Bridged-ring Nitrogen Compounds. Part 10.[1] Synthesis of Bridged 3-Benzazepine Derivatives as Conformationally Restricted Dopamine Analogues

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Ethyl 3,4-dimethoxyphenyl(phenyl)acetate **7**, (R = Et), made by an improved procedure, was converted into ethyl 1,2,3,4-tetrahydro-6,7-dimethoxy-4-oxo-1-phenylnaphthalene-1-carboxylate **15** which was used both in a synthesis of 2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1,4-methano-1*H*-3-benzazepine and as starting material for 2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1,4-ethano-1*H*-3-benzazepine **4** *via* ethyl 1,2,3,4-tetrahydro-6,7-dimethoxy-4-methylene-1-phenylnaphthalene-1-carboxylate **16** and ethyl 6,7,8,9-tetrahydro-2,3-dimethoxy-8-oxo-5-phenyl-5*H*-benzocycloheptene-5-carboxylate **33**. The compound **16** was converted into ethyl 1,2,3,4-tetrahydro-4-hydroxymethyl-6,7-dimethoxy-1-phenylnaphthalene-1-carboxylate **18**, (X = OH) which could not be converted into derivatives of 1,5-ethano-3-benzazepine. Ethyl α-(3,4-dimethoxyphenyl)phenyl acetate was converted in three steps into 6,7,8,9-tetrahydro-2,3-dimethoxy-9-phenyl-6,9-methano-5*H*-benzocycloheptene-5,10-dione **10** (R′ = Ph, $R^2 = R^3$ = OMe) which was selectively reduced and aminated giving 6,7,8,9-tetrahydro-2,3-dihydroxy-9-phenyl-6,9-methano-5*H*-benzocyclohepten-10-amine **6** hydrobromide.

As part of a search for dopamine **1** analogues[2] with selective activity, we became interested in 3-benzazepine derivatives[3] **2** which displayed activity at post-synaptic sites. Tetrahydro-3-benzazepines have degrees of freedom which allow the nitrogen atom to occupy positions on an arc in the *y*-axis of the molecule (Figs. 1 and 2). We presume that particular positions of the nitrogen atom may be associated with particular biological responses. In molecular terms, each position may be defined by the distance from the centre of the aromatic ring and angle above and below the *x*-axis (Fig. 2). It was, therefore, desirable to obtain conformationally restricted analogues of 3-benzazepines: the structural restraints therein should cause the minimum perturbation of the molecules as a whole. That is, large and polar additions were to be avoided in case the biological profile was drastically altered. Using molecular models, we surveyed many structures and selected a few **3**–**6** which offered a variety of 3-benzazepine configurations (Fig. 3). These diagrams arbitrarily illustrate the optical isomer which holds the nitrogen atom in the lower quadrant: clearly their enantiomers would have nitrogen atoms in the upper quadrant. In the event that a racemate showed some biological activity, optical resolution would be imperative.

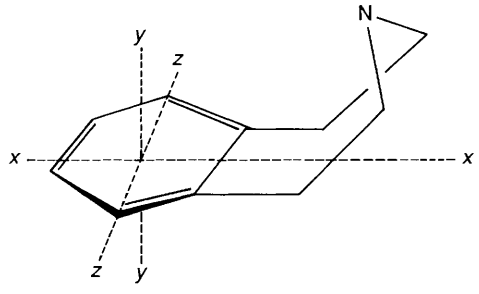


Fig. 1

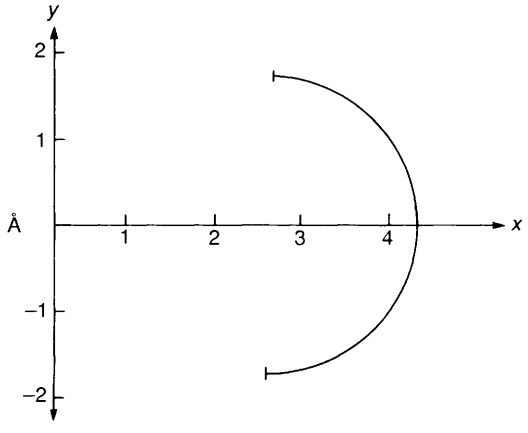


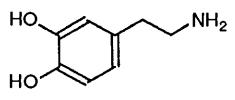
Fig. 2

Discussion

The parent ring systems of our four principal target molecules **3**–**6** are all known. However, the constraints imposed by the substituents in these targets forced us to develop novel syntheses for all but one, **3**, of them. For most of our work the starting material was the ester **7** (R = Et). Although the latter had been previously reported,[4] we were unable to repeat the work involving reaction of veratrole with mandelonitrile but we relied on a reaction of veratrole with mandelic acid (*cf.* ref. 5) in the presence of sulphuric acid. The crude acid **7** (R = H) was esterified *in situ* to yield the desired ester **7** (R = Et) (24%) along with isomer **8** (R = H) (7%). Although deficient in terms of yield and purity, this process afforded large quantities cheaply and of adequate purity for our purposes.

Only target molecule **3**, a 1,4-methano-3-benzazepine, could be made straightforwardly.[6] Our synthesis is shown in Scheme 1 (see Experimental section). It proceeded without serious problems except for the coupling of the carboxylic acid **26** with benzylamine (low yield) and the Wolff–Kishner reduction of the keto lactam **30**. The latter problem was overcome by using the borane–pyridine complex in trifluoroacetic acid.[7]

Target molecule **4** is a 1,4-ethano-3-benzazepine; accordingly we proposed to use modifications of the only known synthesis[8] for such ring systems. However, this proved impossible for the following reasons. Cyclisation of acids **9** gives diones **10**[8,9] and attack on the latter **10** (R^1 = Me; R^2 = OMe, R^3 = H) with nucleophiles (OH^- and $PhCH_2NH^-$) gave the desired product **11** (X = OH + $PhCH_2NH$; R^1 = Me, R^2 = OMe,



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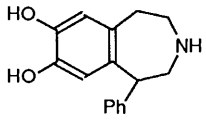

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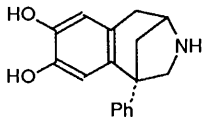

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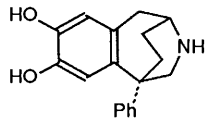

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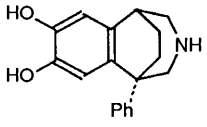

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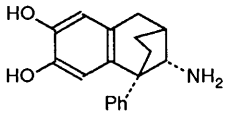

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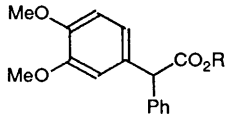

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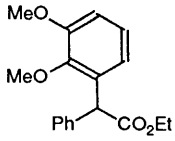

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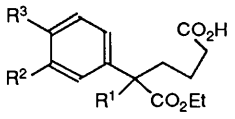

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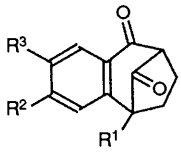

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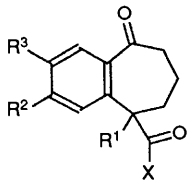

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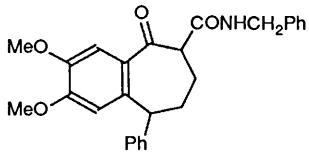
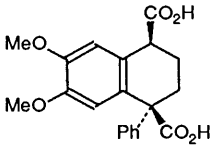


12 a; X = Br
b; X = H



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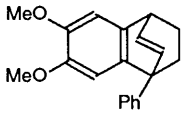

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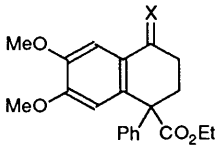
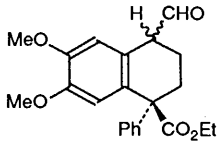


15; X = O
16; X = CH_2



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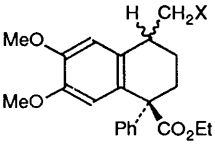

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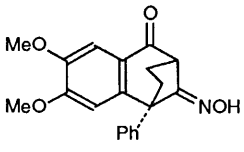

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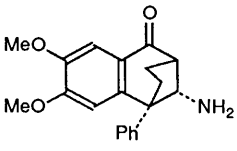

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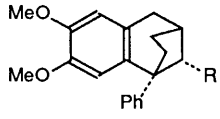
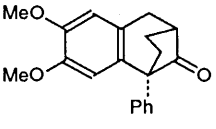


21; R = NH_2
22; R = OH



23

R^3 = H). However, with the dione **10** (R′ = Ph, R^2 = R^3 = OMe), ring opening by sodium benzylamide took a different course, probably influenced by the stability of the intermediate diarylmethyl carbanion: the product was the amide **12**. The structure of the latter was suggested by the fact that bromination gave two epimeric bromo amides, neither of which cyclised with base: it was confirmed by the appearance of two double doublets at δ_H 3.8 and 4.2 in the NMR spectrum of **12**. This data is inconsistent with the structure **11** (R^1 = Ph, R^2 = R^3 = OMe, X = $NHCH_2Ph$) required for further progress. On the other hand, treatment of the dione **10** (R^1 = Ph, R^2 = R^3 = OMe) with aqueous sodium hydroxide gave the required keto acid **11** (R^1 = Ph, R^2 = R^3 = OMe, X = OH) the structure of which was confirmed by attempted esterification which yielded back the dione **10** (R^1 = Ph, R^2 = R^3 = OMe). The failure of repeated attempts to couple the keto acid **11** (R^1 = Ph, R^2 = R^3 = OMe, X = OH) with benzylamine, perhaps attributable to steric hindrance, led to a search for an alternative synthesis of 1,4-ethano-3-benzazepine derivatives.

