Bridged-ring Nitrogen Compounds. Part 7.[1] Synthesis of the 1,4-Ethano-3-benzazepine Ring System

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9-Bromobenzosuberone was converted *via* 9-cyanobenzosuberone into several other 9-substituted benzosuberones, but attempts to cause them to cyclise to the tricyclic 1,4-ethano-3-benzazepine ring system were unsuccessful. Both ethyl phenylacetate and ethyl 3-methoxyphenylacetate were converted by conventional procedures into the corresponding 6,7,8,9-tetrahydro-5-methyl-9,10-dioxo-5,8-methano-5*H*-benzocycloheptenes. The 3-methoxy derivative was further converted into *N*-benzyl-8-bromo-6,7,8,9-tetrahydro-3-methoxy-5-methyl-9-oxo-5*H*-benzocycloheptene-5-carboxamide which could be converted into the tricyclic 3-benzyl-2,3,4,5-tetrahydro-8-methoxy-1-methyl-2,5-dioxo-1,4-ethano-1*H*-3-benzazepine and thence in two steps into both 3-benzyl-2,3,4,5-tetrahydro-8-methoxy-1-methyl-1,4-ethano-1*H*-3-benzazepine and 3-benzyl-2,3,4,5-tetrahydro-8-hydroxy-1-methyl-1,4-ethano-1*H*-3-benzazepine. Also prepared were 3-benzyl-2,3,4,5-tetrahydro-5-hydroxy-8-methoxy-1-methyl-1,4-ethano-1*H*-3-benzazepine and 3-benzyl-3,4-dihydro-8-methoxy-1-methyl-1,4-ethano-1*H*-3-benzazepin-5(2*H*)-one.

The hitherto unreported title ring system (**1**) exhibits, in common with other examples in this series of papers,[1] both similarities and yet subtle stereochemical differences from benzomorphans (**2**). In this paper we present an efficient synthesis of several 2,5-ethano-3-benzazepine derivatives and also describe an unsuccessful approach, for which an explanation is offered.

