# Syntheses of piperidine and perhydroazepine derivatives, precursors of two selective antagonists of muscarinic $M_2$ receptors: AF-DX 384 and its perhydroazepine isomer

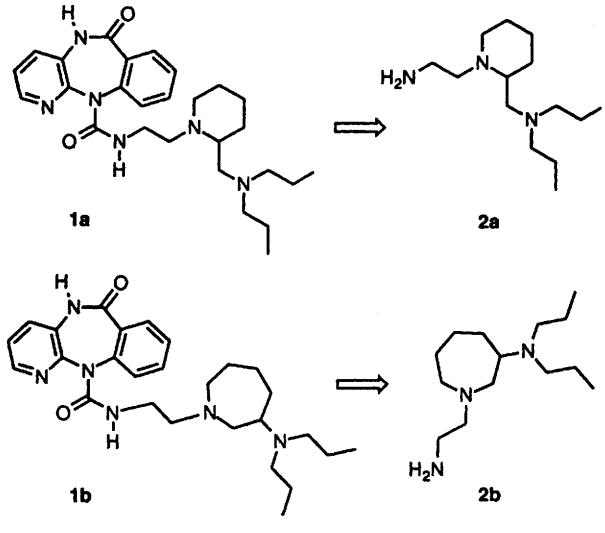
**Cécile Perrio-Huard, Christophe Ducandas, Marie Claire Lasne* and Bernard Moreau**

*Laboratoire de Chimie Moléculaire et Thioorganique (URA CNRS 480), Institut des Sciences de la Matière et du Rayonnement—Université de Caen-Basse Normandie—Cyceron PET Center, 6 Boulevard du Maréchal Juin, 14050 Caen, France*

**Several routes to the synthesis of the polyamines 2a and 2b required for the preparation of the muscarinic antagonists AF-DX 384 1a and its perhydroazepine isomer 1b respectively have been developed and compared. Piperidine 2a has been obtained in 4 steps in 13–15% overall yield from 2-(chloromethyl)-pyridine 3. The perhydroazepine 2b has been prepared in 4 steps in 49% overall yield from 3-aminolactam 7. Transformations of piperidinemethanol 11 afford exclusively compound 2a (5 steps, 17–20% overall yield), *via* the *N*-tosylpiperidine 12, but lead to a 1:1 mixture of isomers 2a and 2b (4 steps, 15–20% overall yield for compounds 2a and 2b) *via* the *N*-(cyanomethyl)piperidine 15. Limitations to the ring enlargement of piperidine derivatives as a function of the heterocyclic nitrogen substituent are defined.**

## Introduction

2-Piperidinemethanamine derivatives belong to the important class of vicinal diamines[1] useful as chelating agents and are valuable precursors for the preparation of several pharmaceuticals.[2–9] Hydrogenation under different catalytic conditions of 2-substituted pyridines[2–4,10–13] has been the most common route to these compounds. More recently, syntheses from pipecolic acid[3–5,14] and from piperidinemethanol[3] have been reported. They all required protection and deprotection steps. As a part of our programme to develop an efficient route to AF-DX 384 **1a**,[15] a potent and selective antagonist of muscarinic $M_2$ receptors,[2,16–18] we have been interested in the preparation of the piperidine **2a** (see Scheme 1). In order to compare



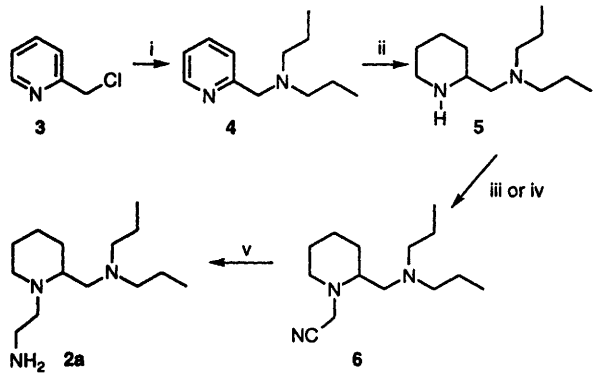

**Scheme 1**

its biological activity with that of its isomer **1b**, we have also prepared the azepine **2b**, perhydroazepine derivatives being known as potential biological active compounds.[2,6,19,20] Attempts to reproduce the synthesis of compound **2a** described in a patent[2] from 2-chloromethylpyridine **3** and involving a catalytic hydrogenation under atmospheric pressure, failed. We first defined new conditions for the obtention of the amine **2a** from 2-(methylchloro)pyridine **3**. We then synthesized the azepine **2b** by an unambiguous route from 3-aminocaprolactam **7**. Piperidinemethanol **11** being commercially available, we also studied its transformation into the amines **2a** and **2b**. The choice of the protecting group on the heterocyclic nitrogen atom appeared to be crucial for the selective preparation of the amine **2a** or for the obtention of a mixture of the amines **2a** and **2b**.

## Results and discussion

**Synthesis of the piperidine 2a from 2-(chloromethyl)pyridine 3**

2-(Chloromethyl)pyridine **3** (Scheme 2) was transformed to the




**Scheme 2** *Reagents and conditions:* i, $HNPr_2$ (1 mol equiv.), $Et_3N$, EtOH, 80 °C, 48 h; ii, $H_2$ (3.5 bar), $PtO_2$, AcOH, rt, 22 h; iii, $BrCH_2CN$, $Et_3N$, MeOH, rt, 24 h; iv, HCHO, KCN, $HCl_{aq}$, rt, 46 h; v, LAH, THF, rt, 2 h

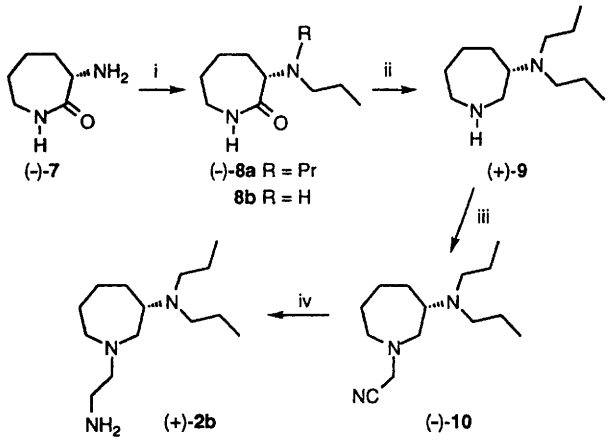
*N*,*N*-dipropylaminopyridine **4** by treatment with dipropylamine and $Et_3N$ in ethanol at 80 °C for 48 h (62% yield).[3] Catalytic hydrogenation of the pyridine **4** over $PtO_2$ in acetic acid at 3.5 bar† for 22 h at room temperature gave the corresponding piperidine **5** (63% yield).[2,21–23] Introduction of the cyanomethyl group that can generate the ethylamino function by reduction was performed by alkylation with bromoacetonitrile and $Et_3N$

† 1 bar = $10^5$ Pa.

in methanol at room temperature for 24 h (71% yield)[24] or by Mannich reaction using HCHO and KCN under acidic condition at room temperature for 46 h (62% yield).[2] Reduction with lithium aluminium hydride (LAH) in tetrahydrofuran (THF) at room temperature for 2 h converted the nitrile **6** into the desired amine **2a** (55% yield).[25] The piperidine **2a** was obtained in 4 steps from 2-(chloromethyl)pyridine **3** in 13–15% overall yield.

**Synthesis of the perhydroazepine 2b from 3-aminocaprolactam 7**

Commercially available L-(−)-3-aminocaprolactam (−)-**7** (Scheme 3) was bisalkylated into the caprolactam (−)-**8a** by



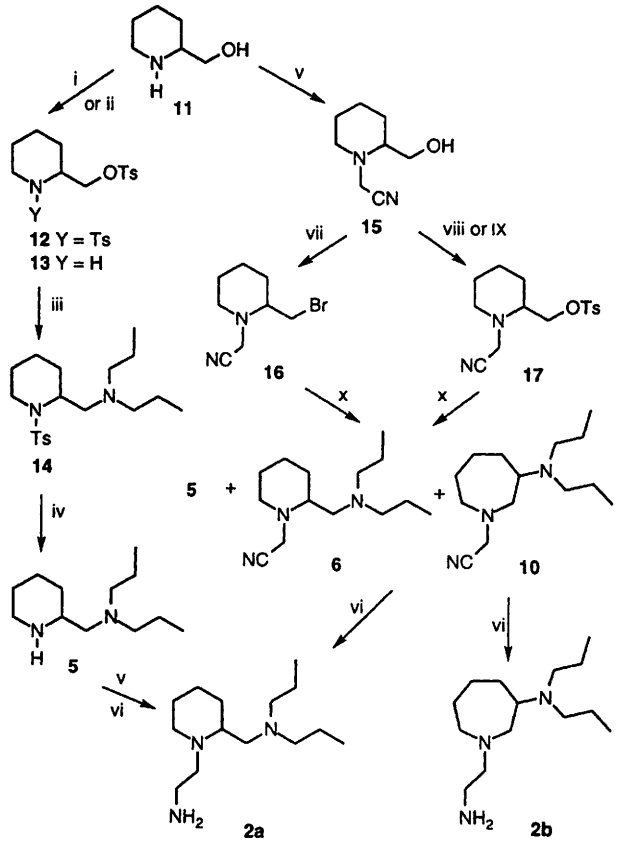

**Scheme 3** *Reagents and conditions:* i, PrBr (excess), $Et_3N$, MeOH, 65 °C, 15 h; ii, LAH, THF, 70 °C, 4.5 h; iii, $BrCH_2CN$, $Et_3N$, MeOH, rt, 24 h; iv, LAH, THF, rt, 2 h

reaction with 1-bromopropane in the presence of $Et_3N$ in methanol at 65 °C for 15 h (66% yield).[26] Although an excess of bromopropane (~5 mol equiv.) was used, small amounts of monoalkylated lactam **8b** were always obtained along with the bisalkylated product (−)-**8a** (~5% yield). The lactam (−)-**8a** was reduced with LAH in THF at 70 °C for 4.5 h to give the perhydroazepine (+)-**9** (90%).[5] Alkylation of the amine (+)-**9** with bromoacetonitrile and $Et_3N$ in methanol at room temperature for 24 h led to the nitrile (−)-**10** (94%).[24] Reduction with LAH in THF at room temperature for 2 h transformed the nitrile (−)-**10** into the desired perhydroazepine (+)-**2b** (88%).[25] Perhydroazepine (+)-**2b** was prepared in 4 steps from 3-aminocaprolactam (−)-**7** in 49% overall yield.