It has been shown that α-tetralones can be converted into benzocyclohepten-6-ones by a 'Wittig–Prevost' procedure.[1,10] Since the tetralone **15** (Scheme 1) had become available, it therefore seemed fruitful to subject it to the procedure. This indeed proved to be the case and a new synthesis of the required 1,4-ethano-3-benzazepine derivatives was developed (Scheme 2). During this work it was discovered beneficial to use the methyltriphenylphosphonium iodide–butyllithium combination for the Wittig reaction and to carry out the $AgNO_3$–I_2 ring-expansion step in aqueous methanol. Reduction of the

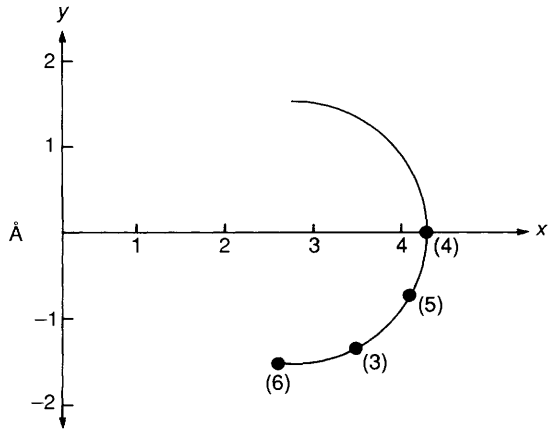
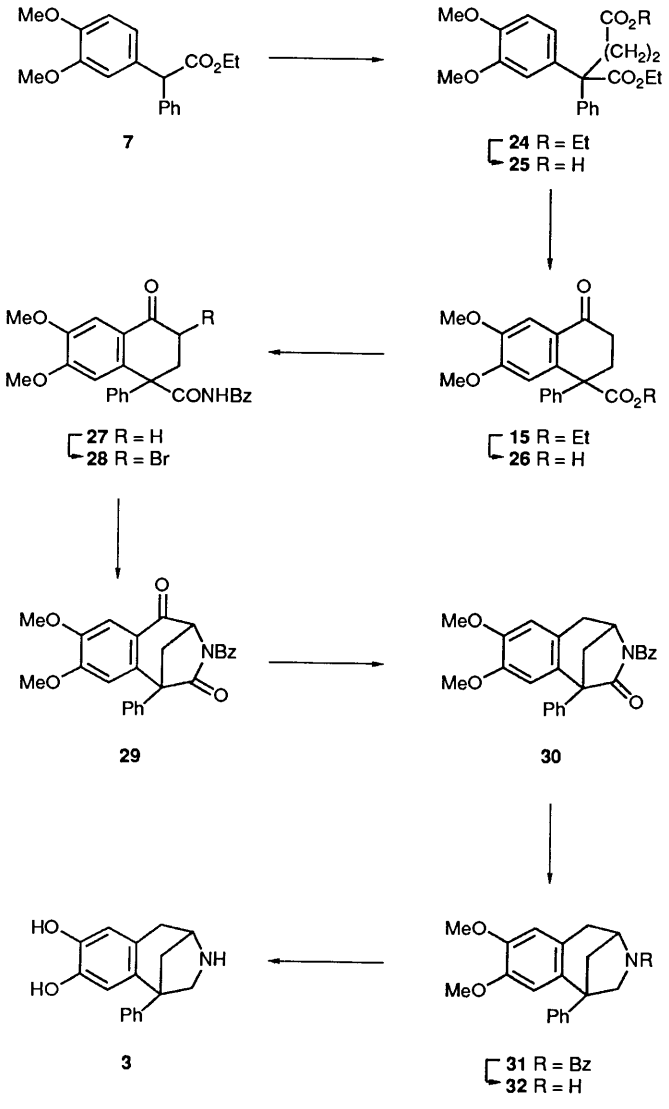
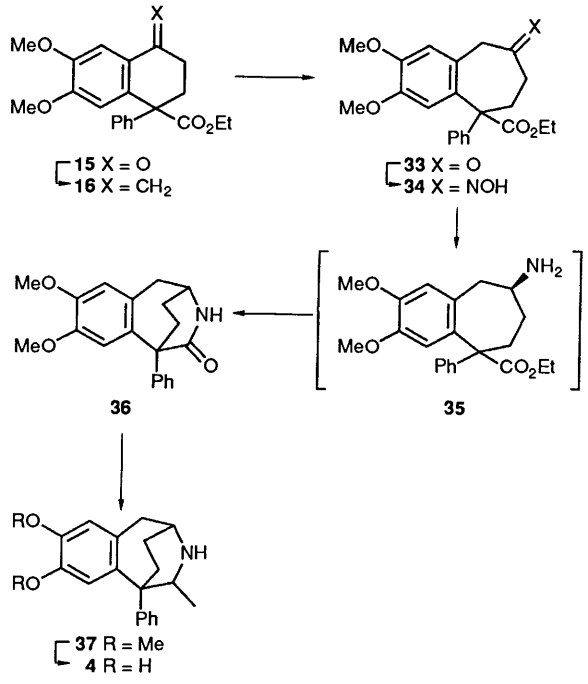


Fig. 3



Scheme 1



Scheme 2

oxime **34** led directly to the cyclised lactam **36** using Raney alloy: otherwise this synthesis was uneventful.

1,5-Ethano-3-benzazepine derivatives (*cf.* **5**) have been made by the research groups of Kitahonoki,[11] Doering[12] and Walter[13] by methods unsuitable for our work. Initially our strategy for compound **5** required the *cis*-diacid **13** *via* the bridged alkene **14**; which, in turn, might be expected to arise either from cycloaddition of a substituted benzyne with 1-phenylcyclohexa-1,3-diene[14] or by carrying out a Diels–Alder reaction between a 4-phenyl-2-naphthol and maleic anhydride.[15] There are precedents for both of these approaches in simpler cases. Preliminary work, however, was discouraging and we had to alter the strategy.

Since the tetralone **15** and the *exo*-methylene compound **16** were available, we sought ways to convert them into a suitable bifunctional intermediate (*e.g.* **17**) towards the target **5**. While the tetralone **15** failed to react with sulphur ylides[16] or with specialised Wittig-type reagents,[17] the *exo*-methylene compound **16** was successfully hydroborated to the alcohol **18** (X = OH). However, all efforts to convert compound **18** (X = OH) into **18** (X = NH_2) were unsuccessful whether directly or *via* the aldehyde **17**. Accordingly compound **5** was not made.

Finally, turning to compound **6** which is an ethano amino tetralin, the dione **10** (R^1 = Ph, R^2 = R^3 = OMe) seemed a logical starting material. It was known[8] that oximation of compound **10** (R^1 = Me, R^2 = OMe, R^3H) proceeded preferentially at the strained cyclopentyl carbonyl group; in the present case, the same preference emerged. Thus compound **19** was obtained and reduced stereospecifically ($Pd/H_2/CH_3CO_2$-H/1 atm) to the amino ketone **20**.

That the amino group and phenyl group were mutually *cis*-was evident from the NMR spectrum. The bridgehead proton appeared as a doublet of doublets centred at δ_H 3.14 and the proton α to the amino group was observed as a doublet located at δ_H 3.47. The magnitude of the coupling between these protons is 6 Hz, implying a dihedral angle of 32° which, when examined with models, is consistent with the geometry depicted in **20** but not the epimer with phenyl and amino groups mutually *trans*. The *N*-trifluoroacetate of compound **20**, was reduced by borane–pyridine complex[7] to compound **21** (60% yield). The latter was demethylated to **6** using boron tribromide. To amplify the chemistry of this group of compounds, the dione **10** (R^1 = Ph, R^2 = R^3 = OMe) was reduced with borane–pyridine complex in TFA (trifluoroacetic acid)[7] stereospecifically to the alcohol **22**. Attempts to invert the stereochemistry by treating the *O*-tosylate with azide ion were unsuccessful but reoxidation by the Swern[19] method gave the ketone **23** whose oxime reacted with Raney alloy yielding a mixture (2:1) (60%) of the amine **20** and

its epimer as judged by NMR spectroscopy. These were not separated.

None of the compounds described in this paper showed any agonist activity at peripheral dopamine receptors. Thus, either the benzazepine **2** does not adopt a conformation at the dopamine receptor exemplified by these systems, or the extra molecular constraints used result in an unfavourable steric interaction.

Experimental

M.p.s were obtained on a Gallenkamp melting point apparatus in open capillaries and are uncorrected.

Mass spectra were determined on an AEIMS9 double focussing mass spectrometer, modified with solid-state console, using a GEC-905 computer based data system.

^{1}H NMR spectra were recorded on Perkin-Elmer R32 spectrometer operating at 90 MHz or on a Bruker SM250 spectrometer operating at 250.13 MHz in Fourier transform mode.

All spectra were recorded using deuteriochloroform as solvent with tetramethylsilane as internal reference, unless otherwise stated. *J* Values are given in Hz.

Chromatographic materials. Short-path[20] columns were run using Merck Art. 7747 KIESELGEL 60PF$_{254}$ and the samples were adsorbed on to Merck 7734 silica gel type 60 prior to loading the column.

Flash columns[21] were run using CAMLAB Art. Nr. 81538 MN Kieselgel 60 (0.04–0.063 mm) and samples were applied to the column in solution, or adsorbed on to Merck 7735 silica gel type 60.

