The Synthesis of Reduced Phenoxazines as Potential Chain-Breaking Antioxidants

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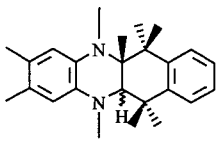
Routes to potential chain-breaking antioxidants, based upon phenoxazines, have been studied and a new synthesis of 1,2,3,4,4a,10a-hexahydro-10*H*-phenoxazines from *trans*-2-[*N*-(2-hydroxyphenyl)-amino]cyclohexanols has been developed using a Mitsunobu reaction to form the oxazine ring.

We are interested in the design of antioxidants which act as chain-breaking radical inhibitors in vivo. Of particular value to us are compounds that have an ionisation potential of +0.4–0.6 volt (vs SCE) and in which the attendant radical cations form redox couples.[1] In principle, such compounds could mimic the way in which vitamin E is believed to act in vivo and be useful in the control of atheroscerlosis.[2]

In previous work[3] we have shown that quinoxaline derivatives such as **1** readily form stable radical cations when oxidised and it became important to us to establish if similar behaviour is exhibited by hexahydrophenoxazines, e.g. **2**. There has been little interest in such compounds in the past,[4] so we needed to develop a simple route to them.



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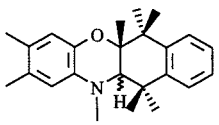

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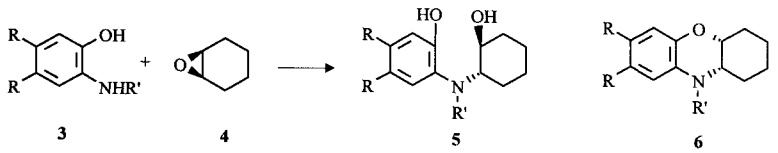
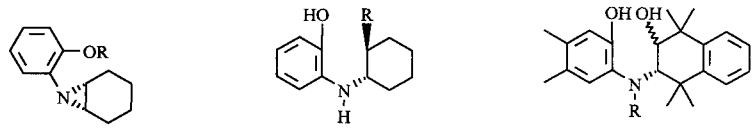
In a trial experiment we found that when 2-aminophenol **3** (R = R′ = H) reacted with cyclohexene epoxide **4**, the initial product is the *trans*-2-[*N*-(2-hydroxyphenyl)amino]cyclohexanol **5** (R = R′ = H). Attempts to cyclise this compound to the oxazine **6** (R = R′ = H) using diethyl azodicarboxylate and tributylphosphine under Mitsunobu reaction conditions afforded only a low yield (7%) of the desired product. The main product was the aziridine **7** (R = H) (47%), plus a small amount of the butyl ether **7** (R = Bu) (6%). Treatment of the aziridine with acetic acid opened the three-membered ring and gave the *O*-acetoxyamine **8** (R = OAc), whereas treatment with hydrochloric acid gave the chloride **8** (R = Cl).

However, when the *N*-benzylaminocyclohexanol **5** (R = H, R′ = Bn) [from **5** (R = H, R′ = H) and benzaldehyde, by reductive alkylation] was reacted under Mitsunobu conditions the expected oxazine **6** (R = H, R′ = Bn) was obtained and this was then *N*-dealkylated by hydrogenolysis over palladium catalyst to afford **6** (R = R′ = H) in 30% overall yield. The procedure has some general applicability and allows the synthesis of the dimethyl analogue **6** (R = Me, R′ = Bn), the *N*-ethyl derivative **6** (R = Me, R′ = Et) and the *N*-hexyl derivative **6** (R = Me, R′ = hexyl) from 2-amino-4,5-dimethylphenol in 99%, 37% and 35% yield, respectively. The *N*-tosyl derivative **5** (R = Me, R′ = Ts) affords **6** (R = Me, R′ = Ts) in 94% yield under the same reaction conditions.