**Transformations of piperidine-2-methanol 11**

Direct conversion of piperidine-2-methanol **11** (Scheme 4) to the corresponding bromide by reaction with tetrabromomethane and triphenylphosphine in dichloromethane[27] did not succeed. Mono-O-tosylation of the amino alcohol **11** using tosyl chloride (1 mol equiv.) in the presence of triethylamine (1.1 mol equiv.) in dichloromethane at room temperature[28] was difficult to control and led to a mixture of the starting material **11**, the ditosyl derivative **12** and the monotosyl ester **13**. Reaction of the alcohol **11** with tosyl chloride (2 mol equiv.) in the presence of $Et_3N$ in dichloromethane at 40 °C for 24 h gave the ditosyl compound **12** (62% yield).[29] This latter was quantitatively converted into the N-tosylated piperidine **14** by reaction with dipropylamine at 110 °C for 48 h in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Deprotection of tosylamide **14** by treatment with phenol and HBr at 100 °C for 2 h gave the piperidine **5** (82% yield).[30] After transformation of the piperidine **5** as previously described, the amine **2a** was obtained within 5 steps from piperidinemethanol **11** in 17–20% overall yield.

In order to minimize steps for the synthesis of the desired amines **2a** or **2b**, we thought to protect the heterocyclic nitrogen atom of piperidinemethanol **11** with the cyanomethyl group,




**Scheme 4** *Reagents and conditions:* i, TsCl (2 mol equiv.), $Et_3N$, $CH_2Cl_2$, 40 °C, 24 h; ii, TsCl (2 mol equiv.), py, rt, 24 h; iii, $HNPr_2$ (excess), DBU, 110 °C, 48 h; iv, PhOH, HBr, 100 °C, 2 h; v, $ClCH_2CN$, $Et_3N$, MeOH, rt, 24 h; vi, LAH, THF, rt, 2 h; vii, $PPh_3$, $Br_2$, MeCN, rt, 150 h; viii, TsCl (1.1 mol equiv.), py, rt, 23 h; ix, TsCl (1.1 mol equiv.), $Et_3N$, $CH_2Cl_2$, rt, 15 h; x, $HNPr_2$ (see Table 1)

precursor of the aminoethyl function. Piperidinemethanol **11** was converted into the *N*-cyanomethyl alcohol **15** by treatment with chloroacetonitrile and $Et_3N$ in methanol at room temperature for 24 h (90% yield).[23] Compound **15** was transformed either into the bromide **16** by reaction with $PPh_3$ and $Br_2$ in acetonitrile at room temperature for 150 h (70% yield)[31] or into the tosyl ester **17** by reaction with tosyl chloride and $Et_3N$ in dichloromethane at room temperature for 15 h (86% yield).[28] Reaction of the bromide **16** and of the tosyl ester **17** with dipropylamine carried out under several conditions of temperature and solvent (Table 1) gave a mixture of the piperidine **6**, the perhydroazepine **10** and the N-deprotected amine **5**. Both isomers **6** and **10** were well distinguished in the crude $^1H$ NMR sample. Protons of the cyanomethyl group appeared as an AX pattern ($\delta$ 3.49 and 4.44) and an AB pattern ($\delta$ 3.52 and 3.60), respectively, for the piperidine **6** and the perhydroazepine **10**. Compounds **5**, **6** and **10** were easily separated by chromatography on silica gel and characterized by comparison of their $^1H$, $^{13}C$ NMR, IR and mass spectra with those of authentic samples previously prepared. In all cases, the isomers **6** and **10** were formed in about the same ratio. The amount of the N-deprotected piperidine **5** was only related to the reaction temperature. This amine **5** was found to be the major product when the reaction was carried out in dipropylamine at 110 °C (68.5% yield). As the temperature decreased, the yield of the amine **5** became lower and the proportion of both isomers **6** and **10** increased. The optimum isolated yields in the isomers **6** and **10** (respectively, 35–43% and 41–53%) were obtained by heating the bromide **16** or the tosyl ester **17** in dipropylamine at 60 °C. After reduction of the nitrile function, the amines **2a** and **2b** were isolated in 4 steps from piperidinemethanol **11**, respectively in 15–19% and 16–20% yield.

Ring enlargement was already reported in a few reactions of

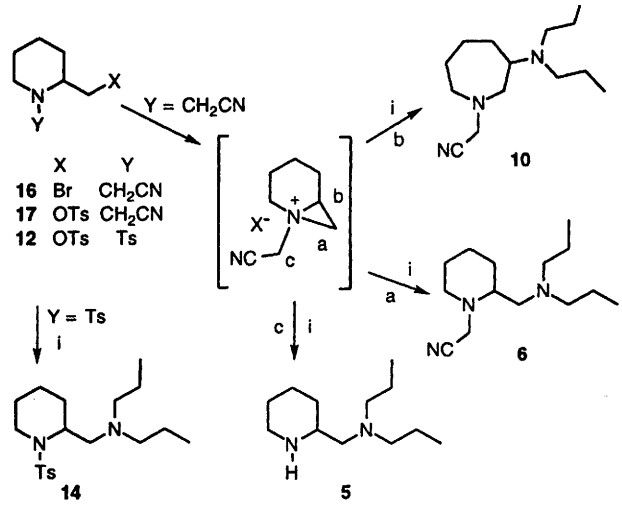
**Table 1** Reactions of compounds **16** or **17** with *N*,*N*-dipropylamine

| Starting material | Reagents | Reaction conditions (*T*/°C); (*t*/h) | Yield (%)[c] **6** | **10** | **5** |
|---|---|---|---|---|---|
| **16** | $HNPr_2$[a] | 60; 3 | 42 | 46 | 2 |
| **17** | $HNPr_2$[a] | 60; 3 | 39 | 43 | 0 |
| **17** | $HNPr_2$[a] | 80; 3 | 31 | 38 | 15 |
| **17** | $HNPr_2$[a] | 110; 3 | 9 | 6.5 | 68.5 |
| **17** | $HNPr_2$[a] | 60; 2 then 110; 1 | 43 | 53 | 2 |
| **17** | EtOH, $Et_3N$[b] | 60; 3 | 35 | 41 | 8 |
| **17** | $CH_3CN$, $Et_3N$[b] | 60; 4 | 36 | 42 | 7 |
| **17** | DMF, $Et_3N$[b] | 60; 4 | 38 | 40.5 | 3 |
| **17** | Toluene, $Et_3N$[b] | 60; 4 | 0[d] | 0[d] | 0[c,d] |
| **17** | Toluene, $Et_3N$[b] | 90; 14 then 110; 2 | 31 | 36 | 15 |

[a] The reaction was carried out in neat $HNPr_2$. [b] $HNPr_2$ (2 mol equiv.). [c] Isolated yields after purification on silica gel. [d] Starting material quantitatively recovered.

**Table 2** Conditions used for the deprotection essays of the nitriles **6** and **10**

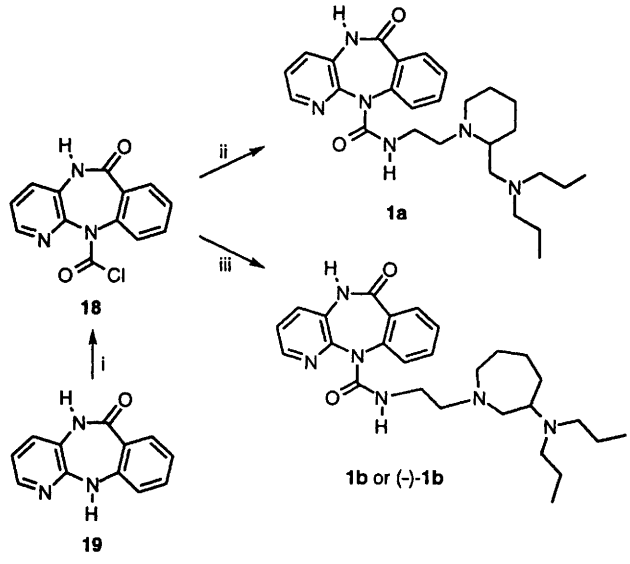
| Reaction medium | Temperature (*T*/°C) | Reaction time (*t*/h) |
|---|---|---|
| $HNPr_2$ | 110 | 3 |
| $HNPr_2$, TsCl (1 mol equiv.) | 60 | 3 |
| $HNPr_2$, TsCl (1 mol equiv.) | 110 | 3 |
| $HNPr_2$, TsOH (1 mol equiv.) | 110 | 3 |
| $Et_3N$ | 90 | 5 |




**Scheme 5** *Reagent:* i, $Pr_2NH$

piperidine derivatives with nucleophiles. An ambident aziridinium intermediate was postulated (Scheme 5)[20,32–35] in the reaction of 2-chloromethyl-N-protected piperidines or morpholines with cyanide,[32–34] azide[35] or phenoxide.[32] It did not occur when methoxide, hydroxide or piperidine[36] were used as nucleophiles and it was not mentioned for the reaction of methylamine on piperidine mesyl ester.[5] In all cases the heterocyclic nitrogen of the piperidines was protected with a methyl,[33,36] benzyl[32,35] or thienylmethyl[34] group. In our experiments, the skeletal rearrangement was only observed when dipropylamine was allowed to react with the *N*-(cyanomethyl)piperidine derivative **16** or **17**. No ring enlargement was observed with the *N*-tosylpiperidine **14** (Scheme 5). In this case, we can suggest that the formation of the postulated aziridinium intermediate was not favoured due to the strong electronic attractive effect of the tosyl group on the heterocyclic nitrogen. Finally the solvent polarity has no influence on the course of the reactions[32] (Scheme 5).