Ethyl 3,4-*Dimethoxyphenyl(phenyl)acetate* **7** (R = Et).[4,5]—Sulphuric acid (98%; 36 cm^3) was added dropwise to a stirred solution of mandelic acid (27.5 g, 0.18 mmol) and veratrole (50 g, 0.36 mmol) in glacial acetic acid (21.7 g) at 0 °C. The solution was then warmed to 70 °C for 1.5 h and cooled; ethanol (92 g) was added to it and the mixture heated under reflux overnight. The reaction product was then poured on to ice–water, basified with concentrated aqueous ammonia and extracted with chloroform. The extracts were washed with saturated brine, dried (Na_2SO_4) and evaporated under reduced pressure to give an oil, which when distilled (Kugelrohr 205 °C/0.03 mbar), gave the title compound as an impure, colourless oil (20 g, 30% as estimated by GLC) (Found: C, 71.2; H, 6.7%; M$^+$, 300.1362. Calc. for $C_{18}H_{20}O_4$: C, 71.9; H, 6.7; *M*, 300.1361); ν_{max}(film)/cm^{-1} 1730 (C=O ester), 1260 (C–O aryl ether) and 1170 (C–O ester); δ_H 7.2 (5 H, m, aromatic), 6.8 (3 H, m, aromatic), 4.95 (1 H, s, benzylic), 4.2 (2 H, q, CH_2CH_3), 3.75 (6 H, s, CH_3O) and 1.2 (3 H, t, CH_2CH_3).

This material contained variable (up to 25%; GLC and NMR spectroscopy) amounts of isomeric impurity **8**, NMR spectroscopy distinguished by δ5.35 (s, benzylic). It was conveniently discarded at the next stage since apparently it failed to undergo alkylation.

Diethyl 2-(3,4-*Dimethoxyphenyl*)-2-*phenylpentane*-1,5-*dioate* **24**.—Ethyl 3,4-dimethoxyphenyl(phenyl)acetate **7** (R = Et) (4 g, 13.2 mmol) and sodium ethoxide (0.9 g, 13.2 mmol) were stirred together in dry THF (tetrahydrofuran) (50 cm^3) for 0.5 h. HMPA (hexamethylphosphoramide) (3 cm^3, 17.2 mmol) was then added and, after 0.5 h, ethyl acrylate (1.45 g, 14.5 mmol) dissolved in dry THF (50 cm^3) was added dropwise. The mixture was stirred at room temp. overnight and then poured into water and extracted with ether. The extracts were dried (Na_2SO_4), and evaporated under reduced pressure to give the *title compound* as an oil (5.1 g, *ca.* 96%) (Found: C, 69.4; H, 6.8%; M$^+$, 400.1887. $C_{23}H_{28}O_6$ requires C, 69.0; H, 7.0%: *M*, 400.1886); ν_{max}(film)/cm^{-1} 1730 (C=O ester); δ_H 7.4–6.8 (8 H, m, aromatic), 4.4–3.9 (4 H, m, CH_2CH_3), 3.85 (3 H, s, CH_3O), 3.75 (3 H, s, CH_3O), 3.0–2.0 (4 H, m, CH_2CH_2) and 1.4–1.0 (6 H, m, CH_2CH_3).

1-*Ethyl Hydrogen* 2-(3,4-*Dimethoxyphenyl*)-2-*phenylpentanedioate* **25**.—Compound **24** (4.7 g, 12 mmol), sodium hydroxide (0.5 g, 13 mmol), ethanol (50 cm^3) and water (50 cm^3) were stirred together at reflux overnight. On cooling, the ethanol was evaporated under reduced pressure, ether added and the acid ester extracted with saturated aqueous sodium hydrogen carbonate. The organic extracts were washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure to give the crude product as a viscous oil, which slowly solidified with time. Trituration with ether–light petroleum gave the *title compound* as white crystals (3.2 g, 73%), m.p. 111–113 °C (Found: C, 67.9; H, 6.5. $C_{21}H_{24}O_6$ requires C, 67.7; H, 6.5%); ν_{max}(film)/cm^{-1} 3400–2500 (OH acid), 1730 (C=O ester) and 1700 (C=O acid); δ_H 10.0 (1 H, s, exch. CO_2H), 7.3–6.85 (8 H, m, aromatic), 4.2 (2 H, q, CH_2CH_3), 3.85 (3 H, s, CH_3O), 3.75 (3 H, s, CH_3O), 3.0–2.0 (4 H, m, CH_2CH_2) and 1.2 (3 H, t, CH_2CH_3).

Ethyl 1,2,3,4-*Tetrahydro*-6,7-*dimethoxy*-4-*oxo*-1-*phenylnaphthalene*-1-*carboxylate* **15**.—Compound **25** (1.2 g, 3.2 mmol) and polyphosphoric acid (20 g) were stirred for 6 h at room temp. The reaction mixture was then poured on to ice–water, and the product extracted with chloroform. The extracts were washed with saturated aqueous sodium hydrogen carbonate, water and brine, dried and evaporated under reduced pressure to give a dark oil which crystallised on trituration with ether. Recrystallisation from ethyl acetate gave the *title compound* as white crystals (0.6 g, 60%), m.p. 140–142 °C (Found: C, 71.1; H, 6.2%; M$^+$, 354.1524. $C_{21}H_{22}O_5$ requires C, 71.2; H, 6.2%; *M*, 354.1467); ν_{max}[tetrachloroethylene (TCE)]/cm^{-1} 1720 (C=O ester) and 1670 (C=O aryl ketone); δ_H 7.6 (1 H, s, aromatic), 7.3–6.9 (5 H, m, phenyl), 6.7 (1 H, s, aromatic), 4.25 (2 H, q, CH_2CH_3), 3.95 (3 H, s, CH_3O), 3.75 (3 H, s, CH_3O), 3.2–2.0 (4 H, m, CH_2CH_2) and 1.25 (3 H, t, CH_2CH_3).

1,2,3,4-*Tetrahydro*-6,7-*dimethoxy*-4-*oxo*-1-*phenylnaphthalene*-1-*carboxylic Acid* **26**.—A solution of compound **15** (30 g, 85 mmol) and sodium hydroxide (3.7 g, 93.2 mmol) in aqueous ethanol (1:1; 200 cm^3) was heated under reflux overnight and then allowed to cool. The ethanol was removed under reduced pressure and the residue worked up to give a foam (29.4 g, *ca.* 96%); ν_{max}(Nujol)/cm^{-1} 3500–2500 (CO_2H stretch), 1730 (C=O acid) and 1670 (C=O aryl ketone); δ_H 10.8 (1 H, br. exch., OH), 7.6 (1 H, s, aromatic), 7.3 (5 H, m, phenyl), 6.7 (1 H, s, aromatic), 3.95 (3 H, s, OCH_3), 3.75 (3 H, s, CH_3O) and 3.0–2.4 (4 H, m, CH_2CH_2). No satisfactory analysis could be obtained as the sample always contained residual solvent.

N-*Benzyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-4-*oxo*-1-*phenylnaphthalene*-1-*carboxamide* **27**.—Compound **26** (0.5 g, 1.53 mmol), triethylamine (0.16 g, 1.64 mmol) and 2-chloro-*N*-methylpyridinium iodide (0.39 g, 1.53 mmol) were stirred together in acetonitrile (20 cm^3) for 0.5 h. Benzylamine (0.17 g, 1.6 mmol) was added as a single portion, and the mixture stirred for a further 0.5 h. The solvent was then removed under reduced pressure, dichloromethane added, and the solution washed successively with 2 mol dm^{-3} hydrochloric acid, saturated aqueous sodium hydrogen carbonate and brine, dried (Na_2SO_4) and evaporated under reduced pressure to give a pale yellow oil which crystallised on trituration with ether. Recrystallisation from ethanol gave the *title compound* as white crystals (0.3 g, 51%), m.p. 159–161 °C (Found: C, 75.2; H, 6.1; N, 3.3%; M$^+$, 415.1745. $C_{16}H_{25}NO_4$ requires C, 75.2; H, 6.1; N, 3.4%; *M*, 415.1783); ν_{max}(TCE)/cm^{-1} 3400 (NH amide) and 1650 (br, C=O

aryl ketone + amide); δ_H 7.6 (1 H, s, aromatic), 7.2 (10 H, m, phenyl), 6.4 (1 H, s, aromatic), 6.0 (1 H, s, exch. NH), 4.5 (2 H, t, CH_2NH), 3.9 (3 H, s, CH_3O), 3.5 (3 H, s, CH_3O) and 3.2–2.3 (4 H, m, CH_2CH_2).

N-*Benzyl*-3-*bromo*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-4-*oxo*-1-*phenylnaphthalene*-1-*carboxamide* **28**.—A solution of phenyltrimethylammonium tribromide (7.25 g, 19.3 mmol) in dry THF (100 cm^3) was added dropwise to a solution of compound **27** (8 g, 19.3 mmol) in THF (140 cm^3) and the mixture stirred at 0 °C for 0.5 h. Stirring was continued for a further 1 h at 20 °C. The mixture was then filtered, concentrated under reduced pressure and the residue dissolved in chloroform. This solution was then washed successively with saturated aqueous sodium hydrogen carbonate and brine, dried (Na_2SO_4) and evaporated under reduced pressure to give an oil which crystallised on trituration with ether (7.81 g, 82%) to an unstable material, m.p. 119–122 °C (Found: M^+, 495.0943. $C_{26}H_{24}BrNO_4$ requires *M*, 495.0869); ν_{max}(bromoform)/cm^{-1} 3410 (NH amide), 1690 (C=O aryl ketone) and 1660 (C–O amide); δ_H 7.65 (1 H, s, aromatic), 7.2 (10 H, m, aromatic), 6.56 (1 H, s, aromatic) and 6.05 (1 H, t, NH). All of these absorbances were paired; 5.1 (1 H, q, CHBr), 4.5 (3 H, m, C*H*Br + $NHCH_2$), 3.95 (3 H, s, CH_3O), 3.55 (3 H, s, CH_3O + impurity) and 3.05 (2 H, q, alicyclic).

