73%, Z isomer only) as a white solid, m.p. 130-132° C. ^{1}H NMR (200 MHz; $CDCl_3$) δ: 7.75 (d, 1H, J=7.75, Ar), 7.3-7.2 (m, 7H, Ar), 6.1 (s, 1H, ArC=C*H*), 5.8 (t, 1H, J=7.55, vinyl CH), 4.5 (s, 1H, -OCHO-), 3.8 (m, 2H, -C=CHCH$_2$C*H*$_2$OTHP), 2.8 (m, 4H, piperidyl methylenes), 2.4 (m, 2H, -C=CHC*H*$_2$CH$_2$OTHP), 1.6 (m, 12H, tetrahydropyranyl and piperidyl methylenes). Anal. calcd. for $C_{28}H_{33}NO_2$: C, 81.15; H, 7.97; N, 3.38. Found: C, 80.99; H, 8.19; N, 3.44.

A solution of the tetrahydropyranyl ether **4** in 0.1N HCl (5 mL) and methanol (25 mL) was stirred for 6 hrs after which the reaction was quenched with saturated aqueous sodium carbonate (10 mL). The methanol was evaporated and the aqueous solution reextracted to give a white crystalline residue in quantitative yield, m.p. 120-122° C. ^{1}H NMR (200 MHz; $CDCl_3$) δ: 8.2 (d, J=7.13, Ar), 7.6-7.2 (m, 8H, Ar), 5.8 (t, 1H, J=7.55, vinyl CH), 4.4, 3.8 (double d, 2H, J_{gem}=13.70, $COCH_2$), 3.8 (t overlap with one of the $COCH_2$ doublets, 3H, -C=CHCH$_2$C*H*$_2$OH), 2.5 (m, 2H, -C=CHC*H*$_2$CH$_2$OH), 1.6 (s, OH, D_2O exchangeable); EIMS m/z (%) 264 ($M^{\cdot+}$, 23), 234 (100), 205 (80), 129 (28), 84 (29); HRMS calcd. for $C_{18}H_{16}O_2$: ($M^{\cdot+}$) 264.11502. Found: 264.1157. Anal. calcd. for $C_{18}H_{16}O_2$.0.5 H_2O: C, 79.09; H, 6.20. Found: C, 79.47; H, 6.37.

(Z)-5-γ-Bromopropylidene-10,11-dihydro-10-oxo-5H-dibenzo[a,d]-cycloheptene (6d).

A solution of the dried alcohol **5c** (1.5 g, 5.7 mmol), carbon tetrabromide (2 g, 1.1 eq)

and triphenylphosphine (0.7 g) in methylene dichloride (25 mL) was stirred for 2 hrs at 0°C. The solvent was evaporated and the resulting oil purified on a silica gel column (benzene: hexane: 90: 10) to give **5d** as a white powder which was recrystallized from benzene (1.2 g, 67%), m. p. 139-141 °C. ^{1}H NMR (200 MHz; $CDCl_3$) δ: 8.1, (d, J=7.50, Ar), 7.8-7.0 (m, 8H, Ar), 5.8 (t, J=7.94, vinyl CH), 4.5, 3.8 (double d, 2H, J_{gem}=13.73, CH_2CO), 3.4 (t, J=6.67, -CH=CHCH$_2$C*H*$_2$Br), 2.9 (m, 2H, -C=CHC*H*$_2$CH$_2$Br); EIMS m/z (%) 328 ($M^{\cdot+}$ + 2, 25), 326 ($M^{\cdot+}$, 100), 254 (35), 247 (98), 190 (60), 176 (30), 165 (55), 152 (30), 101 (30); HMRS calcd. for $C_{18}H_{15}O^{79}Br$ ($M^{\cdot+}$) 326.03067. Found: 326.0309. The structure of **5c** was ascertained by X-ray crystallography (Fig 1).

(R,S)-(Z)-N-methyl-(10,11-dihydro-10-hydroxy-5H-dibenzo-[a,d]-cycloheptene-δ$^{5,\gamma}$-propylamine (6b).

A solution of bromoketone **5d** (1 g, 3 mmol) was dissolved in methanol (15 mL) and reduced with sodium borohydride (0.1 g) at room temperature. After 1hr, the methanol was evaporated, water was added and the resulting solution extracted with methylene dichloride. The organic layer was dried and evaporated to give **6d** as a clear oil in quantitative yield. ^{1}H NMR (200 MHz; $CDCl_3$) δ: 7.8-7.0 (overlap of m, 8H, Ar), 5.8 (t, 1H, J=7.5, vinyl CH), 5.2 (m, 1H, C*H*OH), 3.6, 3.0 (d of m, 2H, CHOHC*H*$_2$-), 3.4 (t, 2H, J=7.37, -CH=CHCH$_2$C*H*$_2$Br), 2.7 (m, 2H, C=CHC*H*$_2$CH$_2$Br), 1.6 (br s, OH); EIMS m/z (%) 330 ($M^{\cdot+}$ + 2, 13), 328 ($M^{\cdot+}$, 25), 310 (23), 231 (23), 221 (39), 217 (53), 215 (50,5), 207 (40), 202 (26), 179 (100); HMRS calcd. for $C_{18}H_{17}O^{79}Br$ (M^+): 328.04632. Found: 328.0469.