Removal of the cyanomethyl function, stable in acidic medium, occurred in general under specific conditions ($AgNO_3$[37] or catalytic hydrogenation in presence of $PtO_2$[24]).




**Scheme 6** *Reagents and conditions:* i, ClCOCl, 1,4-dioxane; ii, **2a**, MeCN, 50 °C, 4 h; then rt, 15 h; iii, **2b** or (+)-**2b**, MeCN, 50 °C, 4 h; then rt, 15 h

The deprotection we observed during the reaction of the bromide **16** or the tosyl ester **17** with dipropylamine could also be explained from the aziridinium intermediate. Nucleophilic attack on the cyanomethyl group led to compound **6** and to the amine **5** (Scheme 5). Indeed, we have checked that no deprotection occurred by reaction of the amine with the nitriles **6** and **10** once formed. Indeed these nitriles were left unchanged and quantitatively recovered by heating under different conditions (Table 2).

### Synthesis of AF-DX 384 1a and its isomers 1b

AF-DX 384 **1a** (Scheme 6) and its racemic or optically active perhydroazepine isomer **1b** or (−)-**1b** were prepared by reaction of the carbamoyl chloride **18** respectively with the amines **2a** (yield: 72%) and **2b** (yield: 65%) in acetonitrile at 50 °C for 4 h.[2] Benzodiazepinone **19** and its carbamoyl chloride derivative **18** were synthesized as previously described.[2]

In summary we have developed a new and efficient synthesis of two ligands of muscarinic receptors, **1a** and **1b**. The key intermediate **2a** was obtained from 2-(chloromethyl)pyridine **3** (4 steps, 13–15% overall yield) or in 5 steps from piperidinemethanol **11** (either *via* the *N*,*O*-ditosyl derivative **12** route (5 steps, 17–20% overall yield) or *via* the *N*-cyanomethyl alcohol **15** (4 steps, 15–19% overall yield).

The perhydroazepine **2b** was prepared either from 3-aminocaprolactam (−)-**7** (4 steps, 49% overall yield) or from the alcohol **15** (4 steps, 16–20% overall yield). An aziridinium

cation was postulated to explain both the ring enlargement and the deprotection of the heterocyclic nitrogen atom. The formation of this reactive intermediate was shown to be strongly dependent on the nitrogen substituent. The nitrile alcohol **15** was the best precursor of the amines **2a** and **2b** both in terms of the number of steps and overall yields. Comparison of the pharmacololgical properties of AF-DX 384 **1a** and of its seven-membered-ring isomer **1b** (racemic or optically active) is now in progress and the synthesis of both enantiomers of compound **1a** is underway.

## Experimental

### General

THF was distilled from sodium–benzophenone. All other reagents were used as obtained from commercial sources (purity > 98%; Janssen Chimica, Aldrich or Sigma). Mps were determined on a Gallenkamp apparatus and are uncorrected. $^1$H NMR and $^{13}$C spectra were obtained for solutions in deuteriochloroform on a Brucker AC-250 spectrometer (250 MHz $^1$H, 62 MHz $^{13}$C) with tetramethylsilane as internal standard. All *J*-values are in Hz. IR spectra were recorded with a Perkin-Elmer 16 PC FT-IR spectrometer. Mass spectra were recorded with a Nermag R10 (EI, 70 eV) and high-resolution mass spectra were measured with a JEOL JMSD 300 spectrometer. Optical rotations were obtained from solutions in chloroform with a Perkin-Elmer polarimeter, and $[\alpha]_D$-values are given in units of $10^{-1}$ deg cm$^2$ g$^{-1}$. TLC was performed on Silica Gel 60 F-254 (0.1 mm, Merck) with iodine and/or UV detection. Column chromatography was carried out on Silica Gel 60-200 (Merck 606). Organic solutions were dried over anhydrous $MgSO_4$ and evaporated at < 50 °C under reduced pressure. Microanalyses were performed by the Central Service of the CNRS (Lyon). Light petroleum refers to the fraction with distillation range 30–40 °C.

### 2-[(*N*,*N*-Dipropylamino)methyl]pyridine 4

A mixture of 2-(chloromethyl)pyridine **3** (1.64 g, 10 mmol), dipropylamine (2.06 cm$^3$, 10 mmol) and triethylamine (2.78 cm$^3$, 20 mmol) in ethanol (20 cm$^3$) was heated at 80 °C for 48 h. After cooling to room temperature, solvent and the excess of triethylamine and dipropylamine were removed by evaporation under reduced pressure at 40 °C. The remaining red solid was diluted in dichloromethane (20 cm$^3$). The organic solution was washed with saturated aq. sodium hydrogen carbonate (5 × 50 cm$^3$), dried, filtered and evaporated. The crude product (1.06 g) was purified by chromatography on silica gel with ethyl acetate–light petroleum (30:70) as eluent to give the pure *title product* (1.19 g, 62%) as a red oil, $R_f$ 0.72 (ethyl acetate–pentane 30:70) (Found: M$^+$, 192.1645. $C_{12}H_{20}N_2$ requires M, 192.1627); $\nu_{max}$(NaCl)/cm$^{-1}$ 2960, 2804, 1590, 1570, 1468 and 1432; $\delta_H$ 0.76 (6 H, t, *J* 7.3, 2 × C*H*$_3$), 1.38 (4 H, sext, *J* 7.3, $CH_3CH_2CH_2N$), 2.33 (4 H, m, $CH_3CH_2CH_2N$), 3.62 (2 H, s, $CH_2NPr_2$), 6.99 (1 H, m, 3-H), 7.41 (1 H, m, 5-H), 7.50 (1 H, m, 4-H) and 8.41 (1 H, m, 6-H); $\delta_C$ 11.9 ($CH_3CH_2CH_2N$), 20.3 ($CH_3CH_2CH_2N$), 56.5 ($CH_3CH_2CH_2N$), 60.8 ($CH_2NPr_2$), 121.6 (C-3), 122.8 (C-5), 136.2 (C-4), 148.8 (C-6) and 161.1 (C-2); *m/z* 192 (M$^+$, 0.7%) and 93 (100).

### Tosylation of piperidine-2-methanol 11

A solution of 2-(hydroxymethyl)piperidine **11** (93% pure; Janssen compound, 4.49 g, 39 mmol), triethylamine (10.85 cm$^3$, 78 mmol) and tosyl chloride (14.87 g, 78 mmol) in dichloromethane (60 cm$^3$) was heated under reflux for 24 h. After cooling, the reaction mixture was washed with water (2 × 50 cm$^3$), dried, filtered and evaporated. The residue was separated on silica gel with ethyl acetate–pentane (1:1) as eluent, to give the N,O-*ditosyl compound* **12** (10.250 g, 62%) then the O-*tosylated compound* **13** (2.724 g, 20%) and unchanged starting material (0.8 g recovery).

***N*-*p*-Tolyl(sulfonyl)piperidin-2-ylmethyl toluene-*p*-sulfonate 12.** Solid, $R_f$ 0.85 (ethyl acetate–pentane 1:1), mp 63 °C (Found: M$^+$, 423.1172. $C_{20}H_{25}NO_5S_2$ requires M, 423.1174); $\nu_{max}$(KBr)/cm$^{-1}$ 3055, 3020, 2930, 2855, 1930, 1810, 1730, 1645, 1590, 1490, 1465, 1445, 1390 (O-$SO_2$), 1350 (N-$SO_2$), 1300, 1285, 1210, 1185, 1170 (N-$SO_2$) and 1155 (O-$SO_2$); $\delta_H$ 1.34–1.56 (5 H, m, 5-H, 4- and 3-$CH_2$), 1.70–1.75 (1 H, m, 5-H), 2.42 (3 H, s, Ar*Me*), 2.47 (3 H, s, Ar*Me*), 2.82 (1 H, m, 6$^{ax}$-H), 3.73 (1 H, m, 6$^{eq}$-H), 4.08 (2 H, m, 2-$CH_2$), 4.30–4.23 (1 H, m, 2-H), 7.27 and 7.67 (4 H, AB, $J_{AB}$ 8.0, OAr) and 7.35 and 7.75 (4 H, AB, $J_{AB}$ 8.3, NAr); $\delta_C$ 18.4 (C-3), 21.6 ($OSO_2C_6H_4CH_3$), 21.8 ($NSO_2C_6H_4CH_3$), 24.3 (C-4), 24.5 (C-5), 41.5 (C-6), 50.5 (C-2), 67.0 ($CH_2OTs$), 127.1 ($NSO_2C_6H_4$), 128.1 ($OSO_2C_6H_4$), 129.8 ($OSO_2C_6H_4$), 130.0 ($NSO_2C_6H_4$), 132.7 ($NSO_2C_6H_4$), 137.9 ($OSO_2C_6H_4$), 143.4 ($OSO_2C_6H_4$) and 145.2 ($NSO_2C_6H_4CH_3$); *m/z* 424 (M + 1$^+$, 1.4%) and 91 (100).