The NMR spectroscopic data is consistent with an approximately 50:50 mixture of diastereoisomeric bromo keto amides.

N-*Benzyl*-2,3,4,5-*tetrahydro*-7,8-*dimethoxy*-1-*phenyl*-1,4-*methano*-1H-3-*benzazepine*-2,5-*dione* **29**.—A solution of compound **28** (0.5 g, 1 mmol) and sodium (0.15 g, 6.5 mmol) in methanol (40 cm^3) was heated under reflux for 2.5 h and then allowed to cool. The solvent was removed under reduced pressure, water added to the residue and the mixture acidified with 2 mol dm^{-3} hydrochloric acid. The product was extracted with chloroform, the extracts washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure to give a pale yellow oil which crystallised on trituration with ether. Recrystallisation from ethyl acetate gave the *title compound* as colourless crystals (0.306 g, 73%), m.p. 147 °C (Found: C, 75.1; H, 5.5; N, 3.2%; M^+, 413.1618. $C_{26}H_{23}NO_4$ requires C, 75.5; H, 5.6; N, 3.4%; *M*, 413.1627); ν_{max}(bromoform)/cm^{-1} 1705 (C=O lactam) and 1695 (C=O ketone); δ_H(DMSO; 100 °C) 8.0–7.0 (11 H, m, aromatic), 6.42 (1 H, s, aromatic), 4.82 (1 H, d, CH_2Ph), 4.05 (1 H, d, CH_2Ph), 4.02 (1 H, d, bridgehead), 3.9 (3 H, s, CH_3O), 3.68 (3 H, s, CH_3O), 3.04 (1 H, d, CH_2) and 2.79 (1 H, d, of d, CH_2).

N-*Benzyl*-2,3,4,5-*tetrahydro*-7,8-*dimethoxy*-1-*phenyl*-1,4-*methano*-1H-3-*benzazepin*-2-*one* **30**.—Borane–pyridine complex (8.8 cm^3, 87.6 mmol) was added dropwise to a stirred solution of compound **29** (12 g, 29.9 mmol) in trifluoroacetic acid (100 cm^3) at −12 °C (ice–methanol). On addition, the temperature was allowed to rise to 20 °C and stirring was continued overnight. The solvent was then removed under reduced pressure, the residue dissolved in ethanol and the solution made alkaline (pH 11) by the addition of 2 mol dm^{-3} aqueous sodium hydroxide. The mixture was heated under reflux for 0.5 h and then cooled to precipitate a white solid. This was collected and recrystallised from ethanol to give the *title compound* as colourless crystals (11.2 g, 97%), m.p. 171–172 °C (Found: C, 77.9; H, 6.4; N, 3.4. $C_{26}H_{25}NO_3$ requires C, 78.2; H, 6.3; N, 3.5%); ν_{max}(bromoform)/cm^{-1} 1685 (C=O lactam); δ_H 7.6–7.1 (10 H, m, aromatic), 6.56 (1 H, s, aromatic), 6.43 (1 H, s, aromatic), 4.86 (1 H, d, CH_2Ph), 4.14 (1 H, d, CH_2Ph), 3.89 (1 H, m, bridgehead), 3.83 (3 H, s, CH_3O), 3.6 (3 H, s, CH_3O), 2.96 (1 H, d, d, $ArCH_2$), 2.85 (1 H, d, of d, $ArCH_2$) and 2.43 (2 H, m, CH_2).

N-*Benzyl*-2,3,4,5-*tetrahydro*-7,8-*dimethoxy*-1-*phenyl*-1,4-*methano*-1H-3-*benzazepine* **31**.—Compound **30** (3.8 g, 9.5 mmol) in THF (70 cm^3) was added dropwise to a stirred suspension of lithium aluminium hydride (LAH) (1.62 g, 40 mmol) in THF (80 cm^3) and the mixture refluxed for 5 h. The solution was then allowed to cool, after which water (0.9 cm^3), 15% aqueous sodium hydroxide (0.9 cm^3) and water (2.9 cm^3) were added sequentially and the suspension stirred for 0.5 h. It was then filtered through Hiflow and the filtrate concentrated under reduced pressure. The residue was dissolved in dichloromethane and the solution washed with water and saturated brine, dried (Na_2SO_4) and evaporated under reduced pressure to give the product as a pale yellow oil (3.09 g, 84%). The product was analysed as its hydrochloride salt (all other data is on the free base), m.p. 256–258 °C (Found: C, 73.9; H, 6.8; Cl, 8.7; N, 3.2%; M^+, 385.2059. $C_{26}H_{27}NO_2$(HCl) requires C, 74.0; H, 6.7; Cl, 8.4; N, 3.3%; *M*, 385.2042); δ_H 7.3 (10 H, m, phenyls), 6.15 (1 H, s, aromatic), 6.0 (1 H, s, aromatic), 4.0 (1 H, d, $PhCH_2$), 3.85 (4 H, m, CH_3O + $PhCH_2$), 3.65 (1 H, m, bridgehead); 3.48 (4 H, m, CH_3O + CH_2NBz), 3.32 (1 H, d, CH_2NBz), 2.98 (2 H, m, $ArCH_2$) and 2.35 (2 H, m, CH_2).

2,3,4,5-*Tetrahydro*-7,8-*dimethoxy*-1-*phenyl*-1,4-*methano*-1H-3-*benzazepine* **32**.—Compound **31** (3 g, 7.1 mmol) in ethanol (120 cm^3) and concentrated hydrochloric acid (15 cm^3) were hydrogenated (1 atm) over 10% palladium on charcoal (0.5 g) for 24 h. The suspension was filtered and evaporated under reduced pressure, water added to the residue and the solution basified with 2 mol dm^{-3} aqueous sodium hydroxide. The product was extracted with chloroform and the combined extracts were washed with saturated brine, dried (Na_2SO_4) and evaporated under reduced pressure to give a brown oil. This was treated with ethereal hydrogen chloride and the resultant brown solid triturated with hot ethyl acetate to give the *title compound* as hygroscopic crystals (2.17 g, 92%), m.p. 258–260 °C (Found: 66.2; H, 6.9; N, 4.0%; M^+, 295.1577. $C_{19}H_{21}NO_2$·HCl 0.5 H_2O requires C, 66.9; H, 6.6; N, 4.1%; *M*, 295.1572); ν_{max}(TCE)/cm^{-1} 3500 (br, NH); δ_H 7.4 (5 H, m, phenyl), 6.75 (1 H, s, aromatic), 6.0 (1 H, s, aromatic), 3.95 (1 H, m, bridgehead), 3.8 (3 H, s, CH_3O), 3.5 (5 H, two s, CH_3O + $ArCH_2$), 3.25 (1 H, d, CH_2N), 2.83 (1 H, d, CH_2N) and 2.38 (3 H, m, CH_2 + NH). NMR and mass spectroscopic data obtained on the free base.

2,3,4,5-*Tetrahydro*-7,8-*dihydroxy*-1-*phenyl*-1,4-*methano*-1H-3-*benzazepine Hydrobromide* **3**·HBr.—A solution of boron tribromide (1 mol dm^{-3}; 6 cm^3, 6 mmol) was added dropwise to a solution of compound **32** (400 mg, 1.2 mmol) in dichloromethane at 5 °C. On addition, the temperature was allowed to rise to 20 °C and stirring was continued for 24 h. Methanol (4 cm^3) was added (**CAUTION**), and the solution stirred for a further 4 h and then evaporated under reduced pressure to dryness. The residue was triturated with ether to give the product as an off-white hygroscopic solid (387 mg, 92%), m.p. 280–282 °C (Found: C, 57.5; H, 5.4; N, 3.8%; M^+, 267.1251. $C_{17}H_{18}BrNO_2$ requires C, 58.6; H, 5.2; N, 4.0%; *M*, 267.1259); ν_{max}(TCE)/cm^{-1} 3500 (OH phenol); δ_H(CD_3OD) 7.5 (5 H, m, phenyl), 6.6 (1 H, s, aromatic), 6.0 (1 H, s, aromatic), 4.45 (1 H, m, bridgehead), 3.8 (2 H, d, of d, CH_2N), 3.3 (3 H, m, benzylic + NH_2), 3.1 (1 H, d, benzylic), 2.8 (1 H, d, CH_2) and 2.3 (1 H, d, of d, CH_2); OH signal obscured by CH_3OH present in CD_3OD.

Diethyl 2-(3,4-*Dimethoxyphenyl*)-2-*phenylhexanedioate* **9** (R^1 = Ph, R^2 = R^3 = OMe, CO_2Et *for* CO_2H).—To lithium diisopropylamide (LDA) [from addition of butyllithium (1.6 mol dm^{-3}; 60 cm^3, 96 mmol) to diisopropylamine (13.5 cm^3, 96 mmol) in dry THF (150 cm^3) at 0 °C under nitrogen] at −72 °C (ethanol–CO_2), ethyl 3,4-dimethoxyphenyl(phenyl)-acetate **7** (R = Et; 19.7 g, 65.6 mmol) in dry THF (50 cm^3) was added dropwise. After 0.5 h, HMPA (30 g, 164 mmol) was added

in a single portion, followed after a further 0.5 h, by the addition of ethyl γ-iodobutyrate (24.6 g) in dry THF (20 cm^3). After 1 h, the solution was allowed to warm slowly to room temp. overnight, after which saturated aqueous ammonium chloride and 2 mol dm^{-3} hydrochloric acid were added. The product was extracted with ether, and the extracts washed successively with saturated aqueous sodium hydrogen carbonate, saturated aqueous sodium metabisulphite and brine. The extracts were dried (Na_2SO_4), and evaporated under reduced pressure to give an oil which crystallised with time. Recrystallisation (methanol) gave the *title compound* as white crystals (22 g, 81%), m.p. 90–91 °C (Found: C, 69.7; H, 7.2%; M^+, 414.2042. $C_{24}H_{30}O_6$ requires C, 69.6; H, 7.3%; *M*, 414.2042); ν_{max}(Nujol)/cm^{-1} 1720 (C=O ester); δ_H 7.2 (5 H, m, aromatic), 6.8 (3 H, m, aromatic), 4.2 (4 H, q, C*H*$_2$CH$_3$), 3.9 (3 H, s, CH_3O), 3.8 (3 H, s, CH_3O), 2.3 (4 H, m, CH_2CH_2) and 1.6–1.1 (8 H, m, CH_2 + CH_2CH_3).

