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THE SYNTHESIS OF 1-[2-(DIMETHYLAMINO)ETHYL]-7,12-DIHYDRO-3H-[2]-BENZOXEPINO[4,3-e]INDOLE

A POTENTIAL ANTIDEPRESSANT AGENT

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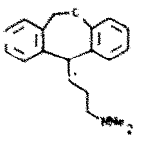
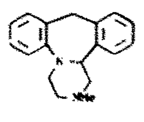
Abstract The structures of doxepin and serotonin were overlayed using molecular graphics and 1 - [2 - (dimethylamino)ethyl] - 7,12 - dihydro - 3H - [2] - benzoxepino[4,3 - e]indole (1) was proposed as a potential antidepressant agent. This paper deals with the synthesis of the title compound. Key steps in the synthesis include a regioselective electrophilic substitution at C-4 of ethyl 5-hydroxy-1-indolecarboxylate (4) and subsequent modification to 7,12-dihydro-3H-[2]-benzoxepino[4,3-e]indole (12). Standard procedures were then used to construct the dimethylaminoethyl side chain to yield the title compound (1).

The precise mode of action of antidepressant drugs remains unclear, but their modulation of central catecholamine and serotonin re-uptake into presynaptic nerve endings has been implicated.[1] In the search for new antidepressants, a vast number of analogues were synthesised which provided important structure-activity information.[2] Interestingly, doxepin[3] and a group of closely related tricyclics which have hindered rotation about the side chain are specific inhibitors of serotonin re-uptake.[1] More rigid analogues, such as mianserin,[4] are also specific inhibitors of serotonin re-uptake.



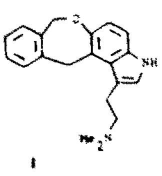
doxepin



mianserin

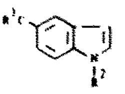
serotonin

In a new approach to the design of antidepressants we examined the crystal-structure[5] of some clinically important tricyclics and serotonin, also the conformation of their side chains in solution was determined by NMR.[6] It is reasonable to suggest that the oxygen substituted benzene ring of doxepin, for example, mimics the oxygen substituted benzene ring of serotonin. Molecular graphic techniques were used to overlay these two structures with minimal conformational changes in the side chains, so that the amino function in both compounds occupied the same position in space (Fig. 1).

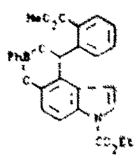


1

This led to the suggestion[7] that compound **1** (illustrated in Fig. 2) might be expected to display antidepressant activity. Our strategy was first to construct the tetracyclic indole (**12**) and then build up the dimethylaminoethyl side-chain using standard procedures. We chose 5-benzyloxyindole (**2**) as a



2 $R^1 = CH_2Ph$, $R^2 = H$
3 $R^1 = CH_2Ph$, $R^2 = CO_2Et$
4 $R^1 = H$, $R^2 = CO_2Et$



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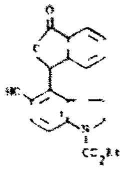

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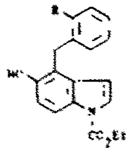
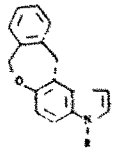
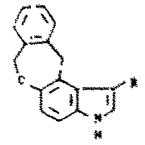


7 $R = CO_2H$
8 $R = CO_2Me$
9 $R = CH_2OH$
10 $R = CH_2Cl$



11 $R = CO_2Et$
12 $R = H$



13 $R = CHO$
14 $R = CH{:}CHNO_2$
15 $R = CH_2CH_2NH_2$
16 $R = COCOCl$
17 $R = COCONMe_2$

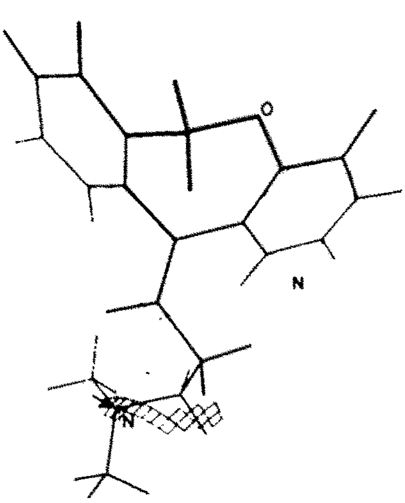


Fig. 1. Overlay of doxepin (——) and serotonin (···). The mesh shown in the lower part of this figure indicates the common area in space where the side chain nitrogen atoms from both structures can be accommodated, within 0.25 Å of each other, allowing for free rotation about single bonds in the side chains.