**Piperidin-2-ylmethyl toluene-*p*-sulfonate 13.** Solid, $R_f$ 0.2 (ethyl acetate–pentane 50:50), mp 81 °C (Found: M$^+$, 270.1182. $C_{13}H_{19}NO_3S$ requires M, 270.1164); $\nu_{max}$(KBr)/cm$^{-1}$ 3528, 2948, 1654, 1326, 1188, 1154, 1118, 1094, 1064, 992, 924, 818 and 738; $\delta_H$ 1.26–1.62 (6 H, m, 5-, 4- and 3-$H_2$), 2.0 (1 H, m, NH), 2.43 (3 H, s, $CH_3$), 3.16–3.05 (1 H, ~td, *J* 13 and 2.5, 6$^{ax}$-H), 3.61–3.51 (1 H, m, C*H*$_2$OTs), 3.91–3.78 (2 H, m, C*H*$_2$OTs and 6$^{eq}$-H), 4.10–4.00 (1 H, m, 2-H), 7.75 and 7.30 (4 H, AB, *J* 8.3, $C_6H_4$); $\delta_C$ 19.3 (C-3), 21.6 ($CH_3$), 24.3 (C-4), 24.9 (C-5), 41.5 (C-6), 54.8 (C-2), 60.8 ($CH_2OTs$), 127.1 ($C_6H_4$), 129.9 ($C_6H_4$), 138.2 ($C_6H_4$) and 143.4 ($C_6H_4$); *m/z* 269 (M$^+$, 0.21%) and 238 (100).

### 2-[(*N*,*N*-Dipropylamino)methyl]-*N*-(*p*-tolylsulfonyl)piperidine 14

A solution of *N*-(*p*-tolylsulfonyl)-2{[(*p*-tolylsulfonyl)oxy]-methyl}piperidine **12** (1.59 g, 3.52 mmol) and DBU (52 µl, 3.52 $10^{-4}$ mol) in dipropylamine (37 cm$^3$, 3.7 mol) was heated under reflux for 48 h, cooled to room temperature and evaporated to dryness. Chloroform (50 cm$^3$) was added and the organic phase was washed successively with saturated aq. sodium hydrogen carbonate (2 × 50 cm$^3$) and brine (50 cm$^3$), dried, filtered and evaporated. The residue was dissolved in dichloromethane (25 cm$^3$) and gaseous hydrochloric acid was bubbled through the ice-cooled organic phase for 3 min. After 3 h at 0 °C, the organic phase was filtered then washed successively with saturated aq. sodium hydrogen carbonate (3 × 25 cm$^3$) and brine (25 cm$^3$), dried, filtered and evaporated. Without further purification the pure *title compound* **14** (1.37 g, 100%) was obtained as an oil, $R_f$ 0.6 (ethyl acetate–pentane, 1:1) (Found: M$^+$ + 1, 353.2260. $C_{19}H_{33}N_2O_2S$ requires M, 353.2263); $\nu_{max}$(NaCl)/cm$^{-1}$ 2956, 2934, 2870, 2808, 1468, 1338, 1304, 1154, 1094 and 928; $\delta_H$ 0.85 (6 H, t, *J* 7.3, 10-Me), 1.52–1.31 (9 H, m, 5-, 4-, 10- and 3$^{eq}$-H), 1.89 (1 H, ~d, *J* 19, 3$^{ax}$-H), 2.46–2.24 (5 H, m, 7-H and 9-$CH_2$), 2.41 (3 H, s, 15-Me), 2.70 (1 H, ~dd, AMX, *J* 12.6, 10.7, ≈0, 7-H), 2.91 (1 H, ~td, *J* 12 and 2.4, 6$^{ax}$-H), 3.72 (1 H, m, 6$^{eq}$-H), 4.0 (1 H, m, 2-H), 7.73 and 7.27 (4 H, AB, $J_{AB}$ 8.2, 12-H, 13-H); $\delta_C$ 11.9 ($MeCH_2CH_2$), 18.5 (C-3), 20.4 ($MeCH_2$), 21.5 (Ar*Me*), 24.8 (C-4), 24.8 (C-5), 41.4 (C-6), 51.1 (2-$CH_2$), 53.2 (C-2), 56.7 ($NCH_2Et$), 127.1 (ArC-*o*), 129.6 (ArC-*m*), 139.0 (ArC-*i*) and 142.8 (ArC-*p*); *m/z* 353 (M$^+$ + 1, 0.74%), 240 (7), 239 (17.3), 238 (100), 226 (7.4), 197 (7.2), 155 (26.3), 114 (71.4), 91 (33.1), 86 (7.4), 84 (8.4), 72 (13), 70 (6.1), 57 (7.2), 56 (13.3), 55 (31.5), 54 (9.6), 44 (14.8), 43 (46.1), 42 (37.5) and 41 (61.3).

### 2-[(*N*,*N*-Dipropylamino)methyl]piperidine 5

**From 2-[(*N*,*N*-dipropylamino)methyl]pyridine 4.** A mixture of 2-(*N*,*N*-dipropylaminomethyl)pyridine **4** (1.37 g, 7.17 mmol) and platinum(IV) oxide (60 mg, 0.264 mmol) in acetic acid (100 cm$^3$) was hydrogenated at room temperature at 3.5 bar for 22 h. Water (100 cm$^3$) was added and the aqueous solution was made basic until pH 9 by addition of sodium hydroxide pellets and then was extracted with dichloromethane (6 × 50 cm$^3$). The combined organic fractions were dried, filtered and evaporated.

Chromatography on silica gel with dichloromethane–methanol–cyclohexane–28% aq. ammonia (68:15:15:2) as eluent yielded the pure amine **5** as a pale red oil (895 mg, 63%).

**From 2-[(*N*,*N*-dipropylamino)methyl]-*N*-(*p*-tolylsulfonyl)piperidine 14.** To a solution of 2-[(*N*,*N*-dipropylamino)methyl]-*N*-(*p*-tolylsulfonyl)piperidine **14** (460 mg, 1.30 mmol) in dichloromethane was added phenol (246 mg, 2.61 mmol), and after being stirred, the solvent was evaporated off. The residue was dissolved in 48% aq. hydrobromic acid (10 $cm^3$) and the solution was heated under reflux for 2 h. After the mixture had cooled to room temperature, dichloromethane (30 $cm^3$) and 5% hydrochloric acid (30 $cm^3$) were added and the aqueous phase was extracted with dichloromethane. The combined organic phases were washed with 5% hydrochloric acid (30 $cm^3$). The aqueous phase was then made basic (aq. sodium hydroxide, 2 mol $dm^{-3}$) and extracted with dichloromethane (3 × 50 $cm^3$). The organic phase was dried, filtered and evaporated. Chromatography on silica gel with cyclohexane–ethyl acetate (4:1), then with dichloromethane–cyclohexane–methanol–28% aq. ammonia (68:15:15:2) as eluent, yielded the amine **5** as a solid (213 mg, 82%), $R_f$ 0.3 (ethyl acetate–pentane 1:1), $R_f$ 0.65 (dichloromethane–cyclohexane–methanol–28% aq. ammonia 68:15:15:2), mp 173 °C (Found: $M^+$, 198.206 23. $C_{12}H_{26}N_2$ requires M, 198.2095); $\nu_{max}$(NaCl)/$cm^{-1}$ 3418 (NH), 2932, 2870, 2804, 1582, 1456, 1378, 1324, 1190, 1076, 932, 892, 838 and 752; $\delta_H$ 0.85 (6 H, t, *J* 7.3, 2 × Me), 1.80–1.21 (9 H, 5-H, 4-$H_2$, 3-$H_2$ and Me$CH_2$), 1.77 (1 H, m, 5-H), 2.68–2.20 (8 H, 2-$CH_2$, 2-H, $6^{eq}$-H, NC$H_2$Et), 3.06 (1 H, ~d, *J* 11.2, $6^{ax}$-H) and 4.8 (1 H, br s, NH); $\delta_C$ 12.2 (Me), 20.7 (Me$CH_2$), 22.7 (C-5), 24.2 (C-4), 29.7 (C-3), 46.5 (C-6), 55.5 (C-2), 56.8 (N$CH_2$) and 60.2 (2-$CH_2$); *m/z* 198 ($M^+$, 0.72%) and 84 (100).