1-*Ethyl Hydrogen* 2-(3,4-*Dimethoxyphenyl*)-5-*phenylhexanedioate* **9** R^1 = Ph, R^2 = R^3 = OMe).—Compound **9** (10 g, 24.1 mmol), sodium hydroxide (1.1 g, 27.15 mmol), ethanol (850 cm^3) and water (50 cm^3) were heated together under reflux for 18 h. After cooling, the ethanol was removed under reduced pressure and the mixture acidified with concentrated hydrochloric acid. Ether was added and the product extracted with saturated aqueous sodium hydrogen carbonate. The organic extracts were then acidified and extracted with chloroform. The latter extract was washed with saturated brine, dried (Na_2SO_4), and evaporated under reduced pressure to give the *title compound* as a viscous oil (8.8 g, 95%). Attempts at distilling this product were unsuccessful (Found: M^+, 386.1731. $C_{22}H_{26}O_6$ requires M^+, 386.1729); ν_{max}(film)/cm^{-1} 3400–2500 (OH acid), 1725 (C=O ester) and 1700 cm (C=O acid); δ_H 10.6 (1 H, s, exch., CO_2H), 7.2 (5 H, s, aromatic), 6.8 (3 H, m, aromatic), 4.2 (2 H, q, C*H*$_2$CH$_3$), 3.8 (3 H, s, CH_3O), 3.7 (3 H, s, CH_3O), 2.3 (4 H, m, CH_2CH_2), 1.4 (2 H, m, CH_2) and 1.2 (3 H, t, CH_2CH_3).

6,7,8,9-*Tetrahydro*-2,3-*dimethoxy*-9-*phenyl*-6,9-*methano*-5H-*benzocycloheptene*-5,10-*dione* **10** (R^1 = Ph, R^2 = R^3 = OMe)—(*a*) Compound **9** (R^1 = Ph, R^2 = R^3 = OMe) (8.8 g, 22.8 mmol) and polyphosphoric acid (135 g) were stirred at room temp. for 15 h after which ice and water were added. The product was extracted with chloroform and the extracts washed successively with saturated aqueous sodium hydrogen carbonate and brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was distilled (Kugelrohr: 250 °C/0.02 mbar) to give a solid which recrystallised from ethyl acetate to give the *title compound* as colourless crystals (3 g, 41%), m.p. 215–217 °C (Found: C, 74.3; H, 5.6%; M^+, 322.1204. $C_{20}H_{18}O_4$ requires C, 74.5; H, 5.6%; *M*, 322.1205); ν_{max}(Nujol)/cm^{-1} 1740 (C=O cyclopentanone) and 1670 (C=O aryl ketone); δ_H 7.5 (1 H, s, aromatic), 7.4 (5 H, m, aromatic), 6.2 (1 H, s, aromatic), 3.9 (3 H, s, CH_3O), 3.7 (1 H, d, bridgehead), 3.5 (3 H, s, CH_3O) and 2.9–1.7 (4 H, m, CH_2CH_2).

(*b*) The ester **9** (R^1 = Ph, R^2 = R^3 = OMe) (4.6 g, 12 mmol), trifluoroacetic anhydride (3.7 cm^3) and trifluoroacetic acid (2 cm^3) were stirred together at 70 °C for 20 h and then poured into ice–saturated aqueous sodium hydrogen carbonate and extracted with chloroform. The extracts were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to give a brown solid which crystallised on trituration with ether (2.6 g, 67%). The product had characteristics identical with those of the product in (*a*) above.

Attempted Preparation of N-*Benzyl*-6,7,8,9-*tetrahydro*-2,3-*dimethoxy*-5-*phenyl*-9-*oxo*-5H-*benzocycloheptene*-5-*carboxamide* **11** (R^1 = Ph, R^2 = R^3 = OMe, X = NHPh).—Benzylamine (1.71 cm^3, 15.7 mmol) was added to a stirred sodium hydride (60% disp.; 0.64 g, 16 mmol) in dry THF (100 cm^3) and the mixture stirred for 1.5 h at room temp. under nitrogen. The suspension was then heated to reflux and the benzocycloheptenedione **10** (R^1 = Ph, R^2 = R^3 = OMe) (5.11 g, 15.8 mmol) was added in small portions over 15 min. After the addition was completed, reflux was continued for 3 h, the suspension was then cooled, water and 2 mol dm^{-3} hydrochloric acid were added, and the non-basic material extracted with ether. The extracts were washed with saturated brine, dried (Na_2SO_4) and evaporated under reduced pressure to give an oil which crystallised on trituration with ether. Recrystallisation from ethanol gave fibrous crystals (3.2 g, 49%), m.p. 174–176 °C.

The NMR spectroscopic data showed the product to be a mixture containing two major and one minor component and was too complex to be interpreted directly; ν_{max}(Nujol)/cm^{-1} 3290 (NH amide), 1660 (C=O aryl ketone), and 1640 (C=O amide).

N-*Benzyl*-6-*bromo*-6,7,8,9-*tetrahydro*-2,3-*dimethoxy*-5-*oxo*-9-*phenyl*-5H-*benzocycloheptene*-6-*carboxamide* **12** (X = Br).—Phenyltrimethylammonium tribromide (3.6 g, 9.2 mmol) in dry THF (60 cm^3) was added dropwise to a stirred suspension of the previous amide (4 g, 9.2 mmol) in dry THF (60 cm^3) at 0 °C. The mixture was stirred for 1 h and then allowed to rise to room temp. over 1 h. The suspension was concentrated under reduced pressure, water, saturated aqueous sodium hydrogen carbonate was added to the residue, and the products were extracted with ether. The combined extracts were washed with saturated brine, dried (Na_2SO_4) and evaporated under reduced pressure to give an oil [fractionated by chromatography (SiO_2; 2.5%) EtOAc–CH_2Cl_2]. Two products were isolated as foams that could be crushed to give powders.

Product A (1.3 g, 30%), m.p. 56–61 °C (Found: M^+, 507.1095. $C_{27}H_{26}BrNO_4$ requires *M*, 507.1046); ν_{max}(bromoform)/cm^{-1} 3400 (NH amide), 1685 (C=O aryl ketone) and 1670 (C=O amide); δ_H 7.3 (11 H, m, phenyl + NH), 6.95 (1 H, s, aromatic), 6.2 (1 H, s, aromatic), 4.6 (1 H, d, of d, C*H*$_2$Ph), 4.48 (1 H, d, of d, CH_2Ph), 4.18 (1 H, d, of d, ArC*H*Ph), 3.85 (3 H, s, CH_3O), 3.63 (3 H, s, CH_3O), 3.1 (1 H, m, alicyclic), 2.5 (2 H, m, alicyclic) and 2.1 (1 H, m, alicyclic).

Product B (*ca.* 1.0 g), m.p. 60–65 °C (Found: M^+, 507.1095. $C_{27}H_{26}BrNO_4$ requires M^+, 507.1046); ν_{max} (bromoform)/cm^{-1} 3410 (NH amide), 1680 (C=O aryl ketone) and 1660 (C=O amide); δ_H 7.55 (1 H, m, NH), 7.3 (10 H, m, phenyl), 7.0 (1 H, s, aromatic), 6.3 (1 H, s, aromatic), 4.5 (3 H, m, C*H*$_2$Ph + Ar C*H*Ph), 3.9 (3 H, s, CH_3O), 3.7 (3 H, s, CH_3O), 2.8 (1 H, m, alicyclic) and 2.4 (3 H, m, alicyclic).

The data on both compounds can be interpreted to be consistent with stereoisomers of either: *N*-benzyl-8-bromo-6,7,8,9-tetrahydro-2,3-dimethoxy-9-oxo-5-phenyl-5*H*-benzocycloheptene-5-carboxamide or *N*-benzyl-6-bromo-6,7,8,9-tetrahydro-2,3-dimethoxy-5-oxo-9-phenyl-5*H*-benzocycloheptene-6-carboxamide.

Neither product gave a satisfactory analysis owing to their instability and difficulty in removing residual solvent from chromatographed fractions.

N-*Benzyl*-6,7,8,9-*tetrahydro*-2,3-*dimethoxy*-5-*oxo*-9-*phenyl*-5H-*benzocycloheptene*-6-*carboxamide* **12**.—The bromobenzocycloheptenecarboxamides from the previous experiment (0.3 g, 0.6 mmol) were added to triphenylphosphine[22] (0.16 g, 0.6 mmol) in benzene (20 cm^3) containing methanol (15 cm^3), and the mixture was refluxed for 20 min. The solution was then cooled, evaporated under reduced pressure and the residue adsorbed on to silica and chromatographed (SiO_2 25% EtOAc–light petroleum). This gave a solid, which when crystallised from ethyl acetate, gave the product as fibrous white crystals (0.18 g, 71%), m.p. 171–173 °C (Found: C, 75.3; H, 6.3; N, 3.0%; M^+,

429.1935. $C_{27}H_{27}NO_4$ requires C, 75.5; H, 6.3; N, 3.3%; *M*, 429.1940); ν_{max}(Nujol)/cm^{-1} 3290 (NH amide), 1660 (C=O aryl ketone) and 1640 (C=O amide); δ_H 7.8 (1 H, t, NH), 7.3 (11 H, m, aromatic), 6.2 (1 H, s, aromatic), 4.5 (2 H, d, CH_2Ph), 4.2 (1 H, d, of d, CHCON), 3.9 (3 H, s, CH_3O), 3.8 (1 H, d, of d, ArC*H*Ph), 3.6 (3 H, s, CH_3O) and 2.6–2.0 (4 H, m, CH_2CH_2).