Results and Discussion

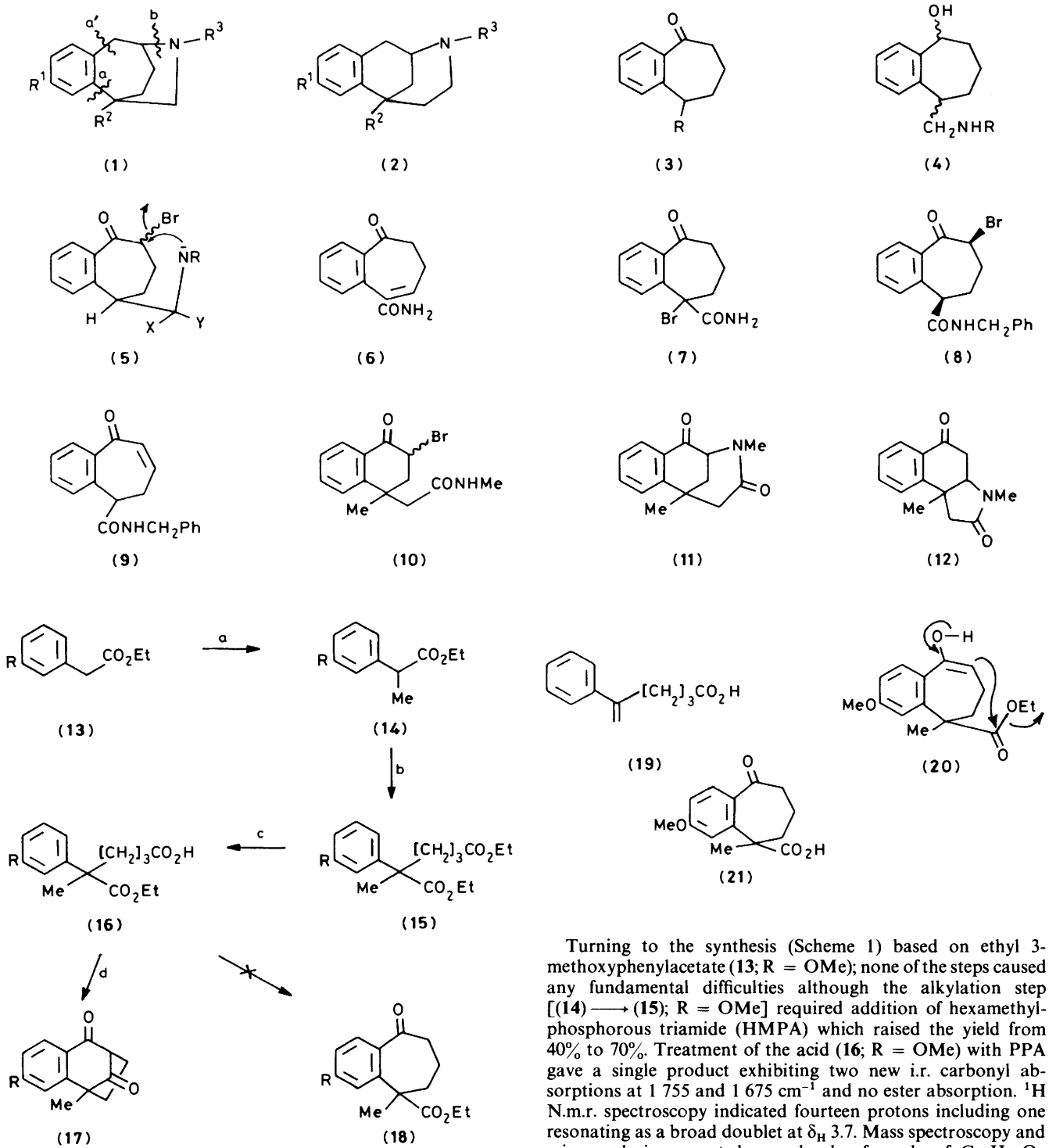
Retrosynthetic analysis of structure (**1**) suggested that plausible bond disconnections involved either 2,5-disubstituted piperidines (a) or 9-substituted benzocycloheptenes (b). The latter appeared the most attractive and initially we studied syntheses commencing with 9-bromobenzosuberone[2] (**3**; R = Br), now made easily in substantially pure state by bromination of benzosuberone with *N*-bromosuccinimide (NBS) in methyl formate (*cf.* ref. 3). Initially we found that bromination of benzosuberone in carbon tetrachloride[2] gave variable amounts of the 6-bromo isomer, recognised by the characteristic 6-H double doublet at δ_H 4.7—4.9. 9-Bromobenzosuberone was converted into 9-cyanobenzosuberone (**3**; R = CN) and thence into both the amide (**3**; R = $CONH_2$) by hydrolysis and into the hydroxyamine (**4**; R = H) by lithium aluminium hydride reduction. Although the stereochemistry of (**4**; R = H) was not ascertained, reoxidation of its *N*-acetate (**4**; R = Ac) with chromium trioxide–pyridine in methylene dichloride yielded the protected amino ketone (**3**; R = CH_2NHAc). Further hydrolysis of the cyano ketone (**3**; R = CN) gave the keto acid (**3**; R = CO_2H) from which the substituted amide (**3**; R = $CONHCH_2Ph$) was obtained using 2-chloro-*N*-methylpyridinium iodide as coupling agent.[4] With these 9-substituted benzosuberone derivatives available, the synthetic strategy shown in structure (**5**), involving intramolecular cyclisation to an α-bromo ketone, was explored.

Bromination of the ketoamide (**3**; R = $CONH_2$) with bromine in acetic acid yielded an exceptionally insoluble bromo compound (no n.m.r. data) which was treated with sodium methoxide in methanol to yield a substance thought to be compound (**6**) since its ^1H n.m.r. spectrum revealed only 5 aromatic and vinyl signals; it was moreover still a primary amide (Experimental section). It follows from this that bromination had given the 5-bromo isomer (**7**) rather than the expected 8-bromo isomer. On the other hand, similar bromination of the benzylamide (**3**; R = $CONHCH_2Ph$) gave the expected 8-bromo isomer (**8**) exhibiting the characteristic 8-H signal at δ_H 4.7; base treatment did not cause cyclisation but gave the αβ-unsaturated keto amide (**9**) which clearly showed *inter alia* two vinylic protons at δ_H 6.0—6.5 and an N–H stretch in the i.r. spectrum.

