Synthesis of 1-amino-1,2,3,14b-tetrahydro-4*H*-pyrido[1,2-*d*]-dibenzo[*b*,*f*][1,4]oxazepine and related compounds

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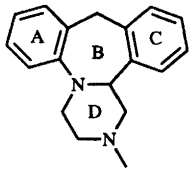
The synthesis is described of the epimeric 1-amino-1,2,3,14b-tetrahydro-4*H*-pyrido[1,2-*d*]dibenzo[*b*,*f*]-[1,4]oxazepines 2 and their *N*-substituted analogues. The *cis*-amines 33, 36 and 38 were prepared from the ketone 31 by reduction of the corresponding oxime whereas the *trans* isomers 12, 50 and 51 were prepared from the 1-ethoxycarbonyl derivative 44 by Curtius degradation. Attempts to convert the *trans* alcohol 7 into the epimeric azido compound by an S_N2 replacement reaction with sodium azide resulted in rearrangement to give the novel ring system, 14-azido-11-methoxy-1,2,14,14a-tetrahydro-4*H*-pyrrolo[1,2-*d*]dibenzo[*b*,*g*][1,4]oxazocine 24 instead of the titled compounds.

Following the discovery of the antidepressant properties of hexahydrodibenzo[*c*,*f*]pyrazino[1,2-*d*]azepine **1** (mianserin)[1] we initiated a programme to synthesize related analogues in order to exploit fully their biological properties. We report here the part of this programme directed towards the synthesis of the 1-amino-1,2,3,14b-tetrahydro-4*H*-pyrido[1,2-*d*]dibenzo-[*c*,*f*] [1,4]oxazepine derivatives **2** in which the aliphatic amine



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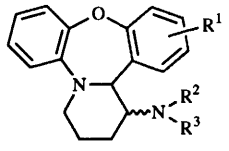


2

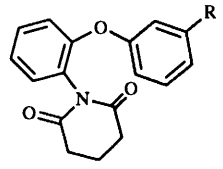
is exocyclic to the ring system rather than part of a piperazine ring. The synthesis of these compounds also relates to our programme concerned with the preparation and biological testing of conformationally restricted phenylethylamines.

Results and discussion

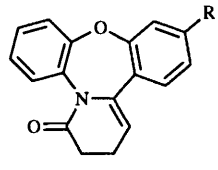
In earlier investigations we had established that *N*-[2-(3-methoxyphenoxy)phenyl]glutarimide **3** readily cyclised with polyphosphoric acid (PPA) to give 2,3-dihydro-4*H*-pyrido-[1,2-*d*]dibenzo[*c*,*f*][1,4]oxazepin-4-one **5** the hydroboration of which, followed by oxidation of the subsequent intermediate organoborane, we anticipated would give the alcohol **7**. This could then be converted into the required epimeric amino compounds **2** by standard procedures.

Our initial target compounds were the unsubstituted 1-amino analogues **2** (R^1 = H) but, unexpectedly, the unsubstituted glutarimide **4** failed to cyclise to the enamide **6** using the above cyclodehydrating conditions. However, so that we could confirm our originally proposed route we continued the synthesis with the methoxyglutarimide **3**. Reaction of the enamide **5** with diborane followed by oxidation with alkaline hydrogen peroxide[2] gave a mixture of products from which *trans*-1,2,3,14b-tetrahydro-4*H*-pyrido[1,2-*d*]dibenzo-[*c*,*f*][1,4]oxazepin-1-ol **7** (the prefix *trans* or *cis* applies to the configuration between C-14b and C-1) was readily isolated by chromatography in *ca.* 45% yield along with smaller amounts of a mixture of the two amines **16** and **19**. The last two compounds were characterised following acetylation of the mixture and separation of the non-basic amide **17** from the amine **19**.

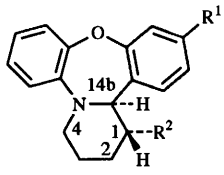
Although treatment of enamines with diborane–alkaline hydrogen peroxide has been described as a method of preparing



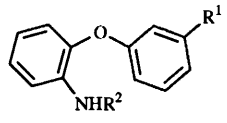
3 R = OMe
4 R = H



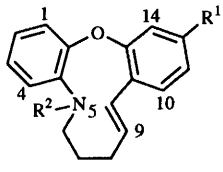
5 R = OMe
6 R = H



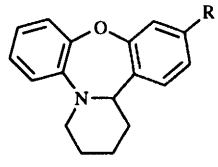
7 R^1 = OMe, R^2 = OH
8 R^1 = OMe, R^2 = OTs
9 R^1 = OMe, R^2 = OAc
10 R^1 = H, R^2 = OH
11 R^1 = H, R^2 = OCH_2SMe
12 R^1 = H, R^2 = NH_2



13 R^1 = OMe, R^2 = H
14 R^1 = R^2 = H
15 R^1 = H, R^2 = $CO(CH_2)_3CH_2Cl$

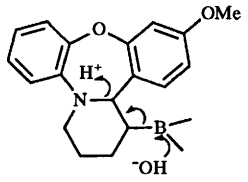


16 R^1 = OMe, R^2 = H
17 R^1 = OMe, R^2 = Ac
18 R^1 = R^2 = H



19 R = OMe
20 R = H

vicinal amino alcohols[2] and, on one occasion, as giving a saturated cyclic amine from the corresponding endocyclic enamine,[3] the formation of cleavage products similar to **16** under these conditions has not, to our knowledge, been described previously. Cleavage of borane intermediates occurs under protolytic conditions[4] in propionic acid at relatively high temperatures. In the present instance decomposition of the boron intermediate **21** could possibly be occurring by nucleophilic attack at boron followed by cleavage, the process being possibly influenced by the mesomeric effect of the methoxy group since in its absence cleavage does not occur (see below). When insufficient diborane for complete reduction of the enamide **5** was used (procedure described in the Experimental section), a small amount of the *trans*-hydroxy

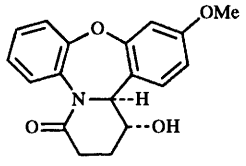


21

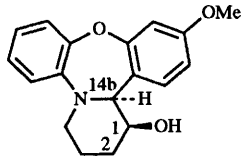
amide **22** was also isolated which, on further reduction with diborane, gave the alcohol **7** quantitatively.

The *trans* configurations of the two alcohols **7** and **22** follow from the known[5] *cis*-hydroxylation that results from the hydroboration/oxidation procedure. The ^{1}H NMR spectrum of the alcohol **7** shows 14b-H as a doublet at δ 3.85 (J 8 Hz) and 1-H as six lines at δ 4.1 (J 8, 8 and 4 Hz) indicating that the hydroxy group has predominantly an equatorial orientation.

The NMR spectrum of the epimeric alcohol **23**, prepared from **7** by oxidation (see below) and reduction with sodium



22

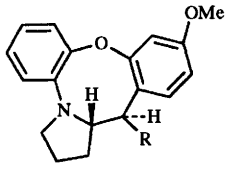


23

boranuide, showed 14b-H as a doublet at δ 3.98 (J 1.5 Hz) and 1-H as a narrow multiplet at δ 3.75 indicating that in the *trans* isomer the hydroxy group has predominantly an axial orientation. The alcohol **22** appears to have a different conformation from the alcohol **7** as the 14b-H appears in the NMR spectrum at δ 4.72 (J 1.5 Hz) and 1-H as a narrow multiplet at δ 4.4.

The alcohol **7** was readily converted into the tosyl derivative **8**, however this, on reaction with sodium azide in *N*-methyl pyrrolidone gave, unexpectedly, in high yield, the rearranged azide **24** (Scheme 1). This was subsequently reduced with lithium aluminium hydride to the primary amine **25**. Similarly, treatment of **8** with ammonium formate in DMSO gave the alcohol **26**.

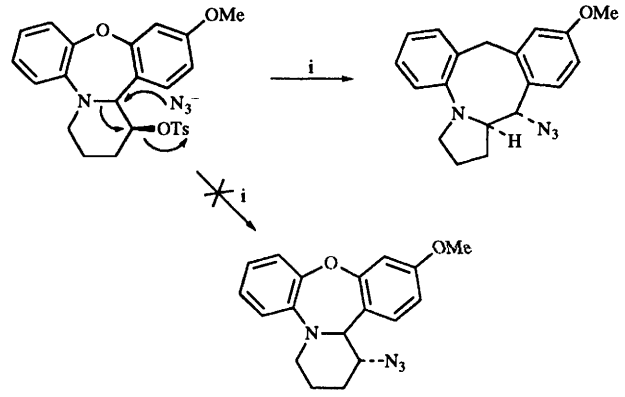
The structures of these rearranged products were deduced from the ^{1}H NMR spectra of the amine **25** and the alcohol **26** which show the signals for the hydrogen atoms adjacent to the



24 R = N_3
25 R = NH_2
26 R = OH
27 R = NHAc
28 R = OAc

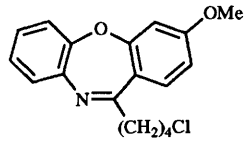
primary amino or hydroxy groups as doublets (J 9 Hz) at 3.5 and 4.3 ppm, respectively, which move to lower field (5.00 and 5.7 ppm) on acylation (compounds **27** and **28**). The 8 Hz coupling constant for these doublets suggests a *trans* orientation of hydrogen atoms (Dreiding models indicate a dihedral angle of *ca.* 90° for the *cis* isomer) and since only one isomer is detected in the rearrangement, the reaction probably occurs by a concerted mechanism with concomitant attack of azide ion at 14b-C with rearside displacement of the tosyl group by the migrating N–C(14b) bond. An inspection of Dreiding models indicates that this is a reasonable process (see Scheme 1).