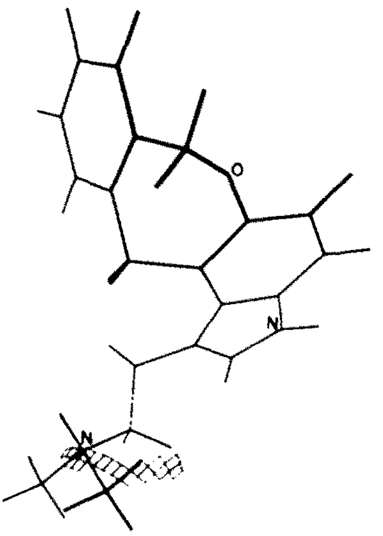


Fig. 2. Proposed antidepressant structure (——). The mesh in the lower part of this figure occupies the same position in space relative to the oxygen substituted benzene ring as determined in Fig. 1.

convenient starting material, which was prepared using the procedure of Batcho and Leimgruber.[8] The sodio salt of **2** was treated with ethyl chloroformate to give the carbamate **3**. Removal of the benzyloxy protecting group by hydrogenation in the presence of Pd–C gave a mixture (1 : 1) of the desired hydroxyindole **4** and the corresponding indoline. The benzyloxy group was removed with boron trichloride (a reagent previously reported[9] to remove methoxy and methylenedioxy groups) but the yield of **4** was only 20%. Deprotection under neutral conditions[10] using chlorotrimethylsilane and sodium iodide afforded a clean, efficient and totally reproducible route to the required 5-hydroxyindole (**4**). Compound **4** was condensed[11] with methyl 2-formylbenzoate[12] and phenylboric acid to give the boronate ester **5** which was treated with 2-methyl-2,4-pentanediol to afford the phthalide **6**. Reduction of **6** with Zn[13] in boiling acetic acid gave the carboxylic acid **7** which was methylated without purification to give the ester **8**. Alternatively, hydrogenolysis of the boronate **5** in the presence of Pd-C also gave the ester **8**, but this procedure was not totally reproducible and did not scale-up. Reduction of **8** with lithium borohydride in tetrahydrofuran afforded the alcohol **9**, which was treated with thionyl chloride to give the chloride (**10**). Cyclisation of **10** to the benzoxepinoindole (**11**) was slow with potassium carbonate in either boiling acetone or dimethylformamide, but was extremely rapid with sodium hydride in tetrahydrofuran. On work-up a mixture of **11** and **12** was obtained; these compounds were not separated since hydrolysis of the reaction mixture gave exclusively compound **12**. Compound **12** was formylated using a modified Vilsmeier–Haack reaction to give **13**, which was condensed with nitromethane to give the nitrovinyl derivative **14**. Reduction of **14** with lithium aluminium hydride gave a low yield of the tryptamine **15**. Following an alternative procedure,[14] the indole **12** was treated with oxalyl chloride to afford the glyoxylyl chloride **16**, which without purification was treated with dry dimethylamine to give the glyoxylamide **17**. Reduction of **17** with lithium aluminium hydride in tetrahydrofuran gave a low yield of the desired product (**1**), which was isolated as the oxalate. However, by simply changing the reaction solvent to ether and using a Soxhlet extraction apparatus we obtained **1** in 57% yield.

A biological evaluation of **1** indicated that it possessed anti-convulsant activity, and in a standard antidepressant test† it was more active than doxepin. In mode of action studies compound **1** did not inhibit the uptake of either serotonin or noradrenaline *in vitro*, but *in vivo* the brain levels of three monoamine metabolites, methoxyhydroxyphenylethyleneglycol sulphate, homovanillic acid and 5-hydroxyindole-3-acetic acid were increased significantly.