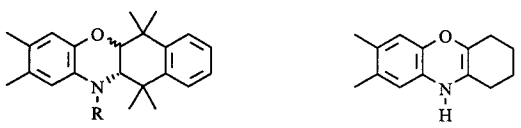
Although the hexahydrophenoxazine **6** (R = Me, R′ = H), undergoes ionisation at +0.4 volts (vs SCE) the radical cation, so formed, is unstable and breaks down by an ECE mechanism, most likely, to the dehydro derivative **11**, or a tautomer, and other products. Consequently **6** (R = Me, R′ = H) and its simple congeners are of no value as chain-breaking antioxidants and there is a requirement for analogues in which the corresponding radical cation is more stable. Unfortunately we have found that the Mitsunobu cyclisation is sensitive to steric hindrance and attempts to cyclise either the *cis* or *trans*



3 **4** **5** **6**



7 **8** **9**



10 **11**

isomers of the hexamethylaminophenol **9** (R = H) to the hexahydrophenoxazine **10** (R = H) failed. As a result we have not extended this approach to other more complex targets where, for example, one or both of the bridging carbon atoms of the heterocycle are alkylated.

It is significant that all attempts to *N*-alkylate the hexamethylaminophenol **9** (R = H) also failed, whereas such reactions with the dimethylated aminophenol **5** (R = Me, R = H) are easily accomplished.

Unless stated otherwise, all solvents used were distilled and dried prior to use. Where necessary dry apparatus was used. Apparatus was dried in an oven and cooled under N_2. Most reactions were monitored by TLC on Whatman aluminium backed UV_{254} silica plates and visualised under UV light, or developed with iodine, or a PMA dip. Flash column chromatography was carried out under medium pressure on Amicon 60 Å silica gel. Solvents were removed by rotary evaporation at, or below, 45 °C. ^{1}H NMR spectra were run in $CDCl_3$ (unless stated otherwise) using TMS as an internal standard, spectra were recorded at 270 MHz on a JEOL JNM GX FT 270 spectrometer. Mass spectra were recorded on a Fisons, VG Autospec instrument and unless stated otherwise were obtained by the method of electron impact at 70 eV.

2-[*N*-(2-Hydroxycyclohexyl)amino]phenol 5 (R = R′ = H):
A mixture of 2-aminophenol (2.2 g) and cyclohexene epoxide (2 g) was heated at 100–110 °C for 3 h, on cooling the mixture a glassy solid formed. This was collected and crystallised from EtOH to afford the title compound as microprisms (3.5 g, 85%), mp 116–118 °C.

^{1}H NMR: δ = 1.0–1.2 (1 H, m), 1.22–1.48 (3 H, m), 1.6–1.8 (2 H, m), 1.95–2.2 (2 H, m), 3.0 (1 H, m), 3.4 (1 H, m), 4.17 (2 H, br s, exchangeable), 6.45 (1 H, td, J = 7.3, 2.6 Hz), 6.70 (3 H, m), 8.8 (1 H, br s, exchangeable).

MS: m/z (%) = 207 (65, M), 148 (100).

[Found: C, 69.8; H, 8.4; N, 6.6 $C_{12}H_{17}NO_2$ requires: C, 69.6; H, 8.2, 6.8%].

***N*-(2-Hydroxyphenyl)cyclohexano[*b*]aziridine 7 (R = H), *N*-(2-Butoxyphenyl)cyclohexano[*b*]aziridine 7 (R = Bu) and 1,2,3,4,4a,10a-Hexahydro-10*H*-phenoxazine 6 (R = R′ = H) (also see below):**
The diol **5** (R = R′ = H) (0.3 g) in anhyd THF (10 mL) was treated with tributylphosphine (0.9 g, 3 eq.) and then diethyl azodicarboxylate (0.75 g, 3 eq) was added. After standing at r.t. for 1 h, the solvent was removed and the oily residue chromatographed eluting firstly with petrol: CH_2Cl_2 (1:1) and then with CH_2Cl_2. The first set of fractions gave a 1:1 mixture of **7** (R = Bu) and **6** (R = R′ = H) (40 mg), whereas elution with CH_2Cl_2 afforded **7** (R = H) (130 mg, 47%) as a colourless gum.