Although the glutarimide **4** failed to give the enamide **6** the

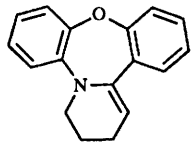


Scheme 1 *Reagent:* i, NaN_3–*N*-methylpyrrolidine

valeramide **15**, prepared from 2-phenoxyaniline and 5-chlorovaleryl chloride, readily cyclised on treatment with PPA to give the imine **29** which, in turn, gave the enamine **30** on treatment



29

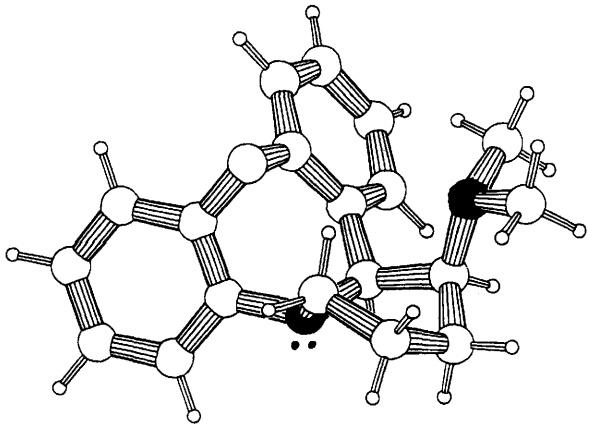


30

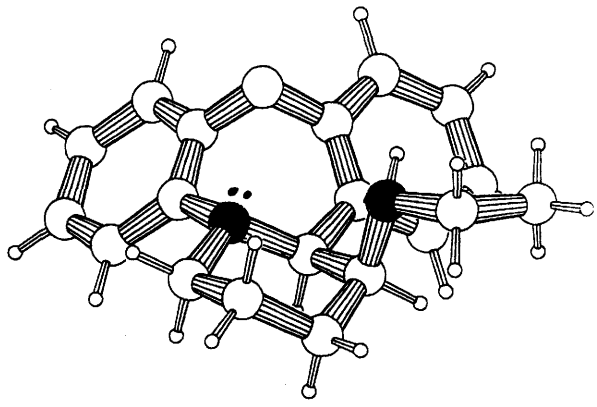
with sodium ethoxide.† Hydroboration–oxidation of the enamine **30** gave essentially the same products as from the enamine **5** with the alcohol **10** being isolated in 55% yield. In this instance, however, an appreciable amount (42%) of the reduced compound **20** was formed and none of the ring-opened product **18** was detected. We did not fully rationalise the difference in reaction paths of these two compounds, although the mesomeric effect of the methoxy group of **5** may be influencing the reaction pathway. Treatment of the organoborane intermediate with hydroxylamine *O*-sulfonic acid[7] did not give the primary amine **12**.

Oxidation of the alcohol **10** was more difficult than expected; methods using Jones' reagent, Sarett's reagent, the Oppenauer reaction (Woodward modification[8]) and some other methods[9] all failed. Oxidation with dimethyl sulfoxide and acetic anhydride[10] however did give the ketone **31** along with a substantial amount of the methyl thiomethyl ether **11**. Although chromotographic separation of these products was possible, since the ketone **31** was an unstable oil a mixture of **31** and **11** was treated with hydroxylamine and the product, containing the oxime **32**, which was not isolated, was reduced with lithium aluminium hydride. This gave, after separation of the basic and neutral fractions, the *cis*-amine **33** as the only basic product, isolated as the maleate salt, and the methylthiomethyl ether **11**. The NMR spectrum of the amine **33** was similar to that of the *cis* alcohol **23**, the 14b-H appearing as a doublet at δ 4.02 (J 1.7 Hz) and 1-H as a narrow multiplet indicating that reduction of the oxime occurs stereospecifically from the rear of the molecule. A minor component formed during the reduction was thought to be the aziridine **39**. This compound was not isolated but its presence was deduced following the isolation of the 1-acetamido-2-chloro compound **35** along with the acetamide **34** after treatment of the amine mother liquors with acetyl chloride and chromatographic separation of the resultant mixture. Aziridines are often formed during the reduction of oximes with lithium aluminium hydride,[11] and the structure of the chloro compound **35** is consistent, in this present instance, with the *trans*-diaxial opening of the aziridino ring during acetylation.

† A similar cyclisation procedure has previously been reported.[6]

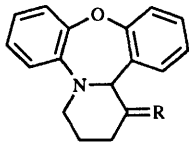


38
syn conformation

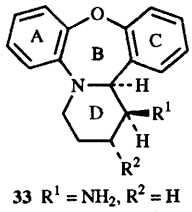


36
anti conformation

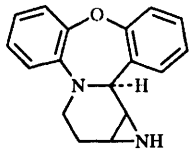
Fig. 1 Energy minimised structures of the *syn* conformation of the *cis*-dimethylamine **38** and the *anti* conformation of the *cis*-ethylamine **36** optimised under MOPAC version 6 AM1



31 R = O
32 R = NOH



33 $R^1 = NH_2$, R^2 = H
34 R^1 = NHAc, R^2 = H
35 R^1 = NHAc, R^2 = Cl
36 R^1 = NHEt, R^2 = H
37 R^1 = OTs, R^2 = H
38 $R^1 = NMe_2$, R^2 = H



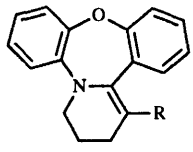
39

Acetylation of the amine **33** gave the acetamide **34** which was reduced, with lithium aluminium hydride, to the ethyl amine **36**. This has the same conformation as the primary amine, the ^1H NMR spectrum indicating that the ethylamino substituent has predominantly an axial orientation since both 1-H and 14b-H appear as narrow multiplets. The NMR spectrum of the dimethyl amine **38**, however, prepared from **33** by reaction with formic acid and formaldehyde, shows the 14b-H signal as a doublet at δ 5.44 (J 5 Hz) and the 1-H singlet as a ddd at δ 2.54 (J 5, 5 and 10). This indicates that the compound has a conformation different from that of the primary and ethyl amines.

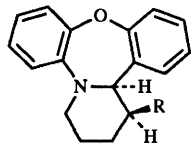
The 1.35 ppm downfield position of the 14b-H signal in the dimethylamine **38** with respect to the chemical shift of the 14b-H of the ethylamine **36** is significant and cannot be attributed to the difference in the chemical-shift effects of these two groups. It has been well established [12] for piperidines that the α protons in the antiperiplanar (*trans* diaxial) position to the nitrogen lone pair are deshielded with respect to the corresponding α protons in the gauche position by *ca.* 1 ppm. This deshielding effect has also been observed [13] in fused ring systems where a nitrogen atom forms part of the bridge and has been attributed [12,14] to the deshielding effect of the nitrogen lone pair on the axial hydrogen (n-σ^* interaction).

Both solution-phase conformational analysis and X-ray analysis of mianserin **1** indicate [14] that this compound has a ring B/D *trans* fused (*anti*) conformation, with the NMR chemical shift of the 14b-H appearing at δ 4.08 and 14b-H to 1-H couplings of 10 and 2.3 Hz. The similar chemical shift and coupling values for the 14b-H of the primary and ethylamines **33** and **36** would, therefore, suggest that these compounds have similar conformations to that found for mianserin. We propose therefore that the amines **33** and **36** have predominantly an *anti* ring B/D conformation and that the downfield position of the 14b-H of the dimethylamine **38** reflects a change in conformation in this molecule to one which has predominantly a *syn* ring B/D ring junction (Fig. 1 represents the energy minimised structures of the *anti* and *syn* conformational forms of the ethyl and dimethylamines **36** and **38**, respectively).

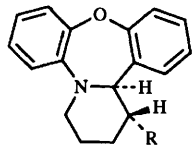
The synthesis of the epimeric *trans* amine **12** using the ketone **31** as an intermediate seemed unattractive since reduction of the oxime **32** gave only the *cis* amine **33** and attempted S_N2 replacement of the tosyl derivative **37**, with sodium azide gave no isolable product. This reaction was not fully investigated but the low yields obtained in the preparation of the alcohol **23** made this potential route unattractive and another approach was, therefore, investigated.