EXPERIMENTAL

NMR spectra were recorded on a Varian T60 and on a Varian XL 100/15 spectrometer with chemical shifts (δ) presented in ppm from internal TMS. Mass spectra were obtained using an AEI MS 902 instrument, IR spectra (Nujol mulls) were determined on a Pye-Unicam SP 1000 spectrophotometer and were consistent with the structures assigned. Elemental analyses were carried out on a Perkin-Elmer Model 240 instrument. Molecular graphics studies were carried out on a Megatek 7000 display processor interfaced to a PDP 11/40 host computer. M.ps were recorded on a Buchi Tottoli apparatus and are uncorrected. Column chromatography was carried out on silica gel, Kieselgel 60, 70–230 mesh (Merck). TLC was carried out using glass-supported Kieselgel 60 F_{254} (0.25 mm) plates supplied by Merck. Solvents (BDH) were used as supplied unless stated. Light petroleum had b.p. 40–60°.

5-*Benzyloxyindole* (2)

A mixture of 3-methyl-4-nitrophenol (15.3 g, 100 mmol), benzyl chloride (14.9 g, 110 mmol) and anhyd K_2CO_3 (15.2 g, 110 mmol) in dry DMF (150 ml) was stirred and heated at 120° for 2 hr. The mixture was poured onto ice (500 g), the solid formed was collected by filtration, and washed with water (50 ml). Recrystallisation from EtOH gave pure 5-benzyloxy-2-nitrotoluene (22.7 g, 93%), m.p. 67–8°. (Found: C, 69.3; H, 5.1; N, 5.9. $C_{14}H_{13}NO_3$ requires: C, 69.1; H, 5.4; N, 5.8%); NMR δ ($CDCl_3$) 2.66 (3H, s, $C\underline{H}_3$), 5.10 (2H, s, $C\underline{H}_2Ph$), 6.8–8.1 (8H, m, $Ar\underline{H}$). A mixture of the above nitrotoluene (6.1 g, 25 mmol) and N,N-dimethylformamide dimethyl acetal (3.6 g, 30 mmol) in dry DMF (60 ml) was heated at 140° for 16 hr so that MeOH was removed from the mixture as it was formed. The cooled soln was evaporated to dryness to afford a dark red oil (7.5 g) that crystallised on standing. The crude enamine was dissolved in EtOH (100 ml) and hydrogenated at atmospheric pressure in the presence of Raney Ni (1.4 g). When the uptake of H_2 was complete the mixture was filtered and the filtrate evaporated to give a brown oil (5.6 g). The product was distilled to give an oil (4.1 g) b.p. 165°/0.1 mm Hg. On standing **2** crystallised and was then recrystallised from EtOH to give white needles (3.2 g, 42%) m.p. 96–98° (lit.[8] 103–105°, lit.[15] 104–106°). (Found: C, 80.4; H, 5.8; N, 6.10. $C_{15}H_{13}NO$ requires: C, 80.5; H, 5.8; N, 6.3%); NMR δ ($CDCl_3$) 5.10 (2H, s, CH_2Ph), 6.4–7.5 (10H, m, $Ar\underline{H}$), 7.90 (1H, br, NH). Alternatively, the crude 5-benzyloxyindole can be purified by dissolving in CH_2Cl_2 and percolation through a column of silica gel (20 g) with CH_2Cl_2 as eluent.

Ethyl 5-benzyloxy-1-indolecarboxylate (3)

A stirred soln of **2** (4.46 g, 20 mmol) in dry DMF (20 ml) under N_2 was cooled to 0° and treated portionwise with 80%

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† Antagonism of Ro 04-1284 induced depression (a benzoquinolizine derivative with a more rapid onset of reserpine-like monoamine depleting action).

NaH (0.6 g, 20 mmol). When the effervescence had ceased the soln was heated to 60° for 1 hr. The stirred soln was then cooled to 0° and ethyl chloroformate (2.2 g, 20 mmol) added dropwise. After 3 hr the mixture was poured into water (100 ml). The solid was collected, dried and recrystallised from EtOH to give pure **3** (5.0 g, 85%) m.p. 54–55°. (Found: C, 73.10; H, 5.9; N, 5.0. $C_{18}H_{17}NO_3$ requires: C, 73.2; H, 5.8; N, 4.7%); NMR δ ($CDCl_3$) 1.45 (3H, t, J = 7 Hz, $CH_2C\underline{H}_3$), 4.5 (2H, q, J = 7 Hz, $C\underline{H}_2CH_3$), 5.10 (2H, s, $C\underline{H}_2Ph$), 6.5–7.5 (10 H, m, ArH).