Examination of molecular models reveals a possible explanation for the failure of bromo amide (**8**) to cyclise. The most stable configuration would have both bromine and amide substituents in a pseudo-equatorial mutually *cis* disposition which renders cyclisation by intramolecular S_N2 mode impossible. A further clue is provided by the work of Walker and Alkalay[5] who showed that bromo keto lactam (**10**) cyclised to the keto amide (**11**) with sodium methoxide; in this case one would expect that in the major (*trans*) isomer the angular methyl group would place the amide side-chain in an axial position. Moreover it was reported[5] that the bromo keto lactam (**10**) yielded the tricyclic product (**12**) when heated in dimethylformamide (DMF), presumably *via* the corresponding αβ-unsaturated ketone. In our case the αβ-unsaturated ketone (**9**) did not cyclise in DMF although this too appears possible by a favoured 5-exo-trig process: models again reveal that in compound (**9**) the angle of approach of the nitrogen atom to the double bond is not very favourable.

These findings suggested that the presence of an additional methyl substituent at C-9 of the benzosuberone skeleton would place the bridge-forming substituents in a favourable mutually *trans* disposition. Since attempts to alkylate the keto nitrile (**3**; R = CN) using lithium di-isopropylamide (LDA) and methyl iodide were unsuccessful, a different approach was devised (Scheme 1).

Dealing first with the series based on ethyl phenylacetate (**13**; R = H); the initial three steps proceeded as planned, the terminal ester group in the diester (**15**; R = H) proved as expected to be more prone to alkaline hydrolysis, since the other ester group was sterically hindered. Cyclisation of the acid (**16**; R = H) produced surprises: polyphosphoric acid (PPA) treatment gave 3-phenylcyclohex-2-enone presumably *via* a de-ethoxycarbonylation reaction involving the ene acid (**19**); on the other hand, when the acid chloride from acid (**16**; R = H) was treated with anhydrous aluminium chloride in methylene dichloride, a mixture of two compounds [M^+, 246.1256



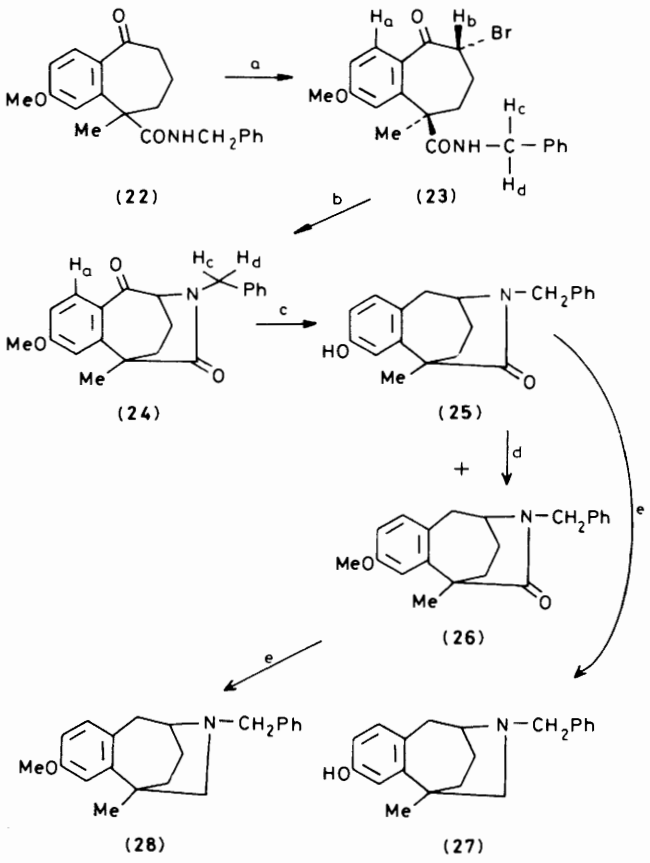
Scheme 1. *Reagents:* a, (i) $NaNH_2$–NH_3; (ii) MeI; b, (i) LDA–HMPA; (ii) ethyl γ-iodobutyrate; c, NaOH–aq.(EtOH; d, PPA

$(C_{15}H_{18}O_3)$ and 200.0837 $(C_{13}H_{12}O_2)$] was obtained. After further work in the 3-methoxyphenylacetic acid series (see below) we realised that the former compound must have been (**18**; R = H) and the latter (**17**; R = H). Since the cyclisation of acid (**16**; R = H) had not been as straightforward as expected, it was deemed necessary to provide an activating group [*e.g.*, (**16**; R = OMe)], and for pharmacological reasons the methoxy group at C-2 of the benzosuberone nucleus was desirable.