40 R = Ac
41 R = CO_2Et
42 R = $COCCl_3$



43 R = Ac
44 R = CO_2Et
45 R = CO_2H



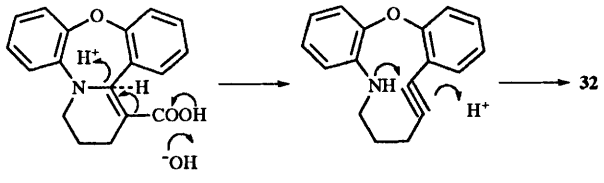
46 R = Ac
47 R = NHAc
48 R = CO_2Et
49 R = CO_2H
50 R = NHEt
51 R = NMe_2

Reaction of the enamine **30** with acetyl chloride gave the acetyl compound **40** which on hydrogenation over Pd–C gave the *cis*-acetyl derivative **43**. Epimerisation of this compound

occurred readily since on elution through alumina the *trans* isomer **46** was isolated quantitatively. The ^{1}H NMR spectrum of the *cis*-isomer **43** shows the 14b-H as a doublet at δ 5.4 (J 5.0 Hz) and the 1-H signal, which is masked in the normal spectrum (60 MHz), appears as a ddd (J 5, 5 and 8 Hz) on addition of Eu(fod)$_3$ to the solution. The spectrum of the *trans*-isomer **46** shows the 14b-H as a doublet at δ 4.3 (J 10.5 Hz) and after addition of Eu(fod)$_3$ the 1-H signal appears as a ddd (J 10.5, 10.5 and 4.5 Hz). Thus, similarly to the situation found for the dimethylamine **38** and ethylamine **36** the chemical shift difference (1.1 ppm) between the 14b-H of the *cis* acetyl compound **43** and that of the *trans* isomer **46** can be rationalised as that which occurs for solutions of the two compounds existing either mainly in the *syn* conformation or mainly in the *anti* conformation, respectively. Vicinal couplings between 14-H and 1-H help to confirm this. It would thus appear that on epimerisation on alumina the acetyl compound **43** is converted from one consisting of predominantly a *syn* ring B/D conformation to one having predominantly an *anti* ring B/D conformation.

Attempted Beckmann rearrangement of the oxime or the oxime tosylate derived from the acetyl compound **46** failed to give the desired acetamide **47**.

Since no reaction occurred between the enamine **30** and ethyl chloroformate, the ester **41** was prepared indirectly by the reaction of the enamine **30** with trichloroacetyl chloride and treatment of the resultant trichloroacetyl compound **42** with sodium ethoxide in ethanol. Interestingly, treatment of the trichloroacetyl compound **42** with aqueous alkali gave only the enamine **30** presumably by base induced decomposition of the αβ-unsaturated acid as proposed in Scheme 2.



Scheme 2

Hydrogenation of the unsaturated ester **41** gave the *cis* isomer **44** which was stable on alumina and also thermally stable up to 250 °C. Equilibration did occur, however, when the compound was heated with sodium ethoxide in ethanol and the *trans* isomer **48** was isolated as the major component from the reaction. Hydrolysis of either ester **44** or **48** gave a mixture of the *trans* and *cis* carboxylic acids **49** and **45** which were readily separated by crystallisation. The ^{1}H NMR spectrum indicates that in $CDCl_3$ solution the *cis* carboxylic acid **45** exists predominantly in the *anti* conformation (δ 14b-H, 4.2, J 2 Hz) whilst in $(CD_3)_2SO$ solution it has predominantly the *syn* conformation (δ 14b-H, 5.16, J 4.7 Hz). We have attributed this change to the presence of an intramolecular bond between the carboxy group and the nitrogen-lone pair in $CDCl_3$ solution which stabilises the *anti* conformation which is absent in DMSO solution allowing the molecule to revert to one having predominantly the *syn* conformation.

Both acids **45** and **49** were converted *via* their acid chlorides into the azides which on treatment under Curtius conditions gave stereospecifically from each, the amines **12** and **33**; the latter amine was identical with that prepared by reduction of the oxime **32**.

The amine **12** was converted into the ethyl- and dimethyl-amines **50** and **51** as described for the epimeric amine **33**. The conformation of these three amines were identical, the 14b-protons appearing at between δ 3.8–4.2 (*J ca.* 9 Hz) and the 1-protons as six lines (*J ca.* 4.5, 9 and 10 Hz). These compounds therefore can be assigned as having predominantly an *anti* B/D ring fused conformation.

Experimental

Mps were determined with a Kofler hot-stage apparatus and are uncorrected. IR spectra were determined with a Perkin-Elmer 457 spectrometer. NMR spectra were recorded for samples in deuteriochloroform solutions (except where stated) at 60, 100, 200 and 400 MHz with a Perkin-Elmer R12B, a Varian Associates XL-100A-12FT, a Brucker W.P.200 and a Brucker DRX-400 spectrometer, respectively. J Values are given in Hz. Gas liquid chromatograms were obtained using 3% OV-17 or OV-1 Chromasorb W-HP 100–120 mesh on 6 ft columns or by using SE-30 fused silica on 25 m capillary columns. Ether refers to diethyl ether throughout and extracts were washed with water and dried over anhydrous sodium sulfate before evaporation under reduced pressure. Amines were converted into their hydrochloride salts by passage of a stream of hydrogen chloride into an ethereal solution of the amines until precipitation was complete. The salts were collected, washed with ether (refers to diethyl ether), and crystallised from methanol–ether. All chiral compounds are racemic mixtures.

N-[2-(3-Methoxyphenoxy)phenyl]glutarimide 3

A suspension of sodium hydride (60% dispersion; 125 g) was washed with light petroleum and added to dimethylformamide (DMF) under nitrogen. A solution of *m*-methoxyphenol (500 g) in DMF (1 dm^3) was slowly added to the mixture which was then stirred at room temperature for 0.75 h. After this the mixture was heated to 100 °C and a solution of 2-chloronitrobenzene (635 g) in DMF (1 dm^3) was added slowly at this temperature. The reaction mixture was then heated at 140 °C for 8 h, cooled and poured into water. The product was isolated, using ether, as a gum which was crystallised, following treatment with charcoal, from isopropyl alcohol to give 2-(3-methoxyphenoxy)nitrobenzene (760 g) which was not further purified. 5% Pd–C (30 g) was added to a solution of the nitrobenzene (300 g) in acetic acid (3 dm^3) and the cooled mixture was shaken in an atmosphere of hydrogen until the nitro group was completely reduced. The mixture was then filtered through Dicalite and the filtrate poured into water and the product isolated, using ether, to give 2-(3-methoxyphenoxy)aniline (200 g) as an oil which was not purified. A mixture of the above aniline (150 g) and glutaric anhydride (80 g) was stirred with cooling for 30 min and poured into water. The precipitate was filtered off, dried, dissolved in benzene (1 dm^3) and treated with thionyl chloride (76 cm^3) over a period of 30 min; the solution was then stirred at room temperature for a further 30 min and then refluxed for 1 h. Evaporation of the solvent at reduced pressure gave the glutarimide **3** (201 g) as a gum which failed to crystallise.

12-Methoxy-2,3-dihydro-4*H*-pyrido[1,2-*d*]dibenzo[*b*,*f*][1,4]-oxazepin-4-one 5

A mixture of crude *N*-[2-(3-methoxyphenoxy)phenyl]glutarimide **3** (60 g) and 86% polyphosphoric acid (370 g) was heated at 110 °C for 10 min and then poured carefully into saturated aq. potassium carbonate (2.5 dm^3) to give a dark-green solid. A solution of the solid in methylene dichloride (2 dm^3) was washed with water, dried and evaporated to give a volume of *ca.* 500 cm^3. This solution was filtered through a short column of silica (400 g) and eluted with methylene dichloride. The filtrate was evaporated to dryness under reduced pressure and the residue crystallised from ether–methylene dichloride to give the *enamide* **5** (31.5 g), mp 159–163 °C; ν_{max}(KCl)/cm^{-1} 1690 (C=O) and 1640 (C=C); δ_H(60 MHz) 2.6 (4 H, m, CH_2CH_2), 3.7 (3 H, s, OCH_3), 5.5 (1 H, m, C=CH), 6.6 (2 H, m, ArH) and 7.3 (5 H, m, ArH) (Found: C, 73.7; H, 5.1; N, 4.6. $C_{18}H_{15}NO_3$ requires C, 73.7; H, 5.2; N, 4.8%).