Ethyl 5-hydroxy-1-indolecarboxylate (4)

A mixture of **3** (29.5 g, 100 mmol) and NaI (30 g, 200 mmol) in acetonitrile (250 ml) was treated with chlorotrimethylsilane (21.7 g, 200 mmol) and stirred at 25° for 17 hr. MeOH (200 ml) was added and the solvents evaporated. The residue was shaken with CH_2Cl_2 (200 ml) and 2 M sodium metabisulphite soln (100 ml). The organic layer was separated, washed with water (50 ml), dried over Na_2SO_4 and evaporated to afford a red oil (27.6 g). The crude product was dissolved in CH_2Cl_2 and applied to a column of silica gel (100 g). Eluting with CH_2Cl_2 gave a mixture of starting material and benzyl iodide. The desired product was then eluted with CH_2Cl_2 : MeOH (99 : 1). Evaporation of appropriate fractions gave an oil that crystallised (17.8 g, 87%). Recrystallisation from CCl_4 gave pure **4** m.p. 89°. (Found: C, 64.5; H, 5.3; N, 7.1. $C_{11}H_{11}NO_3$ requires: C, 64.4; H, 5.4; N, 6.8%); NMR δ ($CDCl_3$) 1.45 (3H, t, J = 7 Hz, $CH_2C\underline{H}_3$), 4.35 (2H, q, J = 7 Hz, $C\underline{H}_2CH_3$), 5.5 (1H, br, O$\underline{H}$), 6.35 (1H, d, J = 4 Hz, Ar$\underline{H}$), 7.50 (1H, d, J = 4 Hz, Ar$\underline{H}$), 7.95 (1H, d, J = 9 Hz, Ar$\underline{H}$), 6.65–7.25 (2H, m, Ar$\underline{H}$).

Ethyl 1,7-dihydro-1-[2-(methoxycarbonyl)phenyl]-3-phenyl-[1,3,2]-dioxaborino[5,4-e]indole-7-carboxylate (5)

A mixture of **4** (0.515 g, 2.5 mmol), phenylboric acid (0.305 g, 2.5 mmol), methyl 2-formylbenzoate (0.41 g, 0.25 mmol) and propionic acid (0.2 ml) in toluene (30 ml) was boiled at reflux for 6 hr so that water was removed from the mixture as it was formed. The mixture was filtered and the filtrate evaporated to give a yellow oil. The crude product was dissolved in CH_2Cl_2 (25 ml), washed with sat $NaHCO_3$ aq (10 ml), water (10 ml), dried over Na_2SO_4 and evaporated to give a yellow oil (0.76 g). Trituration with light petroleum gave a white solid that was recrystallised from CH_2Cl_2/cyclohexane to give pure **5** (0.48 g, 42%) m.p. 164°. (Found: C, 68.6; H, 4.6; N, 3.1. $C_{24}H_{22}BNO_6$ requires: C, 68.6; H, 4.6; N, 3.1%); NMR δ ($CDCl_3$) 1.40 (3H, t, J = 7 Hz, $CH_2C\underline{H}_3$), 4.00 (3H, s, CO_2CH_3), 4.45 (2H, q, J = 7 Hz, $C\underline{H}_2CH_3$), 6.15 (1H, J = 4 Hz, Ar$\underline{H}$), 7.1–8.2 (13H, m, Ar$\underline{H}$ and ArCHAr).

Ethyl 5-hydroxy-4-phthalidyl-1-indolecarboxylate (6)

A soln of **5** (4.55 g, 10 mmol), 2-methyl-2,4-pentanediol (2.36 g, 20 mmol) and glacial AcOH (0.2 ml) in CH_2Cl_2 (20 ml) was stirred for 3 hr. The solvents were evaporated *in vacuo* to afford an oily residue. The crude product was dissolved in CH_2Cl_2 (50 ml), washed with sat $NaHCO_3$ aq (25 ml), water (25 ml), dried and evaporated to give a yellow oil. Trituration with light petroleum and then with diethyl ether gave a white solid (3.4 g). Recrystallisation from EtOH/MeOH gave pure phthalide (**6**) (3.2 g, 95%) m.p. 208°. (Found: C, 67.2; H, 4.7; N, 3.9. $C_{18}H_{15}NO_5$ requires: C, 67.6; H, 4.5; N, 4.2%); NMR δ ($CDCl_3$) 1.39 (3H, t, J = 7 Hz, $CH_2C\underline{H}_3$), 4.42 (2H, q, J = 7 Hz, CH_2CH_3), 5.90 (1H, d, J = 4 Hz, Ar$\underline{H}$), 6.90 (1H, d, J = 8 Hz, Ar$\underline{H}$), 7.20 (1H, s, ArC$\underline{H}$Ar), 7.35 (1H, d, J = 4 Hz, Ar$\underline{H}$), 7.90 (1H, d, J = 8 Hz, Ar$\underline{H}$), 7.25–7.60 (4H, m, Ar$\underline{H}$).