Turning to the synthesis (Scheme 1) based on ethyl 3-methoxyphenylacetate (**13**; R = OMe); none of the steps caused any fundamental difficulties although the alkylation step [(**14**) ⟶ (**15**); R = OMe] required addition of hexamethylphosphorous triamide (HMPA) which raised the yield from 40% to 70%. Treatment of the acid (**16**; R = OMe) with PPA gave a single product exhibiting two new i.r. carbonyl absorptions at 1 755 and 1 675 cm^{-1} and no ester absorption. ^1H N.m.r. spectroscopy indicated fourteen protons including one resonating as a broad doublet at δ_H 3.7. Mass spectroscopy and microanalysis suggested a molecular formula of $C_{14}H_{14}O_3$ which corresponded to the diketone (**17**; R = OMe). This would explain the carbonyl absorption of 1 755 cm^{-1} corresponding to the strained 5-membered-ring ketone and the lack of an ester grouping. The acid ester (**16**; R = OMe) presumably cyclised initially to the keto ester (**18**; R = OMe) which under the reaction conditions enolised and underwent an acid-catalysed Claisen reaction [structure (**20**)]. Formation of tricyclic products in similar situations is precedented.[6,7] Cyclisation of the acid chloride of compound (**16**; R = OMe) with aluminium chloride in methylene dichloride gave a product which initially did not show a cyclopentanone carbonyl absorption at 1 755 cm^{-1} but showed ester absorption at 1 725

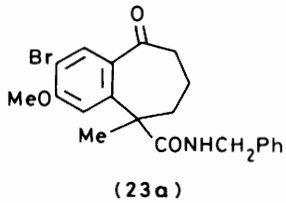
cm^{-1}; however, this product spontaneously crystallised as the diketone (**17**; R = OMe).

Not unexpectedly, the diketone (**17**; R = OMe) proved vulnerable to nucleophilic attack; treatment with either aqueous sodium hydroxide or sodium hydrogen carbonate gave the expected keto acid (**21**), whilst treatment with the sodium salt of benzylamine gave the benzylamide (**22**). The structure of the latter product was confirmed when the same product was obtained on coupling[4] of the keto acid (**21**) with benzylamine. The further steps in the synthesis of 2,5-ethano-3-benzazepine derivatives are shown in Scheme 2. A few comments are in order.



Scheme 2. *Reagents:* a, $PhMe_3N^+Br_3^-$; b, NaH–toluene–15-crown-5; c, KOH–hydrazine–digol; d, KOH–MeI; e, $LiAlH_4$–THF

Bromination of keto amide (**22**) with bromine in acetic acid gave a mixture of the desired compound (**23**) with its isomer (**23a**), but phenyltrimethylammonium perbromide[8,9] gave only the required isomer (**23**).



^1H N.m.r. spectroscopy showed the *peri* hydrogen (H_a) as a doublet at δ_H 7.55 and the 'α-bromo' proton (H_b) as a double doublet at δ_H 4.2. The benzylic protons, H_c and H_d, appeared as a pair of doublets (AB quartet) at δ_H 5.0—4.8. This observed non-equivalence could be due to either restricted rotation about the C–N bond of the amide or the prochirality of the benzylic carbon atom.[10–12] The ^{13}C n.m.r. spectrum exhibited two singlets at δ_C 175.091 and 161.258 p.p.m. due to the ketone and amide carbonyl carbons respectively. The carbon bearing bromine appears as a doublet at δ_C 55.513 p.p.m.

The apparent simplicity of the n.m.r. spectra, especially the double doublet due to the 'α-bromo' proton (H_b) which integrated to one whole proton, would suggest that only one stereoisomer of bromo amide (**23**) was isolated and that it is the *trans* isomer as shown.