Reaction of the enamide 5 with diborane

The enamide **5** (37 g) was suspended in sodium-dried tetrahydrofuran (THF) (350 cm^3) and treated slowly over 1.5 h

with a solution of diborane in THF (0.66 mol dm^{-3}; 900 cm^3). The solution was stirred for a further 0.5 h after which aqueous sodium hydroxide (4 mol dm^{-3}; 35 cm^3) was carefully added to it, followed by a solution of hydrogen peroxide (30%; 35 cm^3). The mixture was stirred at room temperature for 0.5 h after which it was evaporated under reduced pressure to *ca.* 250 cm^3, poured into water and extracted with ether. The product was isolated, as a gum which was dissolved in methylene dichloride and the solution passed through a short column of alumina. Elution with methylene dichloride gave a mixture of products which were re-chromatographed (see below). Elution with ethyl acetate gave a solid which was recrystallised from methanol–methylene dichloride to give trans-1-*hydroxy*-12-*methoxy*-1,2,3,14*b*-*tetrahydro*-4H-*pyrido*[1,2-d]*dibenzo*[b,f][1,4]*oxazepin*-4-*one* **22** (1.7 g), mp 218–219 °C; ν_{max}(KCl)/cm^{-1} 3360 (OH) and 1630 (CO); δ_H(60 MHz) (DMSO) 1.85 and 2.45 (each 2 H, m, $COCH_2CH_2$), 3.72 (3 H, s, OCH_3), 4.4 (1 H, m, C*H*OH), 4.72 (1 H, d, *J* 1.5, 14b-H), 5.47 (1 H, d, OH), 6.7 and 7.25 (2 H and 5 H, m, ArH) (Found: C, 69.5; H, 5.6; N, 4.5. $C_{18}H_{17}NO_4$ requires C, 69.4; H, 5.5; N, 4.5%). The main fraction from the column was taken up in toluene and chromatographed on alumina (600 g). Elution with toluene–ethyl acetate (19:1) gave a fraction which was crystallised from ether to give 13- *methoxydibenzo*[b,j][1,4]*oxazacycloundecine* **16** (1.4 g), mp 101–103 °C; ν_{max}(KCl)/cm^{-1} 3410 sharp (NH); δ_H(60 MHz) 1.8, 2.2 and 3.4 (each 2 H, m, NCH_2 and CH_2CH_2), 3.81 (3 H, s, OCH_3), 4.54 (1 H, m, NH), 5.37 (2 H, m, CH=CH) and 7.1 (7 H, m, ArH) (Found: C, 76.7; H, 6.7; N, 4.7. $C_{18}H_{19}NO_2$ requires C, 76.8; H, 6.8; N, 5.0%). Further elution with this solvent mixture gave mixtures which were combined with the mother liquors from the above crystallisation and treated with acetic anhydride–pyridine as described below. Elution with toluene–ethyl acetate (9:1) gave a fraction which was crystallised from ether to give trans-12-*methoxy*-1,2,3,14*b*-*tetrahydro*-4H-*pyrido*[1,2-d]*dibenzo*[b,f][1,4]*oxazepin*-1-*ol* **7** (16.2 g), mp 103–107 °C; ν_{max}(CH_2Cl_2)/cm^{-1} 3590 (OH); δ_H(100 MHz) 1.65 (1 H, s, OH), 1.75 and 2.2 (3 H and 1 H, m, CH_2Cl_2), 3.08 and 3.6 (each 1 H, m, NCH_2), 3.72 (3 H, s, OCH_3), 3.85 (1 H, d, *J* 8, 14b-H), 4.1 (1 H, ddd, *J* 8, 8 and 4, C*H*OH) and 6.8 (7 H, m, ArH) (Found: C, 72.7; H, 6.4; N, 5.0. $C_{18}H_{19}NO_3$ requires C, 72.7; H, 6.4; N, 4.7%). The above impure fractions were acetylated with acetic anhydride–pyridine and an ethereal solution of the product was extracted twice with dil. hydrochloric acid, washed with water and aq. sodium hydrogen carbonate, dried and evaporated to give a gum. This was crystallised from methanol–methylene dichloride to give 5-*acetyl*-13-*methoxydibenzo*[b,j][1,4]*oxazacycloundecine* **17**, mp 190–193 °C; ν_{max}(KCl)/cm^{-1} 1650 (NAc) (Found: C, 74.1; H, 6.5; N, 4.3. $C_{20}H_{21}NO_3$ requires C, 74.3; H, 6.55; N, 4.3%). The above aq. acidic layer was basified and the product was isolated, using ether, as a gum which was crystallised from methanol to give 12-*methoxy*-1,2,3,14*b*-*tetrahydro*-4H-*pyrido* [1,2-d]*dibenzo*-[b,f][1,4]*oxazepine* **19**, mp 70–72 °C; δ_H(60 MHz) 1.75 [6 H, m, $(CH_2)_3$], 3.0 and 3.4 (each 1 H, m, NCH_2), 3.78 (3 H, s, OMe), 3.9 (1 H, t, 14b-H) and 6.8 (7 H, m, ArH) (Found: C, 76.8; H, 7.0; N, 4.85. $C_{18}H_{19}NO_2$ requires C, 76.8; H, 6.8; N, 5.0%). Acetylation of the alcohol **7** with acetic anhydride in pyridine gave trans-1-*acetoxy*-12-*methoxy*-1,2,3,14*b*-*tetrahydro*-4H-*pyrido*[1,2-d]*dibenzo*[b,f][1,4]*oxazepine* **9** mp 115–116 °C (ether–hexane); ν_{max}(KCl)/cm^{-1} 1730 (OAc); δ_H(60 MHz) 1.87 (3 H, s, $COCH_3$), 1.75 and 2.2 (3 H and 1 H, m, CH_2CH_2), 3.1 and 3.7 (each 1 H, m, NCH_2), 3.7 (3 H, s, OMe), 4.1 (1 H, d, *J* 9.3, 14b-H), 5.3 (1 H, m, CHOAc) and 6.8 (7 H, m, ArH) (Found: C, 70.6; H, 6.2; N, 4.3. $C_{20}H_{21}NO_4$ requires C, 70.8; H, 6.2; N, 4.1%).

trans-12-Methoxy-1-tosyloxy-1,2,3,14b-tetrahydro-4*H*-pyrido[1,2-*d*]dibenzo[*b*,*f*][1,4]oxazepine 8

A solution of toluene-*p*-sulfonyl chloride (6 g) and the oxazepinol **7** (2 g) in dry pyridine (30 cm^3) was kept at room temperature for 16 h after which it was poured into water (300 cm^3). The tosyl derivative **8** was isolated, using methylene dichloride (any remaining pyridine was removed by azeotropic distillation with toluene) as a crude gum (3.5 g) which was not further purified.

Rearrangement of the pyridodibenzooxazepine 8 with sodium azide–*N*-methylpyrrolidone

A solution of the tosyl derivative **8** (3.5 g) in *N*-methylpyrrolidone (40 cm^3) containing sodium azide (3.6 g) in water (4 cm^3) was heated under reflux for 1 h. The cooled solution was poured into water (300 cm^3) and the product was isolated, using ether, as a gum which was redissolved in ether and filtered through a column of alumina (40 g). The eluent was evaporated to dryness and the residue crystallised from ether to give 14-*azido*-11-*methoxy*-1,2,14,14*a*-*tetrahydro*-3H-*pyrrolo*[1,2-d]*dibenzo*[b,g]-[1,4]*oxazocine* **24** (3 g), mp 115–116 °C; ν_{max}(CH_2Cl_2)/cm^{-1} 2100 (N_3); δ_H(60 MHz) 2.0 (4 H, m, CH_2CH_2), 3.1 (2 H, m, NCH_2), 4.3 (3 H, s, OMe), 4.0 (1 H, d, *J* 11, CHN_3), 4.6 (1 H, m, NCH) and 7.0 (7 H, m, ArH) (Found: C, 67.2; H, 5.7; N, 17.3. $C_{18}H_{18}N_4O_2$ requires C, 67.1; H, 5.6; N, 17.4%). This azide (2.5 g) was stirred with a suspension of $LiAlH_4$ (700 mg) in dry ether (150 cm^3) for 1 h. Water (2 cm^3) was then added carefully to the mixture, followed by aqueous sodium hydroxide (4 mol dm^{-3}; 2 cm^3) and finally water (6 cm^3). The mixture was filtered through Dicalite and the filtrate was evaporated to dryness. The residue was crystallised from ether to give 11-*methoxy*-1,2,14,14*a*-*tetrahydro*-3H-*pyrrolo*[1,2-d]*dibenzo*[b,g][1,4]-*oxazocin*-14-*amine* **25** (2 g), mp 124–126 °C; ν_{max}(CH_2Cl_2)/cm^{-1} 3680 and 3600; δ_H(200 MHz) 1.6 (2 H, s, NH_2), 2.0 (4 H, m, CH_2CH_2), 3.1 (2 H, m, NCH_2), 3.5 (1 H, d, *J* 9, $CHNH_2$), 3.7 (3 H, s, OMe), 4.15 (1 H, m, NCH), 6.5 (3 H, m, ArH), 6.7 (1 H, dt, *J* 7.5 and 1.2, 7-H), 6.95 (1 H, dt, *J* 7.3 and 1.4, 6-H), 7.05 (1 H, d, *J* 8.1, 13-H) and 7.3 (1 H, dd, *J* 7.5 and 1.4, 5-H) (Found: C, 72.7; H, 6.8; N, 9.2. $C_{18}H_{20}N_2O_2$ requires C, 73.0; H, 6.8; N, 9.5%).

A sample of this amine was acetylated with acetyl chloride–CH_2Cl_2–pyridine to give the acetamide **27**; δ_H(60 MHz) 1.9 (3 H, s, CH_3CO), 1.9 (4 H, m, CH_2CH_2), 3.1 (2 H, m, NCH_2), 3.6 (3 H, s, OCH_3), 4.2 (1 H, m, N-CH), 5.0 (1 H, t, *J* 9, collapses to d, *J* 9 on exchange with NaOD, 14-H), 5.9 (1 H, br d, *J* 9, NH) and 7.0 (7 H, m, ArH).

Rearrangement of *trans*-12-methoxy-1-tosyloxy-1,2,3,14b-tetrahydro-4*H*-pyrido[1,2-*d*]dibenzo[*b*,*f*][1,4]oxazepine 8 with ammonium formate.