**{2-[(*N*,*N*-Dipropylamino)methyl]piperidin-1-yl}acetonitrile 6**

**Method A.** To a solution of 2-[(*N*,*N*-dipropylamino)methyl]-piperidine **5** (129.4 mg, 0.65 mmol) in methanol (1.5 $cm^3$) were added bromoacetonitrile (0.255 $cm^3$, 3.66 mmol) and triethylamine (0.45 $cm^3$, 3.31 mmol). The mixture was stirred for 24 h at room temperature and the final solution was evaporated to dryness. The residue was diluted in 5% hydrochloric acid (10 $cm^3$) and the resulting aqueous solution was washed with light petroleum (3 × 30 $cm^3$), made basic with aq. ammonia (28%), and extracted with chloroform (3 × 30 $cm^3$). The combined organic fractions were washed with saturated brine (2 × 20 $cm^3$), dried, filtered and evaporated to give the crude product **6** (120 mg, 78%) as a yellow oil (purity determined by $^1H$ NMR: > 98%). Chromatography on silica gel with ethyl acetate–pentane (20:80) as eluent yielded the piperidine **6** (109 mg, 71%), $R_f$ 0.5 (ethyl acetate–pentane 30:70) (Found: $M^+$, 237.2142. $C_{14}H_{27}N_3$ requires M, 237.2199); $\nu_{max}$(NaCl)/$cm^{-1}$ 2958, 2934, 2872, 2808, 2744, 1670, 1456, 1414, 1380, 1338, 1316, 1298, 1276, 1216, 1178, 1126, 1108, 1086, 1074, 1062, 1034, 1012 and 734; $\delta_H$ 0.88 (6 H, t, *J* 7.3, 2 × Me), 1.38–1.55 (6 H, m), 1.52–1.76 (4 H, m), 2.13–2.26 (3 H, m), 2.38–2.60 (5 H, m), 2.70–2.75 (1 H, m), 3.49 (1 H, d, *J* 16.8, 1 H of $CH_2CN$) and 4.44 (1 H, d, *J* 16.8, 1 H of $CH_2CN$); $\delta_C$ 12.1 (Me), 19.9 ($CH_3CH_2CH_2N$), 24.0 (C-4), 25.6 (C-5), 31.6 (C-3), 44.1 ($CH_2CN$), 54.8 (C-6), 56.8 ($CH_3CH_2CH_2N$), 57.0 (C-2), 61.5 ($CH_2NPr_2$) and 115.9 (CN); *m/z* 237 ($M^+$, 3.8%), 236 (2.8), 211 (8.4), 124 (10.5), 123 (100), 114 (26.6), 96 (7.3), 84 (29.4) and 67 (7.7).

**Method B.** To aq. 2-[(*N*,*N*-dipropylamino)methyl]piperidine **5** (160 mg, 0.806 mmol in 1 $cm^3$) cooled at 0 °C were added aq. formaldehyde (30% solution; 84 $cm^3$, 0.91 mmol) and potassium cyanide (55 mg, 0.81 mmol). After being stirred at 0 °C for 1 h, the mixture was treated with 37.5% aq. hydrochloric acid (78 $cm^3$, 0.833 mmol) and the resulting mixture was stirred at room temperature for 46 h. Potassium carbonate (5 mg, 0.402 mmol) was added and the aqueous phase was extracted with dichloromethane (2 × 10 $cm^3$). The combined organic fractions were dried, filtered and evaporated to give a crude oil. Chromatography on silica gel with dichloromethane–cyclohexane–methanol–28% aq. ammonia (68:15:15:0.5) yielded the pure title compound **6** as an oil (119 mg, 62%).

**{2-[(*N*,*N*-Dipropylamino)methyl]piperidin-1-yl}ethanamine 2a**

To a suspension of LAH (260 mg, 6.85 mmol) in anhydrous THF (5 $cm^3$) cooled to 0 °C, under nitrogen, was added dropwise a solution of {2-[(*N*,*N*-dipropylamino)methyl]piperidin-1-yl}acetonitrile **6** (1 g, 4.2 mmol) in anhydrous THF (5 $cm^3$). After 2 h at room temperature, the mixture was cooled to 0 °C and water (10 $cm^3$) was added slowly. The aqueous solution was extracted with chloroform (3 × 20 $cm^3$). The combined organic fractions were washed with saturated brine (20 $cm^3$), dried, filtered and evaporated to give the crude product. Chromatography on silica gel with dichloromethane–methanol–cyclohexane–28% aq. ammonia (68:15:15:2) as eluent yielded the pure title compound **2a** as a pale yellow oil (560 mg, 55%), $R_f$ 0.61 (dichloromethane–methanol–cyclohexane–28% aq. ammonia 68:15:15:2) (Found: $M^+$, 241.2522. $C_{14}H_{31}N_3$ requires M, 241.2511); $\nu_{max}$(NaCl)/$cm^{-1}$ 2956, 2932, 2872, 2800, 1462, 1382 and 1076; $\delta_H$ 0.72 (6 H, t, *J* 7.3, 2 × Me), 1.15–1.75 (10 H, m), 1.85 (2 H, s), 2.10–2.35 (7 H, m), 2.41 (1 H, dd, *J* 12.4 and 4.2) and 2.70–2.83 (3 H, m); $\delta_C$ 12.1 (Me), 20.3 ($CH_3CH_2CH_2N$), 23.1 (C-4), 25.1 (C-5), 29.8 (C-3), 39.6 ($CH_2NH_2$), 51.8 (C-6), 56.2 (C-2), 56.5 ($NCH_2CH_2NH_2$), 56.8 (Et$CH_2N$) and 58.9 ($CH_2NPr_2$); *m/z* 241 ($M^+$, 2.5%), 223 (5.1), 167 (28.5), 98 (15.1), 84 (100) and 69 (17.1).

**Alkylation of 3-aminocaprolactam 7 with 1-bromopropane**

To a solution of L-(−)-3-aminocaprolactam **7** (512 mg, 4 mmol) and triethylamine (2.6 $cm^3$, 19.12 mmol) in methanol (5 $cm^3$) was added, at room temperature 1-bromopropane (1.74 $cm^3$, 19 mmol). After being heated at 65 °C for 15 h, the final solution was evaporated to dryness under reduced pressure. Saturated brine (5 $cm^3$) was added to the residue. The aqueous phase was made basic (pH 9) with saturated aq. sodium hydrogen carbonate (20 $cm^3$) and extracted with dichloromethane (3 × 20 $cm^3$). The combined organic fractions were washed with saturated brine (20 $cm^3$), dried, filtered and evaporated. The crude product (2 g) was separated by chromatography on silica gel with dichloromethane–(dichloromethane–methanol–cyclohexane–28% aq. ammonia 68:15:15:2) (8:2) as eluent to give the pure *dipropylamine* **8a** (560 mg, 66%), then a mixture of the dipropylamine **8a** and the *monopropylamine* **8b** (65 mg), and the pure monopropylamine **8b** (30 mg, 4.4%).

(−)-3-(N,N-*Dipropylamino*)*caprolactam* **8a** was a pale yellow oil, $R_f$ 0.74 (dichloromethane–methanol–cyclohexane–28% aq. ammonia 68:15:15:2) (Found: $M^+$, 212.1891. $C_2H_{24}N_2O$ requires M, 212.1889); $[a]_D$ −24.3 (*c* 5.8); $\delta_H$ 0.86 (6 H, t, *J* 7.3, 2 × Me), 1.33–2.01 (10 H, m), 2.52–2.75 (4 H, m), 3.05–3.20 (1 H, m), 3.34–3.45 (1 H, m) and 3.54 (1 H, m); $\delta_C$ 11.9 (Me), 21.6 ($CH_3CH_2CH_2N$), 27.4 (C-5), 29.2 (C-4 or -6), 29.6 (C-6 or -4), 41.9 (C-7), 53.4 (Et$CH_2N$), 64.3 (C-3) and 178.6 (CO); *m/z* 213 ($M^+$ + 1, 6.8%), 140 (42.5), 96 (5.2), 84 (69.0), 55 (28.6) and 41 (100).

3-(N-*Propylamino*)*caprolactam* **8b** was an oil, $R_f$ 0.47 (dichloromethane–methanol–cyclohexane–28% aq. ammonia 68:15:15:2) (Found: $M^+$, 170.1417. $C_9H_{18}N_2O$ requires M, 170.1419); $\delta_H$ 0.95 (3 H, t, *J* 7.3, Me), 1.40–1.85 (6 H, m), 2.0–2.05 (2 H, m), 2.71 (2 H, t, *J* 7.3), 3.25–3.30 (2 H, m), 3.55 (1 H, m, CHN) and 4.53 (2 H, s, 2 × NH); $\delta_C$ 11.6 (Me), 22.2 ($CH_3CH_2CH_2N$), 27.9 (C-5), 28.8 (C-4), 30.3 (C-6), 41.9 (C-7), 50.1 (Et$CH_2N$), 60.7 (C-3) and 176.4 (CO); *m/z* 171 (M + $1^+$, 0.64%), 96 (2.3), 84 (33.6) and 49 (100).