6,7,8,9-*Tetrahydro*-2,3-*dimethoxy*-9-*oxo*-5-*phenyl*-5H-*benzocycloheptene*-5-*carboxylic Acid* **11** (R^1 = Ph, R^2 = R^3 = OMe, X = OH).—The benzocycloheptenedione **10** (R^1 = Ph, R^2 = R^3 = OMe; 1 g, 3.1 mmol), sodium hydroxide (2 mol dm^{-3}; 50 cm^3) and ethanol (15 cm^3) were stirred together at room temp. until all the solid had dissolved (1.5 h). The solution was then washed with ether, acidified with 2 mol dm^{-3} hydrochloric acid, and then extracted with chloroform. The latter were washed with saturated brine, dried and evaporated under reduced pressure, to give the *title compound* as a foam, which was crushed to give a white powder (0.99 g, 94%), m.p. 65 °C (Found: M^+, 340.1324. $C_{20}H_{20}O_5$ requires *M*, 340.1311); ν_{max}(chloroform)/cm^{-1} 3400–2600 (OH acid), 1710 (C=O acid) and 1680 (C=O ketone); δ_H 7.3 (6 H, m, aromatic), 6.55 (1 H, s, aromatic), 3.9 (3 H, s, CH_3O), 3.65 (3 H, s, CH_3O), 2.5 (4 H, m, alicyclics) and 2.2–1.5 (2 H, m, alicyclics). When this acid was heated under reflux for 1 h with ethanol (excess) containing 5% (v/v) conc. sulphuric acid, the dione **10** (R^1 = Ph, R^2 = R^3 = OMe) was obtained in 70% yield.

Ethyl 1,2,3,4-*Tetrahydro*-6,7-*dimethoxy*-4-*methylene*-1-*phenylnaphthalene*-1-*carboxylate* **16**.—(*a*) Sodium hydride dispersion (50%; 1.75 g, 36.4 mmol) was washed with anhydrous ether under nitrogen. Dry dimethyl sulphoxide (DMSO) (10 cm^3) was added and the suspension stirred at 70 °C for 1 h (**CAUTION**). The mixture was cooled to 30 °C, methyltriphenylphosphonium iodide (13.92 g, 34.4 mmol) and DMSO (10 cm^3) were added, and the reaction mixture was stirred vigorously for 1 h. The tetralone **15** (4.85 g, 13.7 mmol) in DMSO (10 cm^3) was then added in a single portion and the mixture stirred overnight at 70 °C. After cooling, the solution was poured onto ice–water and the product extracted with chloroform. Work-up gave a residue which was chromatographed to give an oil which crystallised on trituration with ethanol, to give the *title compound* as colourless crystals (1.64 g, 34%), m.p. 106–108 °C (Found: C, 74.6; H, 6.9%; M^+, 352.1675. $C_{22}H_{24}O_4$ requires C, 75.0; H, 6.9%; *M*, 352.1674); ν_{max}(chloroform)/cm^{-1} 1710 (C=O ester) and 1600 (C=C aromatic ring and olefin); δ_H 7.2 (6 H, m, aromatic), 6.7 (1 H, s, aromatic), 5.4 [1 H, s, olefinic (*Z*)], 4.9 [1 H, s, olefinic (*E*)], 4.25 (2 H, q, CH_2CH_3), 3.9 (3 H, s, CH_3O), 3.7 (3 H, s, CH_3O), 3.0–2.0 (4 H, m, CH_2CH_2) and 1.25 (3 H, t, CH_2CH_3).

(*b*) To methyltriphenylphosphonium iodide (0.727 g, 1.8 mmol) in dry THF (20 cm^3) at 0 °C under nitrogen butyllithium (1.2 cm^3, 1.8 mmol) was added dropwise and the suspension stirred until all the solid had dissolved. The solution was then warmed to room temp. and the tetralone **15** (0.632 g, 1.8 mmol) suspended in dry THF (20 cm^3), was added in a single portion. The mixture was then refluxed overnight, allowed to cool, and evaporated under reduced pressure. The residue was dissolved in dichloromethane, and the solution washed with water and saturated brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was chromatographed to give an oil, which when triturated with ether–light petroleum mixture, gave the title compound as white crystals (0.353 g, 56%), the characteristics of which were identical with those described above.

Ethyl 6,7,8,9-*Tetrahydro*-2,3-*dimethoxy*-8-*oxo*-5-*phenyl*-5H-*benzocyclohepten*-5-*carboxylate* **33**.—Silver nitrate (0.48 g, 2.84 mmol) was dissolved in refluxing methanol (15 cm^3) containing 5% water. The ester **16** (0.5 g, 1.42 mmol) and iodine (0.36 g, 2.84 mmol) were added sequentially, each washed in with methanol (5 cm^3). The suspension was refluxed for 30 min, cooled (ice), and filtered. The filtrate was diluted with water and the products were extracted with ether. The extract was washed with saturated brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was chromatographed to give an oil which solidified and upon trituration with ether afforded the product as colourless crystals (120 mg, 23%), m.p. 90.3–91 °C (Found: C, 72.1; H, 7.0%; M^+, 368.1631. $C_{22}H_{24}O_5$ requires C, 71.7; H, 6.6%; *M*, 368.1624); ν_{max}(chloroform)/cm^{-1} 1720 (C=O ester) and 1710 (C=O ketone); δ_H 7.3 (3 H, m, phenyl), 7.05 (2 H, m, phenyl), 6.67 (1 H, s, aromatic) 6.65 (1 H, s, aromatic), 4.25 (2 H, q, CH_2CH_3), 4.1 (1 H, d, benzylic), 3.9 (3 H, s, CH_3O), 3.7 (3 H, s, CH_3O), 3.52 (1 H, d, benzylic), 3.23 (1 H, m, COCH), 2.7–2.2 (3 H, m, alicyclics) and 1.25 (3 H, t, CH_3CH_2).

Ethyl 6,7,8,9-*Tetrahydro*-8-*hydroxyimino*-2,3-*dimethoxy*-5-*phenyl*-5H-*benzocycloheptene*-5-*carboxylate* **34**.—Hydroxylamine hydrochloride (15 mg, 0.22 mmol) compound **33** (70 mg, 0.2 mmol), pyridine (0.25 cm^3) and ethanol (20 cm^3) were stirred at reflux for 3 h. The solution was cooled, the solvent removed under reduced pressure and the residue dissolved in chloroform. This solution was washed with 2 mol dm^{-3} hydrochloric acid and saturated brine, dried (Na_2SO_4) and evaporated under reduced pressure to give the title compound as a foam which could be crushed to give a powder (69 mg, 95%); ν_{max}(chloroform)/cm^{-1} 3580 (OH oxime) and 3300 (OH bonded, oxime); δ_H 7.2 (5 H, m, phenyl), 6.75 (1 H, s, aromatic), 6.3 (1 H, s, aromatic), 4.2 (3 H, m, CH_2CH_3 + OH), 3.85 (3 H, s, CH_3O), 3.55 (5 H, m, benzylic + CH_3O), 2.9–2.0 (4 H, m, alicyclics) and 1.2 (3 H, t, CH_2CH_3).

No satisfactory analysis could be obtained on this product.

2,3,4,5-*Tetrahydro*-7,8-*dimethoxy*-1-*phenyl*-1,4-*ethano*-1H-3-*benzazepin*-2-*one* **36**.—To compound **34** (1.1 g, 2.9 mmol) in ethanol (40 cm^3) and 2 mol dm^{-3} aqueous sodium hydroxide (40 cm^3) Raney alloy (1.5 g) was added in portions over 0.5 h and the mixture was stirred at room temp. for 1.5 h. The suspension was then filtered, diluted with water and extracted with chloroform. The extracts were chromatographed to give the product as an oil (450 mg, 40%) which crystallised on trituration with ether, m.p. 170–172 °C (Found: C, 74.0; H, 6.5; N, 4.3%; M^+, 323.1487. $C_{20}H_{21}NO_3$ requires C, 74.3; H, 6.5; N, 4.3%; *M*, 323.1521); ν_{max}(chloroform)/cm^{-1} 3400 (NH, lactam) and 1670 (C=O lactam); δ_H 7.4 (5 H, m, phenyl), 6.55 (1 H, s, aromatic), 6.38 (1 H, d, NH), 6.1 (1 H, s, aromatic), 3.9 (1 H, m, bridgehead), 3.82 (3 H, s, CH_3O), 3.48 (4 H, m, CH_3O + benzylic), 3.05 (1 H, d, of d, benzylic), 2.6 (2 H, m, alicyclics), 2.3 (1 H, m, alicyclic) and 1.9 (1 H, m, alicyclic).