A solution of the pyridodibenzooxazepine **8** (35 g) in DMSO (150 cm^3) was heated under reflux with ammonium formate (25 g) for 1 h. The cooled solution was poured into saturated aq. sodium carbonate (750 cm^3) and stirred for 1 h. The product was isolated, using methylene dichloride, as a gum (21 g), GLC (OV17 at 245 °C,) one major product (75%). This material could not be satisfactorily purified by column chromatography but a pure sample was obtained by preparative TLC [heptane–acetone, (4:1), alumina] to give 11-*methoxy*-1,2,14,14*a*-*tetrahydro*-3H-*pyrrolo*[1,2-d]*dibenzo*[b,g][1,4]*oxazocin*-14-*ol* **26**, mp 184–186 °C from ethanol; ν_{max}(CH_2Cl_2)/cm^{-1} 3600 (OH); δ_H(60 MHz) 2.0 (5 H, m, CH_2CH_2 and OH), 3.1 (2 H, m, NCH_2), 3.7 (3 H, s, OMe), 4.3 (2 H, m, NCH and C*H*OH) and 7.0 (7 H, m, ArH) (Found: C, 72.8; H, 6.6; N, 4.9. $C_{18}H_{19}NO_3$ requires C, 72.7; H, 6.4; N, 4.7%).

A sample of the crude alcohol **26** (500 mg) was acetylated with acetic anhydride (1 cm^3) and pyridine (2 cm^3) and the crude product was chromatographed on alumina to give 14-*acetoxy*-11-*methoxy*-1,2,14,14*b*-*tetrahydro*-3H-*pyrrolo*[1,2-d]-*dibenzo*[b,g][1,4]*oxazocine* **28** (350 mg), mp 142–146 °C (from ether); ν_{max}(CH_2Cl_2)/cm^{-1} 1735 and 1240 (OAc); δ_H(60 MHz) 1.9 (4 H, m, CH_2CH_2), 2.0 (3 H, s, CH_3CO), 3.1 (2 H, m, NCH_2), 3.7 (3 H, s, OMe), 4.7 (1 H, m, NCH), 5.7 (1 H, d, *J* 9, CHOAc) and 7.0 (7 H, m, ArH) (Found: C, 70.9; H, 6.3; N, 4.3. $C_{20}H_{21}NO_4$ requires C, 70.8; H, 6.2; N, 4.1%).

2,3-Dihydro-4*H*-pyrido[1,2-*d*]dibenzo[*b*,*f*][1,4]oxazepine 32
A solution of 5-chlorovaleryl chloride (50 g) in methylene dichloride (50 cm^3) was added over a period of 15 min to a stirred solution of the 2-phenoxyaniline **14** (70 g) in methylene dichloride (300 cm^3) and pyridine (23.8 cm^3) at 20–30 °C under a nitrogen atmosphere. Stirring was continued for 1 h, after which the mixture was treated carefully with water (60 cm^3) and stirred for a further 1 h. The organic layer was separated, washed in turn with dil. aq. hydrochloric acid, water, aq. sodium hydrogen carbonate and water and then dried and evaporated under reduced pressure to give crude 5-chloro-*N*-(2-phenoxyphenyl)-valeramide **15** (100 g) as a dark-brown gum; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3440 (N–H) and 1680 (NCO), which was not purified.

The chlorovaleramide **15** (100 g) in PPA (600 g; 86%) was stirred at 140–150 °C for 30 min after which the warm mixture was poured into saturated aq. sodium carbonate (3 dm^3). The product was isolated using ether to give crude 11-(4-chlorobutyl)dibenzo[*b*,*f*][1,4]oxazepine **29** as a gum (76 g) which was not purified.

A solution of the dibenzooxazepine **29** (76 g) in dry ethanol (120 cm^3) was added to a solution of sodium ethoxide, freshly prepared from sodium (10.2 g) in dry ethanol (300 cm^3) at room temperature, after which the mixture was stirred at reflux, under nitrogen, for 1 h. The cooled solution was poured into water (2.5 dm^3) and left for 1 h, after which the resultant yellow–brown crystalline product was collected, washed several times with water and dried *in vacuo* at room temperature. The product was recrystallised from ether–hexane to give 2,3-dihydro-4*H*-pyrido[1,2-*d*]dibenzo[*b*,*f*][1,4]oxazepine **30** (40 g), mp 110–115 °C; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1630 (C=C); δ_H(60 MHz) 2.15 (4 H, m, CH_2CH_2CH=), 3.68 (2 H, m, NCH_2), 4.78 (1 H, t, *J* 4, CH=C) and 7.15 (8 H, m, ArH) (Found: C, 81.7; H, 6.0; N, 5.7. $C_{17}H_{15}NO$ requires C, 81.9; H, 6.1; N, 5.6%).

***trans*-1,2,3,14b-Tetrahydro-4*H*-pyrido[1,2-*d*]dibenzo[*b*,*f*]-[1,4]oxazepin-1-ol 10**. A solution of diborane in THF (0.7 mol dm^{-3}; 21.9 cm^3) was added evenly over a period of 1 h to a stirred solution of 2,3-dihydro-4*H*-pyrido[1,2-*d*]dibenzo[*b*,*f*]-[1,4]oxazepine **30** (4 g) in THF (20 cm^3) at room temperature under nitrogen. The solution was stirred for a further 15 min after which it was treated with aq. sodium hydroxide (4 mol dm^{-3}; 2 cm^3), added carefully to avoid excess frothing, followed by aq. hydrogen peroxide (30%; 2 cm^3). The mixture was stirred for 30 min after which the THF was distilled off under reduced pressure and replaced with ether. The ethereal layer was dried, filtered through a short column of alumina (10 g) and evaporated under reduced pressure to give a yellow oil (4 g) which was dissolved in toluene and chromatographed on alumina. Elution with 15% ethyl acetate–toluene gave 1,2,3,14b-tetrahydro-4*H*-pyrido[1,2-*d*]dibenzo[*b*,*f*][1,4]oxazepine **20** (1.7 g) as a gum; δ_H(60 MHz) 1.80 and 3.68 (6 H, m, $CH_2CH_2CH_2CH$), 2.7–4.1 (3 H, m, NCH_2 and 14b-H) and 7.04 (8 H, m, ArH). Elution with ethyl acetate gave a product which was crystallised from ether–methylene dichloride to give the *alcohol* **10** (2.3 g), mp 117–118 °C; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3590 (OH); δ_H(60 MHz) (1 H, s, 1-OH), 1.90 (4 H, m, CH_2CH_2), 3.09 and 3.68 (each 1 H, m, NCH_2), 3.92 (2 H, m, 1 and 14b-H) and 6.98 (8 H, m, Ar*H*) (Found: C, 76.4; H, 6.5; N, 5.3. $C_{17}H_{17}NO_2$ requires C, 76.4; H, 6.4; N, 5.2%).

***cis*-1,2,3,14b-Tetrahydro-4*H*-pyrido[1,2-*d*]dibenzo[*b*,*f*][1,4]-oxazepin-1-amine maleate 33**
A solution of the alcohol **10** (35 g) in dimethyl sulfoxide (350 cm^3) and acetic anhydride (175 cm^3) was set aside at room temperature for 3 days after which it was poured into water (3 dm^3) and basified with aq. potassium hydroxide (10 mol dm^{-3}). The mixture was stirred for 1 h to hydrolyse the excess of acetic anhydride after which the product was isolated, using ether, as a mixture consisting [TLC (silica, toluene–ethyl acetate 9:1, two spots); GLC (OV17, 245 °C R_t, 0.52 and 1.24, rel. cholestane)] of the ketone **31** and the methylsulfanylmethyl ether **11**. This was dissolved in ethanol (350 cm^3) containing hydroxylamine hydrochloride (22 g) and sodium acetate (35 g) and the solution was heated under reflux for 1.5 h. It was then cooled and poured into water (2 dm^3), and the crude oxime **32** was isolated, using ether, as a gum which was dissolved in dry THF (50 cm^3). The solution was added carefully to a stirred suspension of $LiAlH_4$ (7 g) in dry THF (50 cm^3) and the reaction mixture was heated under reflux for 2 h. It was then cooled to 10–20 °C, carefully diluted with water (7 cm^3) followed by aq. potassium hydroxide (4 mol dm^{-3}; 7 cm^3) and water (28 cm^3). After this the mixture was stirred for 30 min and filtered. The filtrate was evaporated under reduced pressure, and the product was redissolved in ether (200 cm^3) and the solution washed with aq. hydrochloric acid (2 mol dm^{-3}). The aq. washings were processed as described below.

The ether layer containing neutral material was evaporated and the residue was crystallised from ether–methanol to give trans-1-*methylsulfanylmethoxy*-1,2,3,14*b*-*tetrahydro*-4H-*pyrido*-[1,2-d]*dibenzo*[b,f][1,4]*oxazepine* **11** (9.9 g), mp 101–103 °C; δ_H(60 MHz) 1.74 (3 H, s, SCH_3), 1.77 and 2.03 (3 H and 1 H, m, CH_2CH_2), 3.08 (1 H, m, $W_{\frac{1}{2}}$ 16, 4-H), 3.52–4.42 (5 H, m, 4-H, 1 and 14b-H, and OCH_2) and 6.95 (8 H, m, ArH) (Found: C, 69.9; H, 6.6; N, 4.1; S, 9.4. $C_{19}H_{21}NO_2S$ requires C, 69.7; H, 6.5; N, 4.3; S, 9.8%).