**(+)-3-(*N*,*N*-Dipropylamino)hexahydroazepine 9**

To a suspension of LAH (131 mg, 3.5 mmol) in anhydrous THF (3 $cm^3$) was added, at 0 °C, dropwise and under nitrogen, a solution of (−)-3-(*N*,*N*-dipropylamino)caprolactam **8a** (560 mg, 2.64 mmol) in anhydrous THF (2 $cm^3$). After being heated

at 70 °C for 4.5 h, the mixture was cooled to 0 °C and water (0.250 $cm^3$) was added slowly. After filtration, the aqueous solution was extracted with chloroform (3 × 15 $cm^3$). The combined organic fractions were washed with saturated brine (20 $cm^3$), dried, filtered and evaporated to give the crude product. Chromatography on silica gel with dichloromethane–(dichloromethane–methanol–cyclohexane–28% aq. ammonia 68:15:15:2) (8:2) as eluent yielded the pure title compound **9** as a pale yellow oil (490 mg, 90%), $R_f$ 0.35 (dichloromethane–methanol–cyclohexane–28% aq. ammonia 68:15:15:2) (Found: $M^+$, 198.2100. $C_{12}H_{26}N_2$ requires M, 198.2096); $[\alpha]_D$ +6.7 (*c* 8.5); $\delta_H$ 0.77 (3 H, *J* 7.3, $CH_3$), 0.78 (3 H, *J* 7.3, $CH_3$), 1.25–1.52 (7 H, m), 1.60–1.72 (3 H, m), 2.25–2.32 (4 H, m), 2.65–2.84 (5 H, m) and 2.9–3.0 (1 H, m); $\delta_C$ 11.9 (Me), 22.4 ($CH_3CH_2CH_2N$), 24.8 (C-5), 28.4 (C-4 or -6), 30.9 (C-6 or -4), 49.3 (C-7), 51.3 (C-2), 53.1 (Et$CH_2$N) and 62.5 (C-3); *m/z* 199 (M + $1^+$, 84.4%), 198 ($M^+$, 100), 140 (28.5), 96 (18.1), 55 (32.4) and 43 (58.4).

**(−)-[3-(*N*,*N*-Dipropylamino)hexahydroazepin-1-yl]acetonitrile 10**

To a solution of (+)-3-(*N*,*N*-dipropylamino)hexahydroazepine **9** (250 mg, 1.26 mmol) in methanol (1.5 $cm^3$) were added bromoacetonitrile (0.438 $cm^3$, 6.3 mmol) and triethylamine (0.680 $cm^3$, 5 mmol). The mixture was stirred for 24 h at room temperature and the final solution was evaporated to dryness under reduced pressure. The residue was diluted in 5% hydrochloric acid (8 $cm^3$) and the resulting aqueous solution was washed with light petroleum (3 × 20 $cm^3$), made basic with aq. ammonia (28%), and extracted with dichloromethane (3 × 20 $cm^3$). The combined organic fractions were washed with saturated brine (2 × 20 $cm^3$), dried, filtered and evaporated to give the crude product. Chromatography on silica gel with ethyl acetate–pentane (50:50) as eluent yielded the pure title product **10** as a yellow oil (280 mg, 94%), $R_f$ 0.8 (ethyl acetate–pentane, 30:70) (Found: $M^+$, 237.2208. $C_{14}H_{27}N_3$ requires M, 237.2199); $[\alpha]_D$ −21.1 (*c* 9); $\nu_{max}$(NaCl)/$cm^{-1}$ 2958, 2934, 2872, 2808, 2744, 1670, 1456, 1414, 1380, 1338, 1316, 1298, 1276, 1216, 1178, 1126, 1108, 1086, 1074, 1062, 1034, 1012 and 734; $\delta_H$ 0.86 (6 H, t, *J* 7.3, 2 × Me), 1.30–1.49 (4 H, sext, *J* 7.3), 1.51–1.65 (2 H, m), 1.66–1.88 (4 H, m), 2.26–2.46 (4 H, m), 2.50–2.90 (5 H, m) and 3.52 and 3.60 (2 H, AB, *J* 17.0, $CH_2CN$); $\delta_C$ 11.9 (Me), 22.4 ($CH_3CH_2CH_2N$), 24.4 (C-5), 28.7 (C-6), 28.8 (C-4), 48.1 ($CH_2CN$), 53.1 (C-7), 55.9 (Et-$CH_2$N), 57.3 (C-3), 60.5 (C-2) and 116.0 (CN); *m/z* 237 ($M^+$, 29.9%), 232 (11.6), 194 (10.9), 153 (10.7), 140 (47.1), 123 (24.8), 114 (100), 112 (13.1), 98 (61.9), 96 (23.4), 86 (17.4), 85 (10.4), 84 (19.8), 83 (25.8), 82 (12.1), 72 (19.4), 70 (17.4), 69 (16.6) and 67 (14.7).

**2-[3-(*N*,*N*-Dipropylamino)hexahydroazepin-1-yl]ethanamine 2b**

To a suspension of LAH (313 mg, 8.25 mmol) in anhydrous THF (5 $cm^3$) was added at 0 °C, dropwise and under nitrogen, a solution of (−)- or racemic [3-(*N*,*N*-dipropylamino)-hexahydroazepin-1-yl]acetonitrile **10** (1.2 g, 5.06 mmol) in anhydrous THF (5 $cm^3$). After 2 h at room temperature, the mixture was cooled to 0 °C and water (10 $cm^3$) was added slowly. The aqueous solution was extracted with chloroform (3 × 20 $cm^3$). The combined organic fractions were washed with saturated brine (20 $cm^3$), dried, filtered and evaporated to give the crude product. Chromatography on silica gel with dichloromethane–methanol–cyclohexane–28% aq. ammonia (68:15:15:2) as eluent yielded the pure title compound **2b** as a pale yellow oil (610 mg, overall 50% from **7**, 88% from **10**), $R_f$ 0.55 (dichloromethane–methanol–cyclohexane–28% aq. ammonia 68:15:15:2) (Found: $M^+$, 241.2512. $C_{14}H_{31}N_3$ requires M, 241.2511); $[\alpha]_D$ +4 (*c* 3); $\nu_{max}$(NaCl)/$cm^{-1}$ 2956, 2932, 2870, 2806, 1458, 1378, 1160 and 1068; $\delta_H$ 0.71 (6 H, t, *J* 7.3, 2 × Me), 1.20–1.45 (7 H, m), 1.50–1.75 (4 H, m), 2.18–2.28 (4 H, m), 2.30–2.52 (7 H, m) and 2.55–2.80 (3 H, m); $\delta_C$ 11.9 (Me), 22.4 ($CH_3CH_2CH_2N$), 25.0 (C-5), 28.6 (C-6 or -4), 28.9 (C-4 or -6), 39.7 ($CH_2NH_2$), 53.1 (Et$CH_2$N), 56.1 (C-7), 58.1 (C-3), 60.7 (C-2) and 61.0 ($NCH_2CH_2NH_2$); *m/z* 241 ($M^+$, 5.1%), 223 (17.5), 210 (12.7), 167 (25.1), 138 (3), 110 (10.4), 98 (14.4), 84 (23.9), 72 (31.5) and 58 (100).

**[2-(Hydroxymethyl)piperidin-1-yl]acetonitrile 15**

To a solution of piperidinemethanol **11** (93% pure, Janssen compound; 5.0 g, 43.4 mmol) in methanol (25 $cm^3$) were added chloroacetonitrile (15.5 $cm^3$, 18.5 g, 0.242 mol) and triethylamine (30 $cm^3$, 21.8 g, 0.22 mol). After 24 h at room temperature, the solution was evaporated to dryness and the residue was diluted in 5% hydrochloric acid (100 $cm^3$). The aqueous solution was washed with light petroleum (100 $cm^3$), made basic with 28% aq. ammonia, and extracted with chloroform (3 × 80 $cm^3$). The combined organic fractions were washed with saturated brine (2 × 50 $cm^3$), dried, filtered and evaporated to give the crude product. Chromatography on silica gel with ethyl acetate–pentane (1:1) as eluent yielded the *title compound* **15** as a solid (6.03 g, 90%), $R_f$ 0.3 (ethyl acetate–pentane 1:1); mp 69 °C (Found: C, 61.8; H, 9.2; N, 18.2%; $M^+$, 154.110 32. $C_8H_{14}N_2O$ requires C, 62.3; H, 9.1; N, 18.6%; M, 154.110 61); $\nu_{max}$(KBr)/$cm^{-1}$ 2930, 2240 (CN), 2220, 1450, 1440 and 1420; $\delta_H$ 1.24–1.82 (6 H, m, 3-, 4- and 5-$H_2$), 1.90 (1 H, s, OH), 2.51–2.38 (1 H, m, 2-H), 2.55 (1 H, ~td, $J_{6ax\text{-}6eq}$, $J_{6ax\text{-}5ax}$ 11.4, $J_{6ax\text{-}5eq}$ 3.0, $6^{ax}$-H), 2.78–2.82 (1 H, m, $6^{eq}$-H), 3.52 (1 H, dd, *J* 11.8 and 3.0, $CH_2OH$), 3.81 (1 H, dd, *J* 11.8 and 3.0, $CH_2OH$) and 4.05 and 3.46 (2 H, AB, *J* 17.3, $CH_2CN$); $\delta_C$ 23.8 (C-4), 25.4 (C-5), 28.6 (C-3), 43.4 ($CH_2CN$), 54.1 (C-6), 61.0 (C-2), 64.4 ($CH_2OH$) and 114.1 (CN); *m/z* 154 ($M^+$, 3.8%) and 67 (100).