The ^1H n.m.r. spectrum of keto lactam (**24**) showed that the *peri* hydrogen (H_a) was further deshielded and now appeared at δ_H 8.1. The non-equivalence of the benzylic protons H_c and H_d is now even more pronounced with the two doublets appearing about 0.5 p.p.m. apart. The bridgehead proton H_b appears as an unresolved multiplet at δ_H 4.2.

^{13}C N.m.r. spectroscopy also reveals general downfield shifts: the ketone carbon now appears at δ_C 193.963 p.p.m. compared with δ_C 175.091 p.p.m. in the bromo amide. The lactam carbonyl appears at δ_C 173.878 p.p.m. compared with the amide carbonyl in the starting material at δ_C 161.258 p.p.m.; the bridgehead carbon appears at δ_C 65.767 p.p.m.

Wolff–Kishner reduction of keto lactam (**24**) gave both the expected lactam (**26**) and the demethylated phenolic lactam (**25**). The latter was frequently the major product; demethylation under basic conditions is precedented.[13,14]

Both of the lactams (**25**) and (**26**) exhibited two new non-equivalent benzylic protons in the ^1H n.m.r. spectra; each appearing as a double doublet at δ_H *ca.* 3.0.

In the ^{13}C n.m.r. spectrum of the lactams (**25**) and (**26**), the benzylic carbon is now a triplet (δ_C 48.172, 49.143 p.p.m. respectively) while the aryl ketone carbon present in the keto lactam (**24**) at δ_C 193.963 p.p.m. as a singlet has disappeared.

The phenol (**25**) could be re-alkylated with methyl iodide and potassium hydroxide to yield the methoxy lactam (**26**).

In the case of the final products (**27**) and (**28**), both ^1H n.m.r. spectra were characterised by the appearance of two new non-equivalent protons (H_e, H_f) as a pair of doublets (AB quartet) at δ_H 2.8. It is suggested that the amines (**27**) and (**28**) exist with the piperidine ring in a twist conformation (*e.g.* as shown in Figure 1) with the *endo* proton (H_e) more upfield than the *exo* proton (H_f) due to the shielding effect of the aromatic ring. The non-equivalence of the benzylic protons (H_c and H_d) is more

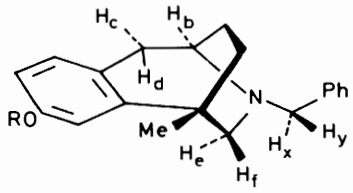


Figure 1.

pronounced than in the corresponding lactams (**26**) and (**25**), with proton H_c as a double doublet at δ_H 2.6—2.7, coupled to both H_d and H_b. Proton H_d appears as a broad doublet, downfield of H_c. Coupling between H_d and H_b is minimal since the dihedral angle is 90°.

The non-equivalence of the *N*-benzylic protons (H_x and H_y) is less pronounced than in the corresponding keto lactam due to the increased similarity of their respective environments once the lactam carbonyl is reduced (see Figure 2).

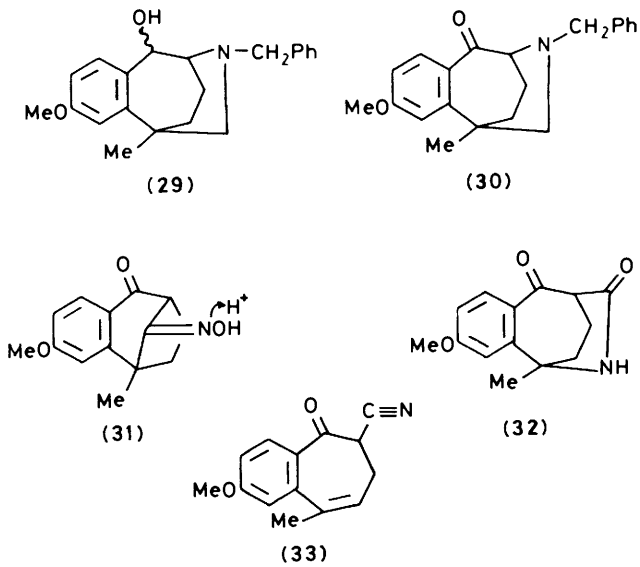
The ^{13}C n.m.r. spectra of the amines (**27**) and (**28**) show absence of the carbonyl singlets at δ_C 175.334 and 174.121 p.p.m. observed for compounds (**25**) and (**26**) respectively. New triplets

Figure 2.

attributed to the methylene carbons α to the nitrogen atoms are apparent at δ_C 62.9112 and 62.8083 p.p.m. for compounds (**28**) and (**27**) respectively.