Ethyl 5-hydroxy-4-[2-(methoxycarbonyl)benzyl]-1-indolecarboxylate (8)

(a) A mixture of **6** (1 g, 3 mmol) and activated Zn dust (2 g, 31.3 mmol) in glacial AcOH (20 ml) was boiled under reflux for 6 hr. The mixture was filtered and the residue washed with boiling glacial AcOH (5 ml). The total filtrate was evaporated to afford crude **7** as a white solid (1.2 g).

MeOH (20 ml) stirred and cooled to −5° was treated dropwise with $SOCl_2$ (1.2 g, 10 mmol) so as to maintain a temp of 5°. After 2 min this soln was added in one portion to the crude acid (1.2 g) and the resulting soln stirred at room temp, following the reaction to completion by TLC (5 hr). The solvent was evaporated to give a white crystalline mass. Recrystallisation from MeOH gave pure **8** (0.84 g, 80%) m.p. 164°. (Found: C, 67.7; H, 5.5; N, 3.9. $C_{20}H_{19}NO_5$ requires: C, 68.0; H, 5.4; N, 4.0%); NMR δ ($CDCl_3$) 1.35 (3H, t, J = 7 Hz, $CH_2C\underline{H}_3$), 3.95 (3H, s, $CO_2C\underline{H}_3$), 4.33 (2H, s, $ArC\underline{H}_2Ar$), 4.40 (2H, q, J = 7 Hz, CH_2CH_3), 6.55 (1H, d, J = 3 Hz, Ar$\underline{H}$), 6.80 (1H, d, J = 9 Hz, ArH), 7.50 (1H, d, J = 3 Hz, Ar$\underline{H}$), 7.70 (1H, d, J = 9 Hz, Ar$\underline{H}$), 6.9–7.4 (5H, m, Ar$\underline{H}$).

(b) A soln of **5** (0.45 g, 1 mmol), trifluoroacetic acid (5 drops) and perchloric acid (70%, 5 drops) in CH_2Cl_2 (10 ml) was hydrogenated over 10% Pd–C (0.1 g) at atmosphere pressure. After 3 hr the mixture was filtered and the filtrate washed with sat $NaHCO_3$ aq (10 ml), dried over Na_2SO_4 and evaporated to afford an oil (0.3 g), which crystallised on standing. Recrystallisation from MeOH gave pure **8** m.p. 164°, identical in all respects to the product obtained in the above procedure.

Ethyl 5-hydroxy-4-[2-(hydroxymethyl)benzyl]-1-indolecarboxylate (9)

A soln of **8** (3.5 g, 10 mmol) in dry THF (35 ml) was treated with fresh lithium borohydride (0.7 g, 32 mmol) and the resulting mixture stirred for 17 hr. MeOH (20 ml) was added cautiously to destroy excess reagent, and after 30 min the solvent was evaporated. The residue was dissolved in CH_2Cl_2 (50 ml), then washed with water (20 ml containing glacial AcOH 0.5 ml). The organic layer was dried over Na_2SO_4 and evaporated to give a crystalline solid. Recrystallisation from EtOAc/toluene gave pure **9** (2.45 g, 76%, m.p. 149–150°). (Found: C, 70.2; H, 5.8; N, 4.4. $C_{19}H_{19}NO_4$ requires: C, 70.1; H, 5.9; N, 4.3%); NMR δ (DMSO-d_6) 1.35 (3H, t, J = 7 Hz, CH_2CH_3), 4.10 (2H, s, $ArC\underline{H}_2Ar$), 4.40 (2H, q, J = 7 Hz, CH_2CH_3), 4.60 (2H, s, $ArC\underline{H}_2OH$), 6.45 (1H, d, J = 3 Hz, H-3), 7.50 (1H, d, J = 3 Hz, H-2), 7.80 (1H, d, J = 9 Hz, H-5), 6.6–7.4 (5H, m, Ar$\underline{H}$).