IR: ν_{max} 3178 cm^{-1}.

MS: m/z (%) = 189 (65, M), 120 (100).

^{1}H NMR: δ = 1.2–1.8 (8 H, m), 2.4 (2 H, m), 6.45 (1 H, br s, exchangeable), 6.68–7.0 (4 H, m).

[Found: m/z 189.1152 $C_{12}H_{15}NO$ requires: 189.1154].

2-[*N*-(2-Hydroxycyclohexyl)-*N*-benzylamino]phenol 5 (R = H, R′ = Bn):
2-[*N*-(2-Hydroxycyclohexyl)amino]phenol **5** (R = R′ = H) (207 mg) in 1,2-dichloroethane (20 mL) was treated with benzaldehyde (110 mg, 1 equiv) and sodium triacetoxyborohydride (0.42 g). After 3 h, the mixture was partitioned between H_2O (20 mL) and CH_2Cl_2 (20 mL), the organic layer collected and the aqueous phase extracted with CH_2Cl_2 (3 × 10 mL). The extracts were combined with the solvent layer and washed with H_2O (20 mL). The solvents were then removed and the residue was chromatographed, eluting with 5% EtOAc in petrol, to give the *N*-benzyl derivative **5** (R = H, R′ = Bn) (160 mg, 40%).

^{1}H NMR: δ = 1.1–2.1 (8 H, m), 2.66 (1 H, ddd, J = 11.8, 10.0, 3.8 Hz), 3.52 (1 H, ddd, J = 14.8, 10.4, 4.6 Hz), 4.20 (1 H, d, J = 14.1 Hz), 4.30 (1 H, d, J = 14.1 Hz), 6.71–7.38 (9 H, m).

MS: m/z (%) = 297 (20, M), 91 (100). This product was used directly in the following cyclisation experiment.

10-Benzyl-1,2,3,4,4a,10a-hexahydro-10*H*-phenoxazine 6 (R = H, R′ = Bn):
2-[*N*-(2-Hydroxycyclohexyl)-*N*-benzylamino]phenol **5** (R = H, R′ = Bn) (90 mg) in THF (5 mL) was treated with tributylphosphine (0.18 g, 3 equiv) and diethyl azodicarboxylate (0.15 g, 3 equiv) at r.t. After 1 h, the solvent was removed and the residual oil was chromatographed eluting with 5% EtOAc in petrol, this gave the title compound (80 mg, 95%), mp 102–104 °C (petrol).

^{1}H NMR: δ = 1.2–1.8 (6 H, m), 2.2 (2 H, m), 3.18 (1 H, ddd, J = 11.5, 2.2, 2.0 Hz), 4.30 (1 H, br d, J = 11.5 Hz), 4.45 (2 H, q, J = 16.6 Hz), 6.5 (1 H, dd, J = 7.8, 1.4 Hz), 6.6 (1 H, td, J = 7.5, 1.5 Hz), 6.74 (1 H, td, J = 7.5, 1.5 Hz), 6.83 (1 H, dd, J = 7.8, 1.5 Hz), 7.3 (5 H, m).

MS: m/z (%) = 279 (70, M), 188 (100).

[Found: C, 81.5; H, 7.6; N, 4.7 $C_{19}H_{21}NO$ requires: C, 81.7; H, 7.6; N, 5.0%].

1,2,3,4,4a,10a-Hexahydro-10*H*-phenoxazine 6 (R = R′ = H) (hydrochloride):
The benzyl compound **6** (R = H, R′ = Bn) (40 mg, 0.15 mM) in EtOH (12 mL) was hydrogenated over 10% Pd/C. The catalyst was removed and the solution was mixed with a few drops of Et_2O previously saturated with HCl, the solvent was then removed. This yielded a colourless foam (30 mg, 94%).

IR: ν_{max} = 3300, (br), 2700–2300 (br) cm^{-1}.

^{1}H NMR: δ = 1.6–2.0 (6 H, m), 2.2 (2 H, m), 3.82 (1 H, ddd, J = 10.3, 4.3, 2.1 Hz), 4.66 (1 H, br s), 7.0–7.6 (4 H, m).