The above acid layer was basified with aq. potassium hydroxide (10 mol dm^{-3}), and the product was isolated, using ether, as a gum (13.5 g). The gum was dissolved in ethanol (10 cm^3) and a solution of maleic acid (5.9 g) in ethanol was added to it; the mixture was then reduced in volume and allowed to recrystallise to give the *amine maleate* **33** (6.5 g), mp 181–184 °C; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ (free base), 3660m, 3580w, 3370m and 3300w (free and bonded NH_2); δ_H(400 MHz) (free base) 1.68 (1 H, m, 3-H), 1.85 and 1.95 (each 1 H, m, 2-H's), 2.05 (1 H, m, 3-H), 2.1 (1 H, br s, NH_2), 2.98 (1 H, s, 1-H), 3.04 (1 H, ddd, *J* 3, 3 and 11.6, 4-H), 3.48 (1 H, br d, *J* 11.6, 4-H), 4.02 (1 H, d, *J* 1.7, 14b-H) and 6.8–7.3 (8 H, m, ArH) (Found: C, 66.2; H, 5.9; N, 7.2. $C_{21}H_{22}N_2O_5$ requires C, 66.0; H, 5.8; N, 7.3%).

The mother liquors (8 g) were basified and the resultant mixture was treated with acetyl chloride (3.9 g) in methylene dichloride (50 cm^3) and pyridine (2.6 cm^3) at 20–30 °C for 30 min. Water (50 cm^3) was added to the mixture which was then stirred at room temperature for 30 min. After this the organic layer was separated and evaporated to give a residue (8.4 g) which was dissolved in toluene and chromatographed on alumina (180 g). Elution with toluene–ethyl acetate (19:1) gave front running material (3.7 g) consisting of several products which were not characterised. Continued elution gave (1R*, 2R*,14bS*)-1-*acetamido*-trans-2-*chloro*-1,2,3,14*b*-*tetrahydro*-4H-*pyrido*[1,2-d]*dibenzo*[b,f][1,4]*oxazepine* **35** (580 mg) which was crystallised from ether–methylene dichloride, mp 167–170 °C; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3405 (NH) and 1685 (C=O); δ_H(60 MHz) 1.84 (3 H, s, CH_3CO), 2.00–2.70 and 3.48 (each 2 H, m, CH_2CH_2), 4.10 (1 H, m, $W_{\frac{1}{2}}$ 8, C*H*NH), 4.40 (1 H, m, $W_{\frac{1}{2}}$ 6, CHCl), 4.75 (1 H, d, *J* 2, 14b-H) and 7.02 (9 H, m, ArH and NH) (Found: C, 66.6; H, 5.8; Cl, 10.3; N, 8.1. $C_{19}H_{19}ClN_2O_2$ requires C, 66.6; H, 5.6; Cl, 10.3; N, 8.2%).

Further elution with toluene–ethyl acetate (19:1) gave cis-1-*acetamido*-1,2,3,14*b*-*tetrahydro*-4H-*pyrido*[1,2-d]*dibenzo*[b,f]-[1,4]*oxazepine* **34** (2.3 g), mp 155–163 °C; $\nu_{max}(CCl_4)/cm^{-1}$ 3420 (OH) and 1680 (C=O); δ_H(60 MHz) 1.80 (3 H, s, CH_3CO), 1.88 (4 H, m, CH_2CH_2), 3.0 and 3.46 (each 1 H, m, NCH_2), 4.06 (2 H, m, C*H*NH and 14b-H) and 6.95 (9 H, m, ArH and NH) (Found: C, 73.7; H, 6.4; N, 9.1. $C_{19}H_{20}N_2O_2$ requires C, 74.0; H, 6.5; N, 9.1%).

***cis*-*N*-Ethyl-1,2,3,14b-tetrahydro-4*H*-pyrido[1,2-*d*]dibenzo-[*b*,*f*][1,4]oxazepin-1-amine 36**
A solution of diborane in THF (0.9 mol dm^{-3}; 8 cm^3) was added to a stirred suspension of the acetamide **34** (1.3 g) in THF (5

cm^3), under nitrogen, and stirring was continued for 30 min at room temperature. The solution was then heated to 60 °C for 1 h, after which it was cooled to 0–5 °C, carefully treated with hydrochloric acid (2 mol dm^{-3}; 5 cm^3) and stirred vigorously at 60 °C for 30 min. After the THF had been removed from the mixture under reduced pressure, the remaining aq. solution was poured into aq. sodium carbonate and the resulting precipitate was isolated using methylene dichloride, to provide the *ethylamine* **36** as an oil. This was treated as a solution in methanol with maleic acid to give the *maleate salt*, mp 167–173 °C (decomp.); δ_H(400 MHz)(free base), 0.87 (3 H, t, *J* 7, CH_2CH_3), 1.65 (1 H, m, 2-H) 2.03 (4 H, m, 2-H, 3-H's and $CHCH_3$), 2.3 (1 H, br s, NH), 2.38 (1 H, m, dq, *J* 7.1 and 11.2, $CHCH_3$), 2.8 (1 H, narrow m, 1-H), 3.03 (1 H, ddd, *J* 2.7, 2.7 and 3.6, 4-H), 3.43 (1 H, br d, *J* 10.4, 4-H), 4.16 (1 H, narrow m, 14b-H) and 6.8 (4 H, m, ArH) (Found: C, 67.4; H, 6.2; N, 6.9. $C_{23}H_{26}N_2O_5$ requires C, 67.3; H, 6.4; N, 6.8%).

cis-*N,N*-Dimethyl-1,2,3,14b-tetrahydro-4*H*-pyrido[1,2*d*]-dibenzo[*b,f*]oxazepin-1-amine 38

The oxazepinamine **35** (3.4 g) was heated under reflux with formic acid (24 cm^3) and formaldehyde (36%; 18 cm^3) for 2 h after which the mixture was poured into water and basified with potassium hydroxide (10 mol dm^{-3}). The precipitate was filtered off and dissolved in methylene dichloride and the solution was evaporated to give an oil. This was dissolved in ether–hexane (1:1) and the solution filtered through alumina. The eluent was evaporated and the product was crystallised from ether to give the *dimethylamine* **38** (1.5 g), mp 127–130 °C; δ_H(400 MHz) 0.9 (4 H, m, CH_2CH_2), 2.26 (6 H, s, NMe_2), 2.5 (1 H, ddd, *J* 5, 5 and 11.5, 1-H), 2.8 (1 H, ddd, *J* 12,5, 12.5 and 2, 4-H), 3.2 (1 H, m, *J* 12.5, 3.5 and 3.5, 4-H), 5.44 (1 H, d, *J* 5, 14b-H), 7.0 (7 H, m, ArH) and 7.8 (1 H, m, ArH) (Found: C, 77.4; H, 7.8; N, 9.4. $C_{19}H_{22}N_2O$ requires C, 77.5; H, 7.5; N, 9.5%).

1-Acetyl-2,3-dihydro-4*H*-pyrido[1,2-*d*]dibenzo[*b,f*][1,4]oxazepine 40

A solution of the oxazepine **30** (8 g), acetyl chloride (16 cm^3) and triethylamine (1.6 cm^3) in dry THF (80 cm^3) was heated under reflux for 8 h. The solution was cooled and poured into saturated aq. sodium carbonate (140 cm^3) and the product was isolated, using ether, as a black gum. This was redissolved in the minimum amount of ether and the solution filtered through a short column of alumina (80 g) and evaporated to dryness. The residue (6.2 g) was crystallised from ether–methylene dichloride to give the *title compound* **40**. Recrystallisation of this from the same solvent gave a pure sample, mp 141–142 °C; ν_{max}(KCl)/cm^{-1} 1630 (C=O); δ_H(60 MHz) 1.5 (3 H, s, $COCH_3$), 2.1 (2 H, m, 3-CH_2), 2.7 (2 H, m, NCH_2), 3.8 (2 H, m, CH_2) and 7.2 (8 H, m, ArH) (Found: C, 78.4; H, 5.8; N, 4.5. $C_{19}H_{17}NO_2$ requires C, 78.3; H, 5.9; N, 4.8%).

cis-1-Acetyl-1,2,3,14b-tetrahydro-4*H*-pyrido[1,2-*d*]dibenzo-[*b,f*][1,4]oxazepine 43

A solution of compound **40** (2 g) in isopropyl alcohol (60 cm^3) was shaken with 5% palladium-on-charcoal (200 mg) under a hydrogen atmosphere at 250 lb in^{-2} and at 60 °C for 10 h after which the catalyst was filtered off and the filtrate was evaporated to dryness. The residue was filtered through a column of silica (40 g) in toluene–ethyl acetate (9:1) to remove a minor impurity. The filtrate was evaporated to dryness to give the *title compound* **43** (1.7 g) as a gum; ν_{max}(CCl_4)/cm^{-1} 1708 (C=O); δ_H(60 MHz) 1.19 (4 H, m, CH_2CH_2), 2.0 (3 H, s, $COCH_3$), 3.1 (3 H, m, 1-H and NCH_2), 5.4 (1 H, d, *J* 5, 14b-H) and 7.0 (8 H, m, ArH); δ_H[60 MHz; $CDCl_3$ + Eu(fod)$_3$(18 mg)] 4.15 [1 H, m (decouples with 14b-H), ddd, *J* 5, 5.5 and 8, 1-H] and 6.07 (1 H, d, *J* 5.5, 14b-H).