7,12-*Dihydro*-3H-[2]-*benzoxepino*[4,3-e]*indole* (12)

A suspension of **9** (3.25 g, 10 mmol) in dry ether (150 ml) was stirred and cooled to 0° and then treated dropwise with excess $SOCl_2$ (2.4 g, 20 mmol). The resulting mixture was stirred at room temp for 18 hr. Sat of $NaHCO_3$ aq (100 ml) was added cautiously; the organic layer was separated, dried over Na_2SO_4 and evaporated to afford **10** as an oil (3.4 g). This crude material was dissolved in CH_2Cl_2 (10 ml) and percolated through a short column of silica gel (15 g), eluting with the same solvent. Evaporation of appropriate fractions gave **10** as a white solid (3.2 g, 93%). NMR δ ($CDCl_3$) 1.40 (3H, t, J = 7 Hz, $CH_2C\underline{H}_3$), 4.20 (2H, s, $ArC\underline{H}_2Ar$), 4.50 (2H, q, J = 7 Hz, $C\underline{H}_2CH_3$), 4.80 (2H, s, $ArC\underline{H}_2Cl$), 6.40 (1H, d, J = 3 Hz, H-3), 6.75 (1H, d, J = 6 Hz, ArH), 7.45 (1H, d, J = 3 Hz, H-2), 7.85 (1H, d, J = 6 Hz, ArH), 6.9–7.3 (4H, m, ArH).

A stirred soln of the chloride (3.8 g) in dry THF (100 ml) was cooled to −5° and then treated with NaH (0.3 g, 80%). The mixture was stirred at room temp for 3 hr. TLC showed no starting material remained but two new components had been formed. The mixture was treated with MeOH (10 ml) and evaporated to dryness. The oily residue was dissolved in MeOH (50 ml) and a soln of KOH (2 g) in water (10 ml) added. After 1 hr TLC showed the presence of a single component. The mixture was evaporated and the residue partitioned between CH_2Cl_2 (100 ml) and water (50 ml). The organic layer was separated, dried and evaporated to afford a pale brown oil (1.9 g). The crude product was dissolved in CH_2Cl_2 (10 ml) and percolated through a short column of silica gel (10 g), eluting with the same solvent. Evaporation of the eluent gave **12** as a white solid (1.43 g, 61%). Recrystallisation from benzene gave an analytical sample m.p. 124°. (Found: C, 81.87; H, 5.48; N, 5.78. $C_{16}H_{13}NO$ requires: C, 81.68; H, 5.57; N, 5.95%); NMR δ ($CDCl_3$) 4.33 (2H, s, $ArCH_2Ar$), 5.30 (2H, s, $ArOCH_2Ar$), 6.4–7.2 (8H, m, Ar$\underline{H}$), 7.85 (1H, br, NH).

7,12 - *Dihydro* - 3H - [2] - *benzoxepino*[4,3 - e]*indole* - 1 - *carboxaldehyde* (13)

$POCl_3$ (0.34 g, 2.2 mmol) was added to DMF (2 ml) cooled and stirred at 0°, and after 15 min a soln of **12** (0.47 g, 2.0 mmol) in DMF (3 ml) was added dropwise. After 30 min at 0°, and 1 hr at room temp crushed ice (5 g) was added to the mixture and stirring continued for 1 hr. A soln of KOH (2.5 g) in water (5 ml) was added and the mixture heated at 90° for 15 min. The product was collected by filtration, washed with water and dried *in vacuo*. The crude product (0.55 g) was recrystallised from EtOAc to give an analytical sample of **13** m.p. 199 200°. (Found: C, 77.7; H, 4.9; N, 5.2. $C_{17}H_{13}NO_2$ requires: C, 77.6; H, 5.0; N, 5.3%); NMR δ (DMSO-d_6) 5.00 (2H, s, $ArCH_2Ar$), 5.24 (2H, s, $ArCH_2OAr$), 6.82–7.50 (6H, m, $Ar\underline{H}$), 8.24 (1H, s, $Ar\underline{H}$), 8.66 (1H, br, $N\underline{H}$), 9.83 (1H, s, $C\underline{H}O$).