MS: m/z (%) = 189 (100, M), 146 (90).

[Found: C, 63.6; H, 7.0; N, 6.5 $C_{12}H_{15}NO.HCl$ requires: C, 63.8; H, 7.2; N, 6.2%].

4,5-Dimethyl-2-(*N*-tosylamino)phenol 3 (R = Me, R′ = Ts):
3,4-Dimethylphenol (12.2 g, 0.1 mol) in pyridine (20 mL) was slowly treated with benzoyl chloride (15 mL), after 1 h the mixture was poured into ice-water and the product, mp 58–59 °C (EtOH), was filtered off. This compound was introduced in small amounts to a mixture of conc. HNO_3 (50 mL) and conc. H_2SO_4 (50 mL) cooled in an ice-bath. After the addition the mixture was warmed to r.t. for 1 h and then heated at 50 °C for 20 min. It was then cooled and poured onto ice-water. The solid which was obtained was collected, washed with Na_2CO_3 solution and H_2O and dried and crystallised from EtOH to give yellow needles of 2-benzoyloxy-4,5-dimethylnitrobenzene, mp 123–125 °C (EtOH). This compound was hydrolysed by treatment with 2 M NaOH in MeOH at reflux for 1 h, and the product was dissolved in EtOH (100 mL) and hydrogenated at 1 atm. pressure over 10% Pd/C catalyst for 3 h. The catalyst was then removed and the solvent evaporated to afford 2-amino-4,5-dimethylphenol (4.0 g, 29% overall), mp 170–173 °C (EtOH). Pyridine (5 mL) was added to a suspension of this product (7.5 g) in CH_2Cl_2 (100 mL) and the mixture was cooled to 0 °C. TSCl (10.6 g) was then introduced in portions. As the reaction proceeded the aminophenol dissolved and pyridine hydrochloride separated out. The mixture was allowed to warm to r.t. and after 2 h, it was mixed with H_2O (100 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The extracts were combined and the solvent was evaporated to give a colourless solid which was chromatographed on silica, eluting with $CHCl_3$, to give 4,5-dimethyl-2-(*N*-tosylamino)-*O*-tosylphenol as colourless prisms (3.6 g, 14.6%), mp 160–162 °C (EtOH).

^{1}H NMR: δ = 2.08 (3 H, s), 2.19 (3 H, s), 2.35 (3 H, s), 2.48 (3 H, s), 6.56 (1 H, s), 6.92 (1 H, s, exchangeable), 7.16 (2 H, d, J = 8.4 Hz), 7.32 (1 H, s), 7.36 (2 H, d, J = 8.6 Hz), 7.60 (2 H, d, J = 8.2 Hz), 7.68 (2 H, d, J = 8.4 Hz).

MS: m/z (%) = 445 (10, M$^+$).

Further elution of the column with 2% MeOH in $CHCl_3$ afforded the title compound as colourless prisms (8.5 g, 54%), mp 125–127°C (EtOAc/petrol).

IR: ν_{max} = 3440, 3260 cm^{-1}.

^1H NMR: δ = 2.08 (3H, s), 2.09 (3H, s), 2.37 (3H, s), 6.56 (1H, s), 6.98 (1H, s), 7.10 (2H, d, J = 8.2 Hz), 7.62 (2H, d, J = 8.2 Hz), 7.79 (1H, br s, exchangeable), 8.32 (1H, br s, exchangeable).

MS: m/z (%) = 291 (10, M^+), 136 (100, M–Ts).

[Found: C, 62.1; H, 5.8; N, 4.8 $C_{15}H_{17}SNO_3$ requires: C, 61.9; H, 5.8; N, 4.8%].