A solution of the bromoalcohol **6d** (0.7 g, 2 mmol) and 40 % aqueous methylamine (5 mL) in acetonitrile (25 mL) was introduced to a pressure bottle which was kept in an oil bath at 60 °C for 5 hrs. Water was added and the resulting mixture extracted with

methylene dichloride. The organic layer was removed, dried over magnesium sulphate and evaporated to give **6b** (0.5 g, 89%) as a yellow oil (NMR parameters identical to reported values)[2,6] which was recrystallized from ethanol in the presence of oxalic acid (1eq) to form the oxalate salt as a white solid; m. p. 138-141 ^{o}C; lit[2,6]: 135-137 ^{o}C; CIMS (NH_3) m/z (%) 280 (MH^+, 100), 262 (46), 218 (45), 203 (24). Anal. calcd. for $C_{19}H_{21}NO.C_2H_2O_4.H_2O$: C, 65.11; H, 6.45; N, 3.61. Found: C, 64.63; H, 6.06; N, 4.06.

(E)-5-(γ-Bromopropylidene-(10,11-dihydro-10-oxo-5H-dibenzo[a,d]-cycloheptene (8d).- To a stirred solution of ketone **2** (4 g, 13.34 mmol) in tetrahydrofuran (20 mL) was added dropwise a solution of cyclopropylmagnesium bromide[8] (1M in THF, 25 mL) at 0^{o}C. The solution was stirred for 3 hrs and the solvent evaporated to give a brown oily residue to which was added water (20 mL). The resulting cloudy solution was extracted with methylene dichloride. The organic layer was removed, dried and evaporated to give **7** as a yellow oil which was found to be too unstable to be purified (EIMS m/z (%) 331 ($M^{\cdot+}$, 100), 248 (53), 219 (70), 178 (40), 97 (90); HMRS calcd. for $C_{23}H_{25}NO$ ($M^{\cdot+}$): 331.1936. Found: 331.1921). The oil was then immediately submitted to boiling in a mixture of 48 % HBr (20 mL) and glacial acetic acid (20 mL) overnight. The resulting dark solution was diluted with 100 mL of water and extracted with ether. The organic layer was separated and reextracted with a saturated sodium carbonate solution. The solvent was evaporated leaving a dark oily residue which was purified on silica gel (benzene: hexane 90:10) to give a white crystalline powder (3 g, 68%, mixture of the two geometric isomers). Recrystallization from a 50:50 benzene/hexane solution gave **8d** (1.8 g) as a crystalline residue, which was further recrystallized from the same solvent system to give the Z isomer in a pure state (1.3 g), m. p. 125-127 ^{o}C. ^{1}H NMR (200 MHz; $CDCl_3$) δ: 8.1, (d, J=7.50, Ar), 7.8-7.0 (m, 8H, Ar), 6.2 (t, J=7.94, vinyl CH), 4.5, 3.8 (double d, 2H, J_{gem}=13.73, CH_2CO), 3.4 (t, J=6.67, -C=CHCH$_2$CH_2Br), 2.8 (m, 2H,

C=CHCH_2CHBr); EIMS m/z (%) 328 ($M^{\cdot+}$ + 2, 22), 326 ($M^{\cdot+}$, 22), 247 (31), 219 (100), 205 (98); HMRS calcd. for $C_{18}H_{15}OBr$ ($M^{\cdot+}$): 326.03067. Found: 326.0309. Anal. calcd. for $C_{18}H_{15}OBr$: C, 66.26; H, 4.60; Br, 24.23 . Found: C, 66.15; H, 4.63; Br, 24.35.

(R,S)-(E)-N-methyl-(10,11-dihydro-10-hydroxy-5H-dibenzo-[a,d]-cycloheptene-$\delta^{5,\gamma}$-propylamine (9b).

The bromoketone **8d** (1g) was reduced with sodium borohydride (0.1 g) in methanol (15 mL) at room temperature. After 1hr, the methanol was evaporated, water was added and the resulting solution extracted with methylene dichloride. The organic layer was dried and evaporated to give a clear oil in quantitative yield. ^{1}H NMR (200 MHz; $CDCl_3$) δ: 7.8-7.0 (overlap of m, 8H, Ar), 5.8 (t, 1H, J=7.5, vinyl CH), 5.2 (m, 1H, C*H*OH), 3.6, 3.0 (d of m, 2H, CHOHCH_2-), 3.4 (t, 2H, J=7.37, -C=CH-CH_2CH_2Br), 2.7 (m, 2H, -C=CH-CH_2CH_2Br), 1.6 (br s, OH); EIMS m/z 330 ($M^{\cdot+}$ +1, 25), 328 ($M^{\cdot+}$, 25), 310 (23), 231 (23), 221 (39), 217 (53), 215 (50,5), 207 (40), 202 (26), 179 (100); HMRS calcd. for $C_{18}H_{17}O^{79}Br$: 328.04632. Found: 328.0469

A solution of the bromoalcohol **9d** (0.7 g) and 40 % aqueous methylamine (5 mL) in acetonitrile (25 mL) was introduced in a pressure bottle which was kept in an oil bath at 60 °C for 5 hrs. Water was added and the resulting mixture extracted with methylene dichloride. The organic layer was removed, dried and evaporated to give **9b** (0.5 g, 89%) as a yellow oil (^{1}H NMR parameters identical to reported values)[2,6], which was recrystallized from acetonitrile in the presence of maleic acid (1eq) to form the maleate, m. p. 150-153 °C; lit (isopropanol)[2]: 156-157 °C. CIMS (NH_3) m/z (%) 280 (MH^+, 100), 262 (66), 218 (36), 203 (16). Anal. calcd. for $C_{19}H_{21}NO.C_4H_4O_4$: C, 69.85; H, 6.37; N, 3.54. Found: C, 69.42; H, 6.46; N, 3.71.

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