7,12 - *Dihydro* - 1 - (2 - *nitrovinyl*) - 3H - [2] - *benzoxepino*[4,3 - e]*indole* (14)

A mixture of **13** (1.05 g, 4.0 mmol) and ammonium acetate (0.1 g) in nitromethane (5 ml) was heated at 95° for 1 hr. The mixture was cooled and the product collected by filtration and dried to afford 0.7 g (60%) of a deep red solid. An analytical sample of **14** was obtained by recrystallisation from nitromethane m.p. 228°. (Found: C, 70.3; H, 4.5; N, 8.9. $C_{18}H_{14}N_2O_3$ requires: C, 70.6; H, 4.6; N, 9.1%); NMR δ ($CDCl_3$) 4.50 (2H, s, $ArC\underline{H}_2Ar$), 5.19 (2H, s, $ArC\underline{H}_2OAr$), 6.70–7.83 (8H, m, $Ar\underline{H}$ and $=C\underline{H}$), 8.66 (1H, d, J = 13 Hz, $C{=}C\underline{H}Ar$), 11.63 (1H, br, $N\underline{H}$).

7,12 - *Dihydro* - N,N - *dimethyl* - 3H - [2] - *benzoxepino*[4,3 - e]*indole* - 1 - *glyoxylamide* (17)

A stirred soln of **12** (1.17 g, 5 mmol) in dry ether (10 ml) was cooled to 0° and treated dropwise with oxalyl chloride (0.75 g, 6 mmol). The resulting yellow soln was allowed to warm to room temp and stirring was continued for 30 min. The solvent was evaporated and the resulting yellow oil was triturated with light petroleum to afford a pale yellow solid (1.6 g) which was dissolved in dry benzene (30 ml) and immediately saturated with dry dimethylamine gas. After 1 hr the resulting pale brown soln was evaporated to afford a brown oil (1.7 g). The crude product was purified by percolation through a column of silica gel (20 g) eluting with CH_2Cl_2 : MeOH (99 : 1). Evaporation of appropriate fractions gave an oil that solidified. Crystallisation from EtOAc gave pure **17** (1.0 g, 59%) m.p. 220°. (Found: C, 71.7; H, 5.4; N, 8.4. $C_{20}H_{18}N_2O_3$ requires: C, 71.8; H, 5.6; N, 8.4%); NMR δ (DMSO-d_6) 2.95 (3H, s, $NC\underline{H}_3$), 3.05 (3H, s, $NC\underline{H}_3$), 4.95 (2H, s, $ArC\underline{H}_2Ar$), 5.20 (2H, s, $ArC\underline{H}_2O$), 6.9–8.0 (7H, m, $Ar\underline{H}$), 11.5 (1H, br, $N\underline{H}$).

1 - [2 - (*Dimethylamino*)*ethyl*] - 7,12 - *dihydro* - 3H - [2] - *benzoxepino*[4,3 - e]*indole* (1)

The amide **17** (0.67 g, 2 mmol) was placed in a Soxhlet extraction apparatus and subjected to continuous extraction into a boiling soln of LAH (0.76 g, 20 mmol) in dry ether (50 ml). After 24 hr the excess reagent was decomposed by addition of EtOAc (5 ml), and then sufficient water added to afford a thick paste. The ether layer was decanted and the residual paste extracted twice with CH_2Cl_2 (20 ml). The combined extracts were evaporated. The resulting oil was taken up in CH_2Cl_2 (50 ml), washed with water (10 ml), dried over Na_2SO_4 and evaporated to afford a colourless foam (0.6 g). A soln of the crude product (0.6 g) in THF (3 ml) was added to a soln of oxalic acid (0.45 g) dissolved in THF (3 ml). A gel formed which slowly changed form to afford a crystalline solid. The solid was filtered and washed exhaustively with THF to give the oxalate salt of **1** (0.45 g, 57%) m.p. 225°. (Found: C, 66.6; H, 6.1; N, 6.9. $C_{22}H_{24}N_2O_5$ requires: C, 66.6; H, 6.1; N, 7.1%); NMR δ (DMSO-d_6) 2.58 (6H, s, $N(C\underline{H}_3)_2$), 3.05 (4H, s, $ArCH_2C\underline{H}_2NMe_2$), 4.22 (2H, s, $ArCH_2Ar$), 5.00 (2H, s, $ArCH_2OAr$), 6.50–7.60 (7H, m, ArH), 10.58 (1H, br, $N\underline{H}$).

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