Keto lactam (**24**) could be reduced to the amino alcohol (**29**) using lithium aluminium hydride: re-oxidation with chromium trioxide–pyridine in methylene dichloride yielded the amino ketone (**30**) but lengthy exposure to the reagent caused the unexpected reappearance of the keto lactam (**24**).

The Beckmann rearrangement has proved a fruitful method for conversion of cyclic ketones into lactams in the field of synthetic analgesics (see, *e.g.*, refs. 15 and 16). Accordingly it was of interest to find if the ketoxime (**31**) underwent



Beckmann rearrangement to give a member of the 1,4-ethano-3-benzazepine ring system or to the isomeric 1,4-ethano-2-benzazepine derivative (**32**). In the event the product was the nitrile (**33**) produced by secondary Beckmann reaction which was favoured presumably by the stability of the benzylic cation intermediate produced [*via* (**31**)]. There is a recent report of a similar reaction.[17]

Preliminary biological results indicate that 3-benzyl-2,3,4,5-tetrahydro-8-hydroxy-1-methyl-1,4-ethano-1*H*-3-benzazepine is an opiate drug of fairly low activity.

Experimental

All m.p.s. were uncorrected.

9-Bromo-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (**3**; R = Br).—1-Benzosuberanone (**3**; R = H) (10.02 g, 63 mmol) and NBS (11.13 g, 63 mmol) were refluxed together in methyl formate (80 cm^3) over a 60-W light bulb for 45 min. The resulting solution was concentrated under reduced pressure, then chloroform (100 cm^3) and water (100 cm^3) were added. The chloroform extracts were washed twice with water, dried, and evaporated under reduced pressure to yield a pale yellow solid which was recrystallised from light petroleum (b.p. 40–60 °C)–diethyl ether as colourless needles (10.8 g, 73%), m.p. 59—60 °C (Found: C, 55.35; H, 4.65; Br, 33.6%; M^+, 239.9969, 237.9999. $C_{11}H_{11}BrO$ requires C, 55.25; H, 4.65; Br, 33.4%; *M*, 239.9974, 237.9994); $\nu_{max.}$(Nujol) 1 680 (C=O) and 1 595 cm^{-1} (C=C); δ_H 7.7—7.1 (4 H, m, ArH), 5.7—5.4 (1 H, m, CHBr), and 3.4—1.7 (6 H, m, 3 × CH_2).

6,7,8,9-Tetrahydro-9-oxo-5H-benzocycloheptene-5-carbonitrile (**3**; R = CN).—A solution of 9-bromo-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (**3**; R = Br) (7.0 g, 29 mmol) in dimethyl sulphoxide (DMSO) (25 cm^3) was added dropwise during 0.5 h to a stirred suspension of sodium cyanide (4.1 g, 84 mmol) in DMSO (40 cm^3) at 75—80 °C. The resulting mixture was heated at that temperature for 4 h, then cooled and poured onto ice and extracted with toluene. The extracts were dried and evaporated under reduced pressure to produce a dark brown viscous liquid (5.3 g). Kugelrohr distillation yielded the *product* (**3**; R = CN) (3.3 g, 60%), b.p. 180—195 °C/0.01 mbar (Found: C, 77.3; H, 6.1; N, 6.95%; M^+, 185.0841. $C_{12}H_{11}NO$ requires C, 77.8; H, 6.0; N, 7.55%; *M*, 185.0841); $\nu_{max.}$ (film)2 240 (C≡N), 1 680 (C=O), and 1 600 cm^{-1} (C=C); δ_H 7.8—7.1 (4 H, m, ArH), 3.3—2.7 (5 H, m), and 2.5—2.0 (2 H, m).