**[2-(Bromomethyl)piperidin-1-yl]acetonitrile 16**

To a solution of triphenylphosphine (524 mg, 2 mmol) in dry acetonitrile (10 $cm^3$) cooled to 0 °C and under nitrogen was added bromine (0.103 $cm^3$, 0.322 g, 2 mmol) dropwise. After stirring of the mixture for 30 min at 0 °C, a solution of [2-(hydroxymethyl)piperidin-1-yl]acetonitrile **15** (309 mg, 2 mmol) in acetonitrile (4 $cm^3$) was added dropwise and the mixture was stirred for 150 h at room temperature. The volatile compounds were evaporated off and the residue was diluted in chloroform (20 $cm^3$). The organic phase was washed successively with saturated aq. sodium hydrogen carbonate (20 $cm^3$) and brine (20 $cm^3$), dried, filtered and evaporated. Chromatography on silica gel with dichloromethane as eluent yielded the *bromo compound* **16** as a solid (304 mg, 70%), $R_f$ 0.6 (dichloromethane); mp 80 °C (Found: C, 43.4; H, 6.0; N, 12.3%; $M^+$, 216.0252 and 218.0223. $C_8H_{13}BrN_2$ requires C, 44.3; H, 6.0; N, 12.9%; M, 216.0286 and 218.0227); $\nu_{max}$(KBr)/$cm^{-1}$ 2934, 2852, 2812, 2770, 2232, 1466, 1438, 1422, 1362, 1326, 1302, 1274, 1244, 1124, 1094, 1066, 1054, 1028, 986, 946, 924, 874 and 860; $\delta_H$ 1.35–1.85 (6 H, m, 3-, 4- and 5-$H_2$), 2.40–2.46 (1 H, m, 2-H), 2.59 (1 H, ~td, *J* 11 and 3.8, $6^{ax}$-H), 2.80–2.85 (1 H, m, $6^{eq}$-H), 3.39 (1 H, dd, *J* 3.9 and 11.7, 1 H of $CH_2Br$), 3.58 (1 H, dd, *J* 3.9 and 11.7, 1 H of $CH_2Br$) and 3.92 and 3.47 (2 H, AB, *J* 17.8, $CH_2CN$); $\delta_C$ 23.6 (C-4), 25.5 (C-5), 30.4 (C-3), 36.0 ($CH_2Br$), 42.8 ($CH_2CN$), 54.0 (C-6), 58.4 (C-2), 114.3 (C-8); *m/z* 218 (M + $2^+$, 1.3%), 216 ($M^+$, 1.3%) and 123 (100%).

**{2-[(*p*-Tolylsulfonyloxy)methyl]piperidin-1-yl}acetonitrile 17**

**Method A.** To a solution of [2-(hydroxymethyl)piperidin-1-yl]acetonitrile **15** (3.28 g, 21.2 mmol) in pyridine (25 $cm^3$) cooled to 0 °C was added dropwise, under nitrogen, a solution of tosyl chloride (4.19 mg, 21.9 mmol) in pyridine (25 $cm^3$). After 23 h at room temperature, chloroform (50 $cm^3$) was added and the organic phase was washed successively with saturated aq. sodium hydrogen carbonate (2 × 50 $cm^3$) and brine (50 $cm^3$), dried, filtered and evaporated. Column chromatography on silica gel, with ethyl acetate–light petroleum (2:3) as eluent yielded the *tosyl derivative* **17** (3.90 g, 59%) as a solid.

**Method B.** To a solution of [2-(hydroxymethyl)piperidin-1-yl]acetonitrile **15** (5.446 g, 35.33 mmol) in triethylamine (25 $cm^3$) cooled to 0 °C was added a solution of tosyl chloride (6.90

g, 36.43 mmol) in dichloromethane (25 $cm^3$). After the mixture had been kept for 15 h at room temperature, chloroform (50 $cm^3$) was added and the organic phase was washed with a saturated aq. sodium hydrogen carbonate solution (2 × 50 $cm^3$) and brine (50 $cm^3$), dried, filtered and evaporated. Column chromatography on silica gel with ethyl acetate–light petroleum (2:3) as eluent gave the *compound* **17** as a solid (9.36 g, 86%), $R_f$ 0.55 (ethyl acetate–pentane 1:1), mp 62 °C (Found: S, 10.2%; $M^+$, 308.126 46. $C_{15}H_{20}N_2O_3S$ requires S, 10.4%; M, 308.119 47); $\nu_{max}$(KBr)/$cm^{-1}$ 2940, 2244 (CN), 1598 (Ar), 1456 ($SO_2$–O), 1370 ($SO_2$), 1185 ($SO_2$) and 1160 ($SO_2$–O); $\delta_H$ 1.23–1.78 (6 H, m, 3-, 4- and 5-$H_2$), 2.43–2.55 (2 H, m, 2-H and $6^{ax}$-H), 2.46 (3 H, s, $CH_3$), 2.71–2.76 (1 H, m, $6^{eq}$-H), 3.77 and 3.39 (2 H, AB, *J* 17.7, $CH_2CN$), 3.94 (1 H, ~dd, *J* 4.6 and 11.1, C*H*$_2$OTs), 4.08 (1 H, ~dd, *J* 2.9 and 11.1, C*H*$_2$OTs), 7.81 and 7.37 (4 H, AB, *J* 8.3, $C_6H_4$); $\delta_C$ 21.7 ($CH_3$), 23.4 (C-4), 25.2 (C-5), 28.7 (C-3), 43.4 (*C*$H_2$CN), 53.9 (C-6), 58.2 (C-2), 70.9 (*C*$H_2$OTs), 114.4 (C-8), 128.0 (*C*$_6H_4$), 130.0 (*C*$_6H_4$), 132.5 (Me–*C*$_6H_4$) and 145.2 ($SO_2$–*C*$_6H_4$); *m/z* 308 ($M^+$, 0.4%) and 41 (100).

### 11-[(2-{2-[(Dipropylamino)methyl]piperidin-1-yl}ethyl)-carbamoyl]-5,11-dihydro-6*H*-pyrido[2,3-*b*]benzo-1,4-diazepin-6-one 1a (AF-DX 384)[2]

A mixture of 6-oxo-5,11-dihydro-6*H*-pyrido[2,3-*b*]benzo-1,4-diazepine-11-carbonyl chloride **18**[2] (0.520 g, 1.9 mmol) and {2-[(*N*,*N*-dipropylamino)methyl]piperidin-1-yl}ethanamine **2a** (0.476 g, 1.975 mmol) in acetonitrile (70 $cm^3$) was heated at 50 °C for 3 h and stirred at room temperature overnight. The final red solution was evaporated to dryness under reduced pressure at 40 °C to give a brown crystalline residue. Chromatography on silica gel with dichloromethane–methanol (95:5) as eluent yielded the pure title compound **1a** (0.654 g, 72%) as a solid, $R_f$ 0.16 (dichloromethane–methanol 90:10), mp 165 °C (Found: $M^+$, 478.3064. $C_{27}H_{38}N_6O_2$ requires M, 478.3056); $\nu_{max}$(NaCl)/$cm^{-1}$ 3332, 3202, 3136, 2956, 2932, 2870, 2802, 1674, 1588, 1506, 1458, 1430, 1360, 1276, 1232, 1169, 1136, 1078 and 902; $\delta_H$ 0.78 (6 H, t, *J* 7.2, 2 × Me), 1.39–1.47 (5 H, m), 1.55–1.85 (4 H, m), 1.85–2.0 (1 H, m), 2.3–2.6 (5 H, m), 2.75–2.95 (1 H, m), 2.95–3.15 (3 H, m), 3.15–3.4 (1 H, m), 3.50–3.65 (1 H, m), 3.65–3.8 (2 H, m), 6.77 (1 H, s), 7.10 (1 H, dd, *J* 7.9 and 4.7), 7.45–7.52 (2 H, m), 7.58 (1 H, d, *J* 7.7), 7.72 (1 H, d, *J* 7.5), 8.23 (1 H, dd, *J* 4.6 and 1.4) and 9.9 (1 H, s); $\delta_C$ 11.8 (Me), 19.3 ($CH_3CH_2CH_2N$), 21.3, 21.6, 26.6, 37.3, 50.2, 52.5, 55.2 and 56.1 (Et*C*$H_2$N), 60.6 (CH*C*$H_2NPr_2$), 124.1, 127.8, 128.8, 129.8, 131.1, 131.3, 131.5, 133.3, 141.5, 145.3, 146.1, 155.3 and 167.6; *m/z* 268 (5%), 211 (5), 154 (9), 153 (80), 152 (11), 125 (14), 116 (10), 115 (10), 114 (100), 112 (6), 110 (9), 96 (18), 86 (14), 84 (8), 72 (7), 70 (13), 57 (5), 56 (16), 55 (20), 44 (14), 43 (41), 42 (40) and 41 (55).