2-[*N*-(2-Hydroxycyclohexyl)-(*N*-tosyl)amino]-4,5-dimethylphenol 5 (R = Me, R′ = Ts):

4,5-Dimethyl-2-(*N*-tosylamino)phenol (2.0 g) in EtOH (20 mL) was treated with NaOEt (1 equiv) in EtOH (5 mL), the solvent was removed and the residue was redissolved in DMSO (10 mL). This solution was heated with cyclohexene epoxide (0.7 g, 1 equiv) at 120°C for 6 h, after cooling, H_2O (20 mL) and EtOAc (20 mL) were added. The organic layer was collected and the aqueous phase was extracted with EtOAc (2 × 20 mL). The extracts and solvent layer were then combined, washed with H_2O (10 mL) and evaporated to give an oil which upon chromatography, eluting with 5% EtOAc in petrol, gave firstly unchanged starting material (0.86 g) and then the title compound as a colourless oil (0.37 g, 24.3%).

IR: ν_{max} = 3300 (br) cm^{-1}.

^1H NMR: δ = 1.1–1.8 (8H, m), 2.04 (3H, s), 2.26 (3H, s), 2.44 (3H, s), 2.96 (1H, ddd, J = 10.0, 10.0, 4.5 Hz), 4.0 (1H, ddd, 11.0, 10.5, 4.5 Hz), 4.22 (1H, s, exchangeable), 6.3 (1H, s), 6.8 (1H, s), 7.27 (2H, d, J = 8.0 Hz), 7.63 (2H, d, J = 8.4 Hz).

MS: m/z (C.I.) (%) = 390 (50, M+1), 235 (100).

This was used directly in the next experiment.

1,2,3,4,4a,10a-Hexahydro-7,8-dimethyl-10-tosyl-10*H*-phenoxazine 6 (R = Me, R′ = Ts):

The product from the previous reaction (0.35 g, 0.9 mmol) in THF (10 mL) was reacted at r.t. with tributylphosphine (0.5 g, 3 equiv) and diethyl azodicarboxylate (0.44 g, 3 equiv). After 2 h, the solvent was removed and the oily residue was chromatographed on silica eluting with 1% EtOAc in petrol. This gave the title compound (0.31 g, 94%) as microprisms, mp 136–139°C (petrol).

^1H NMR: δ = 1.3–1.9 (8H, m), 2.18 (3H, s, Me), 2.22 (3H, s), 2.37 (3H, s), 3.25 (1H, br s), 4.1 (1H, ddd, J = 11.0, 4.0, 3.0 Hz), 6.6 (1H, s), 7.20 (2H, d, J = 7.9 Hz), 7.46 (2H, d, J = 8.2 Hz), 7.60 (1H, s).

MS: m/z (%) = 371 (20, M), 216 (100, M–Ts).

[Found: C, 67.5; H, 6.6; N, 3.7 $C_{21}H_{25}SNO_3$ requires: C, 67.9; H, 6.7; 3.8%].

10-Benzyl-1,2,3,4,4a,10a-hexahydro-7,8-dimethyl-10*H*-phenoxazine 6 (R = Me, R′ = Bn):

A mixture of 2-amino-4,5-dimethylphenol (1.0 g, 7.3 mM) and cyclohexene epoxide (0.72 g, 7.3 mM) was heated at 100–110°C for 3 h. The mixture was then cooled and 2-[*N*-(2-hydroxycyclohexyl)amino]-4,5-dimethylphenol was collected and crystallised from EtOH as colourless prisms (0.3 g). The mother liquor was evaporated and the residue was chromatographed, eluting with 10% EtOAc in petrol, to give a further sample of the product (1.4 g). Total yield 99%, mp 120–123°C (EtOH).

IR: ν_{max} = 3449, 3319, 3167 cm^{-1}.

^1H NMR: δ = 1.0–2.2 (8H, m), 2.05 (3H, s), 2.08 (3H, s), 2.65 (1H, m), 3.4 (1H, m), 6.7 (1H, s), 6.9 (1H, s).

MS: m/z (%) = 235 (100, M).

[Found: C, 71.2; H, 8.9; N, 5.8 $C_{14}H_{21}NO_2$ requires: C, 71.5; H, 8.9; N, 6.0%].