2,3,4,5-*Tetrahydro*-7,8-*dimethoxy*-1-*phenyl*-1,4-*ethano*-1H-3-*benzazepine* **37**.—Compound **36** (5 g) in dry THF (100 cm^3) was added dropwise over 30 min to LAH (0.7 g) stirred under N_2 in THF (100 cm^3) and the mixture was then stirred and refluxed for 20 h. On cooling, water (4 cm^3), aqueous sodium hydroxide (2 mol dm^{-3}; 4 cm^3) and water (4 cm^3) were added sequentially. After 0.5 h, filtration through Kieselguhr was followed by addition of chloroform and water (excess) to the filtrate. Work-up of the organic layer and chromatography gave an oil (4.7 g) which crystallised on trituration with ether: m.p. 102 °C (Found: C, 77.4; H, 7.7; N, 4.5%; M^+, 309.1708. $C_{20}H_{23}NO_2$ requires C, 77.65; H, 7.5; N, 4.5% *M*, 309.1729); δ_H 7.1–7.5 (5 H, m, aryl), 6.67 (1 H, s, aryl), 5.86 (1 H, s, aryl), 3.85 (3 H, s, OMe), 3.41 (3 H, s, OMe), 3.2–3.9 (5 H, m, $2CH_2$ + CH), 3.1 (1 H, s, exch. NH) and 1.5–2.4 (4 H, m, $2CH_2$).

2,3,4,5-*Tetrahydro*-7,8-*dihydroxy*-1-*phenyl*-1,4-*ethano*-1H-3-

benzazepine Hydrobromide **4**·HBr.—A solution of boron tribromide (1 mol dm^{-3}; 6 cm^3) in dichloromethane (10 cm^3) was added dropwise under nitrogen to compound **37** (0.5 g, 1.62 mmol) in dichloromethane (50 cm^3) with stirring at 0–5 °C for 1 h and then at room temp. overnight. Work-up as described for compound **3**, gave a powder (0.52 g) which crystallised from ethanol to afford the cream coloured, hydrated ethanol adduct, (300 mg), m.p. 192 °C [Found: C, 55.8; H, 5.8; N, 3.3%. $C_{18}H_{20}BrNO_2 \cdot C_2H_5OH \cdot H_2O$ requires C, 56.3; H, 6.5; N, 3.3%; *M* 281.1414 (100%). $C_{18}H_{19}NO_2$ requires *M*, 281.1416]; δ_H (D_2O; 250 MHz) 1.0 (3 H, t, CH_3CH_2O), 1.55–1.75 (1 H, m, CHH), 2.0–2.15 (2 H, m, CH_2), 2.3–2.42 (1 H, m, CHH), 3.05–3.4 (3 H, m, CH_2 + CH), 3.48 (2 H, q, OCH_2CH_3), 3.82–3.97 (2 H, m, CH_2), 5.65 (1 H, s, aryl), 6.62 (1 H, s, aryl) and 6.8–7.38 (5 H, m, aryl).

cis- *and* trans-*Ethyl* 1,2,3,4-*Tetrahydro*-4-*hydroxymethyl*-6,7-*dimethoxy*-1-*phenylnaphthalene*-1-*carboxylate* **18** (X = OH).—The ester **16** (1 g), borane–pyridine complex[23] (4 cm^3) and diglyme (40 cm^3) were heated and stirred under N_2 for 18 h. After cooling, aqueous sodium hydroxide (2 mol dm^{-3}; 3 cm^3) and hydrogen peroxide (100 vol; 1 cm^3) were added and stirring continued for 24 h. Work-up[23] gave an oil (1.1 g), purified further by chromatography ($SiO_2/CHCl_3$) to give the product (1.02 g, 97%), b.p. 175 °C/0.05 mbar (Found: C, 70.8; H, 6.95%; M^+, 370.1799. $C_{22}H_{26}O_5$ requires C, 71.35; H, 7.0%, *M* 370.1780); δ_H 7.0–7.35 (5 H, m, aryl), 6.6–6.8 (2 H, 4s, aryl), 4.25 (2 H, dq, CH_2CH_3), 3.9 (3 H, s, OMe), 3.7 (3 H, s, OMe), 2.5–3.0 (3 H, m, CH_2 + CH), 1.6–2.1 (4 H, m, $2CH_2$), 1.55 (1 H, s, exch. OH) and 1.22 (3 H, dt, CH_3CH_2).

6,7,8,9-*Tetrahydro*-10-*hydroxyimino*-2,3-*dimethoxy*-9-*phenyl*-6,9-*methano*-5H-*benzocyclohepten*-5-*one* **19**.—The benzocycloheptenedione **10** (R^1 = Ph, R^2 = R^3 = OMe) (1 g, 3.1 mmol), hydroxylamine hydrochloride (0.22 g, 3.2 mmol), pyridine (1 cm^3) and ethanol (30 cm^3) were refluxed for 1.5 h after which the ethanol was evaporated under reduced pressure to give a white, crystalline residue. This was dissolved in dichloromethane and the solution washed successively with 2 mol dm^{-3} hydrochloric acid and brine. The organic solution was then dried (Na_2SO_4), and concentrated under reduced pressure to give a crystalline residue. Recrystallisation of this from 40% aqueous ethanol gave the product (0.918 g, 88%); m.p. 222 °C (Found: C, 71.2; H, 5.6; N, 3.9%; M^+, 337.1294. $C_{20}H_{17}NO_4$ requires C, 71.2; H, 5.6; N, 4.3%; *M* 337.1314); ν_{max}(Nujol)/cm^{-1} 3500–3200 (bonded OH), 1690 (C=O aryl ketone) and 1660 (C=N oxime); δ_H 8.1 (1 H, s, exch. OH), 7.5 (1 H, s, aromatic), 7.4 (5 H, m, phenyl), 6.1 (1 H, s, aromatic), 4.5 (1 H, d, bridgehead), 3.9 (3 H, s, CH_3O), 3.6 (3 H, s, CH_3O) and 3.0–1.5 (4 H, m, CH_2CH_2).

(±)-10-*Amino*-6,7,8,9-*tetrahydro*-2,3-*dimethoxy*-9-*phenyl*-6,9-*methano*-5H-*benzocyclohepten*-5-*one* **20**.—Compound **19** (0.9 g, 1.48 mmol) in acetic acid (60 cm^3) was stirred under hydrogen (1 bar) over 10% Pd/C (300 mg) for 24 h after which the mixture was evaporated under reduced pressure. The residue dissolved in 2 mol dm^{-3} hydrochloric acid was then washed with ether and the aqueous phase basified with saturated aqueous sodium hydrogen carbonate and extracted with dichloromethane. The extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give an oil which when triturated with ether, gave the *title compound* as white crystals (0.278 g, 58%), m.p. 145–148 °C (Found: C, 74.3; H, 6.6; N, 4.5. $C_{20}H_{21}NO_3$ requires C, 74.3; H, 6.6; N, 4.3%); ν_{max}(Nujol)/cm^{-1} 3360, 3300 (NH primary amine) and 1670 (C=O aryl ketone); δ_H 7.7–7.3 (6 H, m, aromatic), 6.25 (1 H, s, aromatic), 3.95 (3 H, s, CH_3O), 3.62 (3 H, s, CH_3O), 3.47 (1 H, d, $CHNH_2$), 3.14 (1 H, q, bridgehead), 2.84 (1 H, m, CH_2CH_2), 2.34 (1 H, m, CH_2CH_2), 2.15 (1 H, m, CH_2CH_2), 1.60 (1 H, m, CH_2CH_2) 1.39 (2 H, br. exch. NH_2).

(±)-6,7,8,9-*Tetrahydro*-2,3-*dimethoxy*-9-*phenyl*-10-*trifluoroacetylamino*-6,9-*methano*-5H-*benzocyclohepten*-5-*one* (N-CF_3-CO deriv. of **20**).—Compound **20** 0.14 g, 0.43 mmol), dichloromethane (20 cm^3) and trifluoroacetic anhydride (0.5 cm^3) were stirred at room temp. for 10 min. The solution was washed once with phosphate buffer (pH 6.8), dried (Na_2SO_4) and evaporated to dryness to give the product as a white solid (0.16 g, 90%), m.p. 179–181 °C (Found: C, 62.7; H, 5.1; N, 3.2. $C_{22}H_{20}F_3NO_4$ requires C, 63.0; H, 4.8; N, 3.3%); ν_{max}(bromoform)/cm^{-1} 1725 (C=O trifluoroacetamide) and 1675 (C=O aryl ketone); δ_H 7.6–7.3 (6 H, m, aromatic), 6.33 (1 H, s, aromatic), 6.3 (1 H, d, NH), 4.68 (1 H, d, of d, CHNH), 3.97 (3 H, s, CH_3O), 3.66 (3 H, s, CH_3O), 3.4 (1 H, d, of d, bridgehead) and 3.0–1.6 (4 H, m, CH_2CH_2).

(±)-10-*Amino*-6,7,8,9-*tetrahydro*-2,3-*dimethoxy*-9-*phenyl*-6,9-*methano*-5H-*benzocycloheptene Hydrochloride* **21**·HCl.—Borane–pyridine complex (0.6 cm^3, 6 mmol) was added dropwise to a stirred solution of the preceding compound (0.75 g, 1.8 mmol) in trifluoroacetic acid (20 cm^3) at −12 °C (ice–ethanol–salt). On addition, the temperature was allowed to rise to 20 °C and stirring was continued for 3.5 h. The solvent was then evaporated and the residual yellow oil refluxed in 2 mol dm^{-3} aqueous sodium hydroxide containing an equal volume of ethanol for 0.5 h. The solution was extracted with dichloromethane and the extracts were dried (Na_2SO_4), concentrated under reduced pressure, and purified by flash chromatography [(SiO_2); CH_2Cl_2, EtOH, NH_3; 300:8:1]. The resultant oil was treated with ethereal hydrogen chloride to give a solid which crystallised (330 mg, 59%) on trituration with acetone; m.p. 251 °C (colour change at 210 °C).