***trans*-1-Acetyl-1,2,3,14b-tetrahydro-4*H*-pyrido[1,2-*d*]dibenzo-[*b,f*][1,4]oxazepine 46**

The oxazepine **43** (1 g) was dissolved in toluene and the solution filtered through a column of alumina (30 g). Elution with toluene–ethyl acetate (4:1) gave a product which was crystallised from ethe to give the *title compound* **46** (780 mg), mp 109–110 °C; ν_{max}(CCl_4)/cm^{-1} 1710 (CO); δ_H(60 MHz) 1.6 (3 H, $COCH_3$), 1.8 (4 H, m, CH_2CH_2), 3.3 (1 H, m, 4 *ax*-H), 3.9 (2 H, m, 1-H and 4 *eq*-H), 4.3 (1 H, d, *J* 11, 14b-H) and 7.0 (8 H, m, ArH); δ[$CDCl_3$ + Eu(fod)$_3$ (32 mgs)], 4.6 (1 H, ddd, *J* 10, 10 and 4.5, 1-H), 5.6 (1 H, d, *J* 10, 14b-H) (Found: C, 78.0; H, 6.8; N, 4.7. $C_{19}H_{19}NO_2$ requires C, 78.0; H, 6.5; N, 4.8%).

1-(Trichloroacetyl)-2,3-dihydro-4*H*-pyrido[1,2-*d*]dibenzo[*b,f*]-[1,4]oxazepine 42

A solution of the oxazepine **30** (23.4 g) and trichloroacetyl chloride (11.7 cm^3) in dry benzene (160 cm^3) was stirred under nitrogen at room temperature for 15 min, during which period a salt was precipitated. Triethylamine (10.3 cm^3) was added carefully over a period of 15 min to the mixture which was then stirred under reflux for 1 h. After this it was cooled and water (100 cm^3) added to the resulting suspension to dissolve the precipitated salt. The remaining residue was filtered off, washed twice with methanol and once with ether and dried *in vacuo* at room temperature to give the title compound **42** (31 g), mp 171–175 °C (decomp); ν_{max}(CCl_4)/cm^{-1} 1650 (C=O); δ_H[60 MHz; $(CD_3)_2SO$] 2.10 and 2.85 (each 2 H, CH_2CH_2), 3.90 (2 H, m, NCH_2) and 7.20 (8 H, m, ArH) (Found: C, 57.8; H, 3.5; Cl, 26.8; N, 3.3. $C_{19}H_{14}Cl_3NO_2$ requires C, 57.8; H, 3.6; Cl, 27.0; N, 3.6%).

Ethyl 2,3-dihydro-4*H*-pyrido[1,2-*d*]dibenzo[*b,f*][1,4]oxazepine-1-carboxylate 41

A solution of sodium ethoxide [sodium (4.4 g) dissolved in dry ethanol (75 cm^3)] was added carefully to a stirred suspension of compound **42** (16 g) in dry ethanol (50 cm^3) under nitrogen and stirring was continued for 20 min at *ca.* 25 °C. The solution was then heated under reflux for 20 min after which it was cooled and poured into ice–water (600 cm^3). The resulting white precipitate was extracted into 10% methylene dichloride in ether. The extract was washed until neutral with water and then dried and evaporated to give a gum which, on crystallisation from ether–hexane, gave the title compound **41** (14 g), mp 101–103 °C; ν_{max}(KCl)/cm^{-1} 1690 (C=O); δ_H(60 MHz) 0.82 (3 H, t, CH_3CH_2), 2.05 and 2.63 (each 2 H, m, CH_2CH_2), 3.78 (2 H, q, CH_2CH_3), 3.78 (2 H, m, CH_2N) and 7.02 (8 H, m, ArH) (Found: C, 74.8; H, 6.0; N, 4.2. $C_{20}H_{19}NO_3$ requires C, 74.8; H, 6.0; N, 4.2%).

Ethyl *cis*-1,2,3,14b-tetrahydro-4*H*-pyrido[1,2-*d*]dibenzo[*b,f*]-[1,4]oxazepine-1-carboxylate 44

A suspension of the ester **41** (9 g) and 5% palladium–charcoal in isopropyl alcohol (80 cm^3) was shaken for 12 h under hydrogen at 70 °C and at 250 p.s.i. Methylene dichloride (40 cm^3) was added to the cooled solution which was then filtered through Dicalite to remove the catalyst. The filtrate was evaporated and the residue was crystallised from methylene dichloride–ethanol to give the title compound **44** (8.5), mp 108–109 °C; ν_{max}(KCl)/cm^{-1} 1730 (CO_2); δ_H(60 MHz) 0.98 (3 H, t, CH_3CH_2), 2.00 (4 H, m, CH_2CH_2), 3.04 (3 H, m, CH_2N and CHCO), 3.96 (2 H, q, CH_2CH_3), 5.17 (1 H, d, *J* 5, 14b-H) and 6.9 (8 H, m, ArH) (Found: C, 74.2; H, 6.5; N, 4.3. $C_{20}H_{21}NO_3$ requires C, 74.3; H, 6.6; N, 4.3%).

Ethyl *trans*-1,2,3,14b-tetrahydro-4*H*-pyrido[1,2-*d*]dibenzo[*b,f*]-[1,4]oxazepine-1-carboxylate 48

The ester **44** (1 g) was added to a solution of sodium (100 mg) in dry ethanol (10 cm^3) and the resulting solution was heated under reflux, under nitrogen, for 30 min. The cooled solution was poured into water (60 cm^3) and the precipitate was isolated, using ether, as a gum. This crystallised from ether–hexane to give the title compound **48** (90 mg), mp 108–111 °C; ν_{max}(KCl)/cm^{-1} 1720 (CO_2); δ_H(60 MHz) 0.84 (3 H, t, CH_3CH_2), 1.80 (4 H, m, CH_2CH_2), 3.50 (3 H, m, NCH_2 and

CHCO), 3.74 (2 H, q, CH_2CH_3), 4.33 (1 H, d, *J* 9, 14b-H) and 6.86 (8 H, m, ArH) (Found: C, 74.5; H, 6.7; N, 4.5. $C_{20}H_{21}NO_3$ requires C, 74.3; H, 6.6; N, 4.3%).

The mother liquors (70 mg) consisted of a 2:1 mixture of starting material **44** and product (NMR evidence).

Hydrolysis of the ester 44

A solution of the ester **44** (82 g) in ethanol (1.6 dm^3) containing aq. sodium hydroxide (4 mol dm^{-3}; 164 cm^3) was refluxed for 90 min and then reduced to a volume of *ca.* 600 cm^3 by distillation under reduced pressure. The cooled solution was filtered to remove a small amount of insoluble material after which it was poured into water (5 dm^3) and acidified with hydrochloric acid (5 mol dm^{-3}) to precipitate the product. The white precipitate was filtered off, washed several times with water then dried to constant weight (73 g) at 60 °C *in vacuo*. The solid was triturated with warm methylene dichloride–ether and the remaining insoluble material (20.4 g) was filtered off, washed with ether and dried to give cis-1,2,3,14b-*tetrahydro*-4H-*pyrido*[1,2-*d*]*dibenzo*[b,f][1,4]*oxazepine*-1-*carboxylic acid* **45**, mp 249–250 °C (decomp.); ν_{max}(Nujol)/cm^{-1} 2000–2800 and 1710 (CO_2H); δ_H(60 MHz; $CDCl_3$) for *anti* conformation 2.1 (4 H, m, CH_2CH_2), 3.1 (1 H, m, CHCO), 3.2 and 3.6 (each 1 H, m, NCH_2), 4.2 (1 H, d, *J* 2, 14b-H) and 7.1 (8 H, m, ArH); δ_H[60 MHz; $(CD_3)_2SO$] for *syn* conformation 1.9 (4 H, m, CH_2CH_2), 3.0 (3 H, m, NCH_2 and CHCO), 3.5 (1 H, br s, CO_2H), 5.16 (1 H, d, *J* 4.7, 14b-H) and 7.1 (8 H, m, ArH) (Found: C, 71.6; H, 6.2; N, 4.5. $C_{18}H_{17}NO_3 \cdot 0.5\ H_2O$ requires C, 71.0; H, 6.3; N, 4.6%). The above filtrate was reduced in volume and allowed to crystallise to give trans-1,2,3,14*b*-*tetrahydro*-4H-*pyrido*[1,2-d]*dibenzo*[b,f][1,4]*oxazepine*-1-*carboxylic acid* **49** (43 g), mp 188–191 °C; ν_{max}(Nujol)/cm^{-1}) 2000–2800 and 1695 (CO_2H); δ_H(60 MHz) 1.6 and 2.0 (4 H, m, CH_2CH_2), 3.3 (2 H, m, 4-H and 1-H), 3.9 (1 H, m, 4-H), 4.4 (1 H, d, *J* 10, 14b-H), 7.1 (8 H, m, ArH) and 11.8 (1 H, br s, CO_2H) (Found: C, 73.2; H, 6.0; N, 4.7. $C_{18}H_{17}NO_3$ requires C, 73.2; H, 5.8; N, 4.7%).