This product (0.88 g, 3.7 mM) in 1,2-dichloroethane (40 mL) was treated with benzaldehyde (0.4 g, 1 equiv) and sodium triacetoxyborohydride (1.65 g, 2 equiv) and the mixture was stored for about 120 h. The solvent was then removed and the residue was partitioned between H_2O (30 mL) and CH_2Cl_2 (30 mL). The organic phase was collected and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phase and the extracts were washed with H_2O (2 × 10 mL) and evaporated to yield the benzyl derivative of the diol (1.1 g, 92%). This material (0.92 g) in THF (20 mL) was treated with tributylphosphine (1.7 g) and diethyl azodicarboxylate (1.3 g) and after 2 h the solvents were removed. The residue was then chromatographed eluting with 1% EtOAc in petrol and the product was crystallised from petrol/EtOAc as colourless prisms (0.86 g, 99%), mp 85–86°C.

^1H NMR: δ = 1.15–1.88 (7H, m), 2.07 (3H, s), 2.12 (3H, s), 2.17 (1H, m), 3.1 (1H, br d, J = 10.7 Hz), 4.23 (1H, br s), 4.4 (2H, q, J = 16.5 Hz), 6.35 (1H, s), 6.65 (1H, s), 7.22–7.51 (5H, m).

MS: m/z (%) = 307 (100, M), 216 (96).

[Found: C, 82.0; H, 8.2; N, 4.5 $C_{21}H_{25}NO$ requires: C, 82.1; H, 8.1, N, 4.6%].

1,2,3,4,4a,10a-Hexahydro-7,8-dimethyl-10*H*-phenoxazine 6 (R = Me, R′ = H) (hydrochloride):

A solution of 10-benzyl-1,2,3,4,4a,10a-hexahydro-7,8-dimethyl-10*H*-phenoxazine (0.5 g, 1.6 mM) in EtOH (50 mL) was hydrogenated over 10% Pd/C during 3 h. The catalyst was then removed and Et_2O (3 mL), previously saturated with HCl, was added. Most of the solvents were then removed and on cooling, colourless, fine needles of the hydrochloride salt of the title compound separated (0.38 g, 91%), mp 193–196°C (EtOH/Et_2O).

IR: ν_{max} = 3401, 2355–2700 cm^{-1}.

^1H NMR: δ = 1.4–2.2 (8H, m), 2.20 (3H, s), 2.22 (3H, s), 3.78 (1H, ddd, J = 10.3, 4.5, 3.0 Hz), 4.6 (1H, br d, J = 3.0 Hz), 6.78 (1H, s), 7.32 (1H, s), 11.6 (2H, br s, exchangeable).

MS: m/z (%) = 217 (100, M), 174 (80).

[Found: C, 66.0; H, 7.9; N, 5.3 $C_{14}N_{20}NOCl$ requires: C, 66.3; H, 7.9; N, 5.5%].

The *N*-ethyl and *N*-hexyl derivatives of the title compound were also obtained as hydrochloride salts:

10-Ethyl-1,2,3,4,4a,10a-hexahydro-7,8-dimethylphenoxazine Hydrochloride **6** *(R = Me, R′ = Et)*: mp 176–179°C.

^1H NMR: δ = 1.4 (3H, t, J = 7 Hz), 1.5–2.2 (7H, m), 2.21 (3H, s), 2.22 (3H, s), 2.5 (1H, br s), 3.5 (3H, m), 4.6 (1H, br s), 6.67 (1H, s), 7.44 (1H, s).

MS: m/z (%) = 245 (100, M), 230 (90, M-15).

[Found: C, 68.0; H, 8.5; N, 4.7 $C_{16}H_{24}NOCl$ requires: C, 68.2; H, 8.5; N, 5.0%].

10-Hexyl-1,2,3,4,4a,10a-hexahydro-7,8-dimethylphenoxazine Hydrochloride **6** *(R = Me, R′ = Hex)*: mp 100–102°C (Et_2O).