### 11-({2-[3-(Dipropylamino)hexahydroazepin-1-yl]ethyl}-carbamoyl)-5,11-dihydro-6*H*-pyrido[2,3-*b*]benzo-1,4-diazepin-6-one 1b

Following the same procedure as above for the preparation of AF-DX 384 **1a** and starting from 6-oxo-5,11-dihydro-6*H*-pyrido[2,3-*b*]benzo-1,4-diazepine-11-carbonyl chloride **18** (0.3745 g, 1.35 mmol) and racemic or (+)-2-[3-(*N*,*N*-dipropylamino)hexahydroazepin-1-yl]ethanamine **2b** (0.33 g, 1.35 mmol), the pure *title compound* **1b** (0.419 g, 65%) was obtained as a solid, $R_f$ 0.16 (dichloromethane–methanol 90:10), mp 158 °C (Found: $M^+$, 478.307 52. $C_{27}H_{38}N_6O_2$ requires M, 478.305 62); $[\alpha]_D$ −39.3 (*c* 1.95); $\nu_{max}$(NaCl)/$cm^{-1}$ 3332, 3202, 3136, 2956, 2932, 2870, 2802, 1674, 1588, 1506, 1458, 1430, 1360, 1276, 1232, 1169, 1136, 1078 and 902; $\delta_H$ 0.93 (6 H, t, *J* 7.3, 2 × Me), 1.25–1.65 (3 H, m), 1.67–1.95 (6 H, m), 1.97–2.11 (1 H, m), 2.35–2.55 (1 H, m), 2.58–2.91 (9 H, m), 2.96. 3.20 (3 H, m), 6.72 (1 H, s), 7.28 (1 H, dd, *J* 8.0 and 4.4), 7.35–7.42 (1 H, m), 7.53–7.59 (2 H, m), 7.77 (1 H, d, *J* 7.2),7.87 (1 H, d, *J* 7.6), 8.31 (1 H, dd, *J* 4.7 and 1.6) and 9.9 (1 H, s); $\delta_C$ 11.9 (Me), 18.5 and 21.8 ($CH_3CH_2CH_2N$), 24.5, 28.2, 29.1, 29.8, 38.3 and 53.2 ($CH_2NPr_2$), 53.6, 55.2, 56.8, 57.2, 61.4, 123.8, 127.6, 129.0, 129.6, 131.2, 131.4, 131.5, 133.4, 142.2, 144.8, 146.9, 155.0 and 168.4; *m/z* 479 ($M^+$ + 1, 2.0%), 478 ($M^+$, 2.6), 224 (10.3), 212 (24.6), 211 (100), 210 (19.7), 209 (12.5), 195 (30.8), 183 (10.7), 182 (20.6), 167 (15.2), 153 (14.2), 140 (19.5), 139 (10.7) and 138 (20.0).

### Reaction of [2-(bromomethyl)piperidin-1-yl]acetonitrile 16 or {2-[(*p*-tolylsulfonyloxy)methyl]piperidin-1-yl}acetonitrile 17 with *N*,*N*-dipropylamine

A mixture of [2-(bromomethyl)piperidin-1-yl]acetonitrile **16** or {2-[(*p*-tolylsulfonyloxy)methyl]piperidin-1-yl}acetonitrile **17** (0.10–1 g, 1 equiv.) and eventually triethylamine (2 mol equiv.) in a solvent (4–20 $cm^3$) was heated at the temperature and for the time given in Table 1. After cooling to room temperature, the excess of solvent was removed by evaporation and the residue was diluted in dichloromethane (10–30 $cm^3$). The organic solution was washed successively with saturated aq. sodium hydrogen carbonate (20 $cm^3$) and with saturated brine (20 $cm^3$), dried, filtered and evaporated. The residue was purified on silica gel with ethyl acetate–pentane (20:80), then with ethyl acetate–pentane (50:50) as eluent, to give the *N*-(cyanomethyl)piperidine **6**, then the hexahydroazepine **10** and finally the piperidine **5** as yellow oils. Yields are summarized in Table 1.

### Stability of the nitriles 6 and 10 under tosylation conditions

A solution of nitrile **6** or **10** (50–100 mg, 1 mol equiv.) and eventually tosyl chloride or toluene-*p*-sulfonic acid (2 mol equiv.) in dipropylamine or triethylamine (4–7 $cm^3$) was heated at the temperature and for the time given in Table 2. After cooling to room temperature, the excess of solvent was removed and the residue was diluted in dichloromethane (15 $cm^3$). The organic solution was washed successively with saturated aq. sodium hydrogen carbonate (10 $cm^3$) and then with saturated brine (10 $cm^3$), dried, filtered and evaporated. $^1H$ NMR analysis of the crude product showed only the starting material. This latter was quantitatively recovered.

## References


1 R. K. Dieter, N. Deo, B. Lagu and J. W. Dieter, *J. Org. Chem.*, 1992, **57**, 1663 and references cited therein.
2 W. W. Engel, G. W. Eberlein, G. Mihm, G. Trummlitz, N. Mayer and A. De Jonge, *Ger. Offen.*, DE 3 643 666, 1988 (*Chem. Abstr.*, 1989, **110**, 39029f).
3 D. I. C. Scopes, N. F. Hayes, D. E. Bays, D. Belton, J. Brain, D. S. Brown, D. B. Judd, A. B. McElroy, C. A. Meerholz, A. Naylor, A. G. Hayes, M. J. Sheehan, P. J. Birch and M. B. Tyers, *J. Med. Chem.*, 1992, **35**, 490.
4 V. Vecchietti, A. Giordani, G. Giardina, R. Colle and G. D. Clarke, *J. Med. Chem.*, 1991, **34**, 397.
5 B. R. de Costa, C. Dominguez, X. S. He, W. Williams, L. Radesca and W. Bowen, *J. Med. Chem.*, 1992, **35**, 4334.
6 W. W. Engel, G. W. Eberlein, G. Mihm, R. Hammer and G. Trummlitz, *J. Med. Chem.*, 1989, **32**, 1718.
7 E. H. Banitt and G. J. Conard, *J. Labelled Compd. Radiopharm.*, 1981, **18**, 713.
8 T. R. Norton, A. A. Benson, R. A. Seibert and F. W. Bergstrom, *J. Am. Chem. Soc.*, 1946, **68**, 1330.
9 A. Terada, Y. Iizuka, K. Wachi and K. Fujibayashi, *Eur. Pat. Appl.*, EP 356 247, 1990 (*Chem. Abstr.*, 1990, **113**, 7819q).
10 F. F. Blicke and J. L. Hughes, *J. Org. Chem.*, 1961, **26**, 3257.
11 M. Freifelder, R. M. Robinson and G. R. Stone, *J. Org. Chem.*, 1962, **27**, 284.
12 M. Freifelder and G. R. Stone, *J. Org. Chem.*, 1961, **26**, 3805.
13 V. Baliah, R. Jeyaraman and L. Chandrasekaran, *Chem. Rev.*, 1983, **83**, 379.
14 J. Perumattam, B. G. Shearer, W. L. Confer and R. M. Mathew, *Tetrahedron Lett.*, 1991, **32**, 7183.
15 M. C. Lasne, L. Barré, C. Huard, C. Ducandas and E. T. MacKenzie, *J. Labelled Compd. Radiopharm.*, 1994, **35**, 425.
16 M. Entzeroth and N. Mayer, *Biochem. Pharmacol.*, 1990, **40**, 1674.

17 I. Aubert, D. Cécyre, S. Gauthier and R. Quirion, *Eur. J. Pharmacol.*, 1992, **217**, 1674.
18 P. Mickala, H. Boutin, C. Bellaner, C. Chevalier, E. T. MacKenzie and F. Dauphin, *Nucl. Med. Biol.*, 1996, **23**, 173.
19 E. Albertini, A. Barco, S. Benetti, C. De Risi, G. P. Pollini and V. Zanirato, *Synlett*, 1996, 29.
20 D. Alker, R. J. Bass and P. E. Cross, *Eur. Pat. Appl.*, EP 404 359, 1990 (*Chem. Abstr.*, 1991, **115**, 29390f).
21 P. L. Ornstein, J. M. Schaus, J. W. Chambers, D. L. Huser, J. D. Leander, D. T. Wong, J. W. Paschal, N. D. Jones and J. B. Deeter, *J. Med. Chem.*, 1989, **32**, 827.
22 W. F. Minor, J. B. Hoekstra, D. Fisher and J. Sam, *J. Med. Pharm. Chem.*, 1962, **5**, 96.
23 N. Sperber, D. Papa, E. Schwenk, M. Sherlock and R. Fricano, *J. Am. Chem. Soc.*, 1951, **73**, 5752.
24 A. Benarab, S. Boyé, L. Savelon and G. Guillaumet, *Tetrahedron Lett.*, 1993, **34**, 7567.
25 M. Hudlicky, *Reductions in Organic Chemistry*, Ellis Horwood, Chichester, 1986, pp. 173 and 207.
26 J. March, *Advanced Organic Chemistry*, Wiley, Chichester, 4th edn., 1992, p. 411.
27 R. G. Weiss and E. I. Snyder, *J. Org. Chem.*, 1971, **36**, 403.
28 A. Gaucher, J. Ollivier and J. Salaün, *Synlett*, 1991, 151.
29 S. K. Hendrie and J. Leonard, *Tetrahedron*, 1987, **43**, 3289.
30 H. R. Snyder and R. E. Heckert, *J. Am. Chem. Soc.*, 1952, **74**, 2006.
31 G. A. Wiley, R. L. Hershkowitz, B. M. Rein and B. C. Chung, *J. Am. Chem. Soc.*, 1964, **86**, 964.
32 G. R. Brown, A. J. Foubister and B. Wright, *J. Chem. Soc., Perkin Trans. 1*, 1987, 553.
33 N. M. Deo and P. A. Crooks, *Synth. Commun.*, 1995, **25**, 691.
34 D. Berkes and B. Decroix, *Bull. Soc. Chim. Fr.*, 1994, **131**, 986.
35 T. Morie, S. Kato, H. Harada, I. Fujiwara, K. Watanabe and J. I. Matsumoto, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2565.
36 L. Stella, B. Raynier and J. M. Surzur, *Tetrahedron*, 1981, **37**, 2843.
37 L. E. Overman and J. Shim, *J. Org. Chem.*, 1991, **56**, 5005.

*Paper* 6/03198F
*Received* 7*th May* 1996
*Accepted* 9*th August* 1996