The salt failed to give a satisfactory analysis as it was very hygroscopic. However, the trifluoroacetamide (m.p. 138–139 °C) of the free base gave the following analysis (Found: C, 64.6; H, 5.5; N, 3.3. $C_{22}H_{22}F_3NO_3$ requires C, 65.4; H, 5.6; N, 3.5%); ν_{max}(Nujol)/cm^{-1} 3200 (NH amine); δ_H(D_2O) 7.44 (5 H, m, aromatic), 6.8 (1 H, s, aromatic), 6.18 (1 H, s, aromatic), 3.83 (3 H, s, CH_3O), 3.48 (3 H, s, CH_3O), 3.43 (1 H, d, $CHNH_3$), 3.3 (3 H, m, NH_3), 3.18 (1 H, d, of d, benzylic) and 2.9–1.6 (6 H, m, ethano + bridgehead + benzylic).

(±)-10-*Amino*-6,7,8,9-*tetrahydro*-9-*phenyl*-6,9-*methano*-5H-*benzocycloheptene*-2,3-*diol Hydrobromide* **6**·HBr.—Boron tribromide (1 mol dm^{-3}; 3 cm^3, 3 mmol) was added dropwise to the preceding compound (0.24 g; 0.78 mmol) in dichloromethane (20 cm^3) at 5 °C. The temperature was allowed to rise to 20 °C, and stirring was continued for 22 h. Methanol was added (**CAUTION**) and the solution stirred for a further 4 h after which it was evaporated to dryness. The residue was a pale brown solid (0.163 g, 93%); no distinct m.p. (Found: C, 56.5; H, 5.5; N, 3.3%; M^+, 281.1409. $C_{18}H_{20}BrNO_2 + H_2O$ requires C, 56.8; H, 5.7; N, 3.7%; *M*, 281.1416); ν_{max}(Nujol)/cm^{-1} 3500 (br OH phenol); δ_H(D_2O) 7.3 (5 H, m, phenyl), 6.6 (1 H, s, aromatic), 6.1 (1 H, s, aromatic), 3.33 (1 H, c, $CHNH_3$), 3.22 (3 H, m, NH_3), 2.9 (1 H, d, benzylic), 2.6 (3 H, m, benzylic + alicyclic), 2.1 (1 H, m, alicyclic), 1.83 (1 H, m, alicyclic) and 1.4 (1 H, m, alicyclic).

(9S,10R)-6,7,8,9-*Tetrahydro*-2,3-*dimethoxy*-9-*phenyl*-6,9-*methano*-5H-*benzocyclohepten*-10-*ol* **22**.—Borane–pyridine complex (1 cm^3, 9.9 mmol) was added dropwise to a stirred solution of benzocycloheptenedione **10** (R^1 = Ph, R^2 = R^3 = OMe) (1 g, 3.1 mmol) in trifluoroacetic acid at −12 °C. The reaction mixture was allowed to rise to room temp. and stirring was continued overnight. The solvent was then evaporated

under reduced pressure and ethanol and 2 mol dm^{-3} sodium hydroxide solution added to the residue. This mixture was then stirred on a steam-bath for 0.5 h to give a white precipitate which recrystallised from methanol (544 mg, 54%) and had m.p. 149–150 °C (Found: C, 77.3; H, 7.1%; M^+, 310.1566. $C_{20}H_{22}O_3$ requires C, 77.4; H, 7.1%; *M*, 310.1569); $\nu_{max}(CHCl_3)/cm^{-1}$ 3580 (OH, alcohol); δ_H 7.6 (2 H, d, *ortho*-phenyl), 7.3 (3 H, m, aromatic), 6.67 (1 H, s, aromatic), 6.1 (1 H, s, aromatic), 4.12 (1 H, d, *J* 6, C*H*OH), 3.85 (3 H, s, CH_3O), 3.52 (3 H, s, CH_3O), 3.4 (1 H, d, of d, benzylic) and 2.7–1.4 (7 H, m, bridgehead + benzylic + alicyclics).

6,7,8,9-*Tetrahydro*-2,3-*dimethoxy*-9-*phenyl*-6,9-*methano*-5H-*benzocyclohepten*-10-*one* **23**.—(*a*) A mixture of chromium trioxide (1.48 g, 14.8 mmol) and pyridine (1.58 g, 20 mmol) dissolved in dichloromethane (30 cm^3) was set aside for 30 min. The previous compound **22** (0.5 g, 1.6 mmol) in dichloromethane (30 cm^3) was then added dropwise and the reaction mixture stirred at room temp. for 2 h. It was then filtered through Hiflo and the filtrate washed with water and 2 mol dm^{-3} hydrochloric acid, dried (Na_2SO_4) and evaporated under reduced pressure. Trituration of the residue with cold methanol gave a solid, which when crystallised from methanol gave the *title compound* as off-white crystals (0.28 g, 56%), m.p. 125–126 °C (Found: C, 77.9; H, 6.5%; M^+, 308.1385. $C_{20}H_{20}O_3$ requires C, 77.6; H, 6.8; *M*, 308.1412); ν_{max}(Nujol)/cm^{-1} 1740 (C=O cyclopentanone); δ_H 7.32 (5 H, m, phenyl), 6.6 (1 H, s, aromatic), 5.87 (1 H, s, aromatic), 3.82 (3 H, s, CH_3O), 3.46 (4 H, m, CH_3O + bridgehead), 3.25 (1 H, m, benzylic), 3.1 (1 H, m, benzylic) and 3.0–2.0 (4 H, m, CH_2CH_2).

(*b*) The benzocycloheptenol **22** (2 g, 6.4 mmol), DMSO (4.8 cm^3), HMPA (10 cm^3) and dichloromethane (10 cm^3) were mixed and the solution cooled to −20 °C (CCl_4 + CO_2); benzoyl chloride (1.48 cm^3, 12.8 mmol) was then added. After 0.5 h, triethylamine (1.9 cm^3, 14 mmol) was added as a single portion and the temperature maintained at −20 °C for 2 h. The reaction mixture was allowed to warm slowly to room temp. when the dichloromethane was removed under reduced pressure, ether was added and the solution washed successively with water, 2 mol dm^{-3} hydrochloric acid, saturated aqueous sodium hydrogen carbonate and brine. The ethereal solution was then dried (Na_2SO_4), and evaporated under reduced pressure to give an oil which solidified with time. Trituration with ether gave a crystalline solid, which when recrystallised from methanol, gave the product as white crystals (1.7 g, 86%), identical with those in (*a*).

6,7,8,9-*Tetrahydro*-2,3-*dimethoxy*-9-*phenyl*-6,9-*methano*-5H-*benzocyclohepten*-10-*one Oxime* (*Oxime of* **23**).—A mixture of compound **23** (1 g, 3.2 mmol), hydroxylamine hydrochloride (0.45 g, 6.4 mmol), pyridine (1 cm^3) and ethanol (50 cm^3) was refluxed overnight. The mixture was cooled, the ethanol was removed under reduced pressure, chloroform added and the solution washed successively with 2 mol dm^{-3} hydrochloric acid, water and brine. It was then dried (Na_2SO_4) and evaporated under reduced pressure to give a white solid which when recrystallised from methanol, gave the *title compound* (0.75 g, 72%), m.p. 179–180 °C (Found: C, 74.1; H, 6.5; N, 4.3%; M^+, 323.1539. $C_{20}H_{21}NO_3$ requires C, 74.3; H, 6.6; N, 4.3%; *M*, 323.1521); ν_{max}(Nujol)/cm^{-1} 3300 (OH br); δ_H 7.32 (6 H, m, phenyl + OH), 6.55 (1 H, s, aromatic), 5.93 (1 H, s, aromatic), 3.80 (4 H, m, CH_3O + bridgehead), 3.46 (4 H, m, CH_3O + benzylic) and 3.0–1.7 (5 H, m, CH_2CH_2 + benzylic).

(9S,10R)-(±)-6,7,8,9-*Tetrahydro*-2,3-*dimethoxy*-9-*phenyl*-6,9-*methano*-5H-*benzocyclohepten*-10-*yl Toluene*-p-*sulphonate* **22** *Tosylate*).—To the benzocycloheptenol **22** (4.51 g, 14.5 mmol) and toluene-*p*-sulphonyl chloride (3.05 g, 16 mmol) in ether (100 cm^3) at 0 °C, ground potassium hydroxide (5.4 g, 96 mmol) was added in portions over 15 min. The mixture was stirred vigorously for 2 h, and then set aside at *ca.* 0 °C overnight. The suspension was then poured into ice–water, the ether layer collected and evaporated under reduced pressure and the aqueous layer extracted with chloroform. The extracts were combined with the ethereal residue and the resultant solution was washed with saturated aqueous sodium hydrogen carbonate and brine, dried (Na_2SO_4), and concentrated under reduced pressure to give an oil which solidified with time.

Trituration of the oil with ether gave a crystalline solid, which when recrystallised from ethanol, gave the *title compound* (4.52 g, 57%), m.p. 166–168 °C (Found: C, 70.1; H, 6.2; S, 6.9%; M^+, 464.1627. $C_{27}H_{28}O_5S$ requires C, 69.8; H, 6.1; S, 6.9%; *M* 464.1657); $\nu_{max}(CHCl_3)/cm^{-1}$ 1350 (S=O sulphonate ester) and 1170 (S=O sulphonate ester); δ_H 7.8 (2 H, m, aromatic), 7.45 (7 H, m, aromatic), 6.8 (1 H, s, aromatic), 6.2 (1 H, s, aromatic), 4.88 (1 H, d, CHOTS), 4.08 (3 H, s, CH_3O), 3.7 (3 H, s, CH_3O), 3.60 (1 H, d, of d, benzylic), 3.0 (1 H, m, bridgehead), 2.78 (1 H, d, of d, benzylic), 2.63 (3 H, s, CH_3Ar) and 2.8–1.7 (4 H, m, CH_2CH_2).

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