^1H NMR: δ = 0.88 (3H, t, J = 7.0 Hz), 1.3–2.2 (15H, m), 2.21 (3H, s), 2.22 (3H, s), 2.60 (1H, m), 3.35 (2H, q, J = 7.0 Hz), 3.49 (1H, m), 3.56 (1H, m), 6.78 (1H, s), 7.45 (1H, s).

[Found: C, 70.8; H, 9.65; N, 4.19 $C_{20}H_{32}NOCl$ requires: C, 71.1; H, 9.5; N, 4.15%].

3-(2-Hydroxy-4,5-dimethylphenylamino)-1,1,4,4-tetramethyltetralin-2-ol 9 (R = H):

2-Amino-4,5-dimethylphenol (0.91 g, 6.6 mM) and 1,1,4,4-tetramethyltetralin-2,3-dione (1.44 g, 1 equiv) in 1,2-dichloroethane was treated with sodium triacetoxyborohydride (2.4 g, 2 equiv). The mixture was stirred for 24 h, and then mixed with H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with H_2O (20 mL), dried and evaporated to give an oil which was chromatographed eluting with 2% EtOAc in petrol to give 3-(2-hydroxy-4,5-dimethylphenylamino)-1,1,4,4-tetramethyltetralin-2-one as colourless needles (1.10 g, 50%), mp 157–160°C.

IR: ν_{max} = 3483, 3366, 1702 cm^{-1}.

^1H NMR: δ = 1.0 (3H, s), 1.47 (3H, s), 1.48 (3H, s), 1.60 (3H, s), 2.09 (3H, s), 2.12 (3H, s), 4.2 (1H, s), 4.6 (1H, br s, exchangeable), 5.67 (1H, br s, exchangeable), 6.49 (1H, s), 6.63 (1H, s), 7.29–7.5 (4H, m).

MS: m/z (%) = 337 (40, M).

This product (1.07 g) in anhyd THF (50 mL) was heated under reflux with $LiAlH_4$ (0.22 g, 2 equiv) under N_2 for 6 h. Sat. NH_4Cl solution (1 mL) was added and the mixture was diluted with EtOAc (50 mL), filtered, dried and evaporated to give the title compound as a mixture of two diastereomers. These were separated by chromatography to give the individual isomers:

(i) R_f (petrol:EtOAc 7:3) = 0.6. Yield 0.43 g (40%), mp 192–195°C.

IR: ν_{max} = 3449, 3390, 3225 cm^{-1}.

^1H NMR (CD_3SOCD_3): δ = 1.30 (3 H, s), 1.43 (6 H, s), 1.49 (3 H, s), 2.11 (3 H, s), 2.14 (3 H, s), 3.45 (1 H, br s, exchangeable), 3.72 (1 H, d, J = 7.5 Hz, 3.75 (1 H, d, J = 7.5 Hz), 4.4 (1 H, br s, exchangeable), 6.5 (1 H, s), 6.6 (1 H, s), 7.1–7.4 (4 H, m).

[Found: C, 77.6; H, 8.8; N, 3.9 $C_{22}H_{29}NO_2$ requires: C, 77.9; H, 8.6; N, 4.1%]

(ii) R_f (petrol:EtOAc 7:3) = 0.7. Yield 0.2 g (27.5%), mp 112–114°C.

IR: ν_{max} = 3373 (br) cm^{-1}.

^1H NMR (CD_3SOCD_3): δ = 1.19 (6 H, s), 1.24 (3 H, s), 1.35 (3 H, s), 2.01 (6 H, s), 3.4 (1 H, dd, J = 11.0, 8.8 Hz), 3.55 (1 H, dd, J = 11.0, 4.4 Hz), 4.10 (1 H, d, J = 8.8 Hz, exchangeable), 4.52 (1 H, d, J = 4.4 Hz, exchangeable), 6.46 (1 H, s), 6.47 (1 H, s), 7.2–7.3 (4 H, m), 8.98 (1 H, br s, exchangeable).

MS: m/z (%) = 339 (100, M^+).

[Found: C, 77.5; H, 8.8; N, 3.8 $C_{22}H_{29}NO_2$ requires: C, 77.9; H, 8.55; N, 4.1%].

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