1,2,3,14b-Tetrahydro-4*H*-pyrido[1,2-*d*]dibenzo[*b*,*f*][1,4]oxazepin-1-amine maleate 12

Triethylamine (17.5 cm^3) was added carefully to a stirred suspension of the acid **49** (33 g) in acetone (200 cm^3) and water (7 cm^3) at 0–5 °C. Ethyl chloroformate (11.9 cm^3) was added to the resultant solution and the mixture was stirred at 0–5 °C for 30 min. It was then treated with a solution of sodium azide (11.2 g) in water (45 cm^3) and stirring continued for a further 1 h. After this the mixture was poured into water (1.5 dm^3) and the resulting white precipitate was filtered off, dissolved in chloroform (600 cm^3) and the solution heated under reflux for 4 h. The mixture was then evaporated under reduced pressure to give the intermediate isocyanate as a light pink gum to which was added aq. sodium hydroxide (10 mol dm^{-3}; 45 cm^3) in methoxyethanol (300 cm^3). The mixture was then heated under reflux for 17 h after which it was cooled and poured into water (3 dm^3) to afford a gummy precipitate. This was filtered off and redissolved in methylene dichloride (200 cm^3). The solution was filtered to remove a small amount of insoluble material and the filtrate was washed with water, dried and evaporated under reduced pressure to give the title compound **12** as a gum (20 g). Maleic acid (1.7 g) in ethanol (5 cm^3) was added carefully to a solution of the amine **12** (3.5 g) in ethanol (10 cm^3) after which the mixture was concentrated, diluted with ether and allowed to crystallise. This gave the *maleate salt*, mp 173–177 °C; δ_H(400 MHz) (free base) 1.7 (2 H, s, NH_2), 1.45 (1 H, m, 2-H), 1.6 (1 H, m, 3-H), 1.72 (1 H, m, 3-H), 2.18 (1 H, m, 2-H), 3.15 (1 H, dd, *J* 2.7 and 13, 4-H), 3.45 (1 H, ddd, *J* 9, 9 and 4), 3.77 (1 H, d, *J* 9, 14b-H), 3.86 (1 H, br d, *J* 13.4, 4-H) and 6.7–7.3 (8 H, m, ArH) (Found: C, 66.1; H, 5.7; N, 7.5. $C_{21}H_{22}N_2O_5$ requires C, 66.0; H, 5.8; N, 7.3%). In a similar manner *cis*-1,2,3,14b-tetrahydro-4*H*-pyrido[1,2-*d*]dibenzo[*b*,*f*][1,4]-oxazepine-1-carboxylic acid **53** was converted into the primary amine **33**.

***trans*-1-Acetamido-1,2,3,14b-tetrahydro-4*H*-pyrido[1,2-*d*]-dibenzo[*b*,*f*][1,4]oxazepine 47**

The amine **12** was treated with acetyl chloride in pyridine as described for the amine **33** to give the acetamide **47**, mp 201–205 °C; ν_{max}(KCl)/cm^{-1} 3320 (NH) and 1650 (CO); δ_H[60 MHz; $CDCl_3$] 1.96 (3 H, s, CH_3), 1.9 and 2.02 (4 H, m, CH_2CH_2), 3.16 and 3.31 (each 1 H, m, NCH_2), 4.52 (1 H, d, *J* 5.5, 14b-H), 4.62 (1 H, m, 1-H), 6.06 (1 H, d, *J* 8, NH) and 7.0 (8 H, m, ArH); δ_H[$(CD_3)_2SO$] 1.66 (3 H, s, CH_3), 1.82 and 2.12 (4 H, m, CH_2CH_2), 3.22 and 3.82 (each 1 H, m, NCH_2), 4.12 (1 H, d, *J* 10, 14b-H), 4.38 (1 H, m, $W_{\frac{1}{2}}$ 28, 1-H), 6.8 (1 H, m, ArH), 7.22 (7 H, m, ArH) and 7.82 (1 H, d, *J* 8, NH) (Found: C, 74.0; H, 6.8; N, 9.2. $C_{19}H_{20}N_2O_2$ requires C, 74.0; H, 6.5; N, 9.1%).

***trans*-1-*N*-Ethyl-1,2,3,14b-tetrahydro-4*H*-pyrido[1,2-*d*]dibenzo-[*b*,*f*][1,4]oxazepin-1-amine maleate 50**

The above acetamide **47** was reduced as described for the acetamide **34** to give the ethyl amine **50** as the maleate salt, mp 167–173 °C (decomp.); δ_H(400 MHz) free base) 0.89 (3 H, t, *J* 7.1, CH_3), 1.1 (1 H, br m, NH), 1.47 (1 H, ddd, *J* 4, 10 and 12, 2-H), 1.75 (2 H, m, 3-H's), 2.23 (2 H, m, 2-H and C*H*CH_3), 2.55 (1 H, dq, *J* 11.4 and 7.1, $CHCH_3$), 3.17 (1 H, ddd, *J* 3.1, 11 and 13.6, 4-H), 3.42 (1 H, ddd, *J* 4.8, 9.7 and 9.7, 1-H), 3.8 (1 H, ddd, *J* 3.4, 3.4 and 13.3, 4-H), 4.06 (1 H, d, *J* 9.7, 14b-H) and 6.5–7.3 (8 H, m, ArH) (Found: C, 67.1; H, 6.6; N, 6.7. $C_{23}H_{26}N_2O_5$ requires C, 67.3; H, 6.4; N, 6.8%).

***trans*-*N*,*N*-Dimethyl-1,2,3,14b-tetrahydro-4*H*-pyrido[1,2-*d*]-dibenzo[*b*,*f*][1,4]oxazepin-1-amine maleate 51**

The amine **12** was treated with formic acid and formalin as described for the amine **33** to give the *dimethylamine maleate* **51**, mp 148–150 °C; δ_H(60 MHz) (free base) 1.72 and 2.2 (4 H, m, CH_2CH_2), 2.2 (6 H, s, NMe_2), 3.1 and 3.9 (each 1 H, m, NCH_2), 3.65 (1 H, m, 1-H), 4.26 (1 H, d, *J* 9, 14b-H) and 6.82, 6.94 and 7.2 (8 H, m, ArH) (Found: C, 62.7; H, 6.5; N, 6.4. $C_{23}H_{24}N_2O_5$ requires C, 62.2; H, 6.4; N, 6.3%).

***cis*-12-Methoxy-1,2,3,14b-tetrahydro-4*H*-pyrido[1,2-*d*]dibenzo-[*b*,*f*][1,4]oxazepin-1-ol 23**

The oxazepinol **7** (5 g) was oxidised with acetic anhydride in dimethyl sulfoxide as described for the alcohol **10** after which the crude reaction product was dissolved in methanol (40 cm^3) and treated slowly with sodium boranuide (1 g). The mixture was stirred for 30 min after which it was poured into water to afford the product. This was collected, dissolved in toluene and chromatographed on silica. Elution with toluene–ethyl acetate (19:1) gave some methylsulfanylmethyl ether (1.5 g) which was discarded. Further elution gave the alcohol **23** which was crystallised from ether–cyclohexane to give crystals (1.76 g), mp 105–107 °C; ν_{max}(KCl)/cm^{-1} 3520 (OH); δ_H(60 MHz) 1.85 (4 H, m, CH_2CH_2), 1.8–3.6 (2 H, m, NCH_2), 3.1 (1 H, d, OH), 3.72 (3 H, s, OCH_3), 3.75 (1 H, m, 1-H), 3.98 (1 H, d, *J* 1.5, 14b-H) and 6.9 (7 H, m, ArH). A satisfactory analysis was not obtained for this compound since it decomposed when dried. Acetylation in the normal manner gave cis-1-*acetoxy*-12-*methoxy*-1,2,3,14*b*-*tetrahydro*-4H-*pyrido*[1,2-d]*dibenzo*[b,f][1,4]*oxazepine*, mp 180–185 °C; ν_{max}(Nujol)/cm^{-1} 1730; δ_H(60 MHz) 1.9 (3 H, s, $COCH_3$) 1.95 (4 H, m, CH_2CH_2), 2.9–3.7 (2 H, m, NCH_2), 3.75 (3 H, s, OMe), 4.12 (1 H, d, *J* 2, 14b-H), 5.12 (1 H, m, $W_{\frac{1}{2}}$ 6, 1-H) and 6.9 (7 H, m, ArH) (Found: C, 70.7; H, 6.5; N, 4.1. $C_{20}H_{21}NO_4$ requires C, 70.8; H, 6.2; N, 41%).

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