6,7,8,9-Tetrahydro-9-oxo-5H-benzocycloheptene-5-carboxamide (**3**; R = $CONH_2$).—6,7,8,9-Tetrahydro-9-oxo-5*H*-benzocycloheptene-5-carbonitrile (**3**; R = CN) (2.94 g, 16 mmol) and conc. hydrochloric acid (8.4 cm^3) were stirred at 50 °C for 4 h. The resulting dark red solution was cooled, poured onto ice (20 cm^3), then basified with 2M-sodium hydroxide and extracted with ethyl acetate. The extracts were dried and evaporated under reduced pressure to yield a light brown gum which crystallised on trituration with diethyl ether. Recrystallisation from methanol yielded the *product* (**3**; R = $CONH_2$) as colourless needles (1.51 g, 47%), m.p. 148 °C (Found: C, 71.0; H, 6.35; N, 6.5%; M^+, 203.0933. $C_{12}H_{13}NO_2$ requires C, 70.9; H, 6.45; N, 6.9%; *M*, 203.0946); $\nu_{max.}$(Nujol) 3 390, 3 210 (N–H), 1 660 (C=O, aryl ketone), 1 620 (C=O, amide), and 1 595 cm^{-1} (C=C); δ_H 7.5—7.2 (4 H, m, ArH), 5.8 and 5.5 (each 1 H, br s, exch. with D_2O, $CONH_2$), 3.3—2.9 (4 H, m), 2.85—2.65 (1 H, m), and 2.25—2.1 (2 H, m).

8(or 5?)-Bromo-6,7,8,9-tetrahydro-9-oxo-5H-benzocycloheptene-5-carboxamide.—A solution of bromine in acetic acid (6.2 cm^3 of 2% v/v solution; 2.40 mmol) was added dropwise during 0.25 h to a stirred solution of 6,7,8,9-tetrahydro-9-oxo-5*H*-benzocycloheptene-5-carboxamide (**3**; R = $CONH_2$) (503 mg, 2.48 mmol) in acetic acid (30 cm^3) at room temperature. The mixture was stirred for a further 1 h until the orange colour had completely discharged. The solution was evaporated under reduced pressure to yield an off-white solid which was leached with hot toluene (2 × 10 cm^3) to yield the *product* as a powder (615 mg, 88%), m.p. 162—166 °C (decomp.) (Found: C, 51.4; H, 4.3; N, 4.75; Br, 28.4%; M^+, 283.0009, 281.0044. $C_{12}H_{12}BrNO_2$ requires C, 51.1; H, 4.3; N, 4.95; Br, 28.3%; *M*, 283,0032, 281.0052); $\nu_{max.}$(Nujol) 3 395, 3 185 (N–H), 1 665 (C=O, aryl ketone), 1 620 (C=O, amide), and 1 595 cm^{-1} (C=C).

Attempted Cyclisation of 8(or 5?)-*Bromo-6,7,8,9-tetrahydro-9-oxo-5H-benzocycloheptene-5-carboxamide using Sodium Methoxide.*—The bromoamide (1.0 g, 3.5 mmol) was added in portions to a stirred solution of sodium (0.244 g, 10.7 mmol) in methanol (30 cm^3) at room temperature under nitrogen. The resulting solution was stirred for 3 h at room temperature then concentrated under reduced pressure. Water (10 cm^3), and then 2M-hydrochloric acid (20 cm^3) were added and the mixture was extracted with chloroform. The extracts were dried and evaporated under reduced pressure to yield a light brown gum which

crystallised upon trituration with diethyl ether. Recrystallisation from methanol–diethyl ether yielded the *product* (see Discussion section) as an off-white powder (450 mg, 64%), m.p. 129—131 °C (Found: C, 71.6; H, 5.45; N, 6.6%; M^+, 201.0771. $C_{12}H_{11}NO_2$ requires C, 71.0; H, 5.5; N, 6.95%; *M*, 201.0790); $\nu_{max.}$(Nujol) 3 370, 3 170 (N–H), 1 675, 1 650, 1 630 (C=O), and 1 610, 1 595 cm^{-1} (C=C); δ_H 8.1—8.0 (1 H, dd, ArH), 7.6—7.0 (4 H, m), 6.0 (2 H, br s, exch., $CONH_2$), and 3.9—3.6 (4 H, m).

6,7,8,9-*Tetrahydro*-9-*oxo*-5H-*benzocycloheptene*-5-*carboxylic Acid* (**3**; R = CO_2H).—(i) 6,7,8,9-Tetrahydro-9-oxo-5*H*-benzocycloheptene-5-carbonitrile (**3**; R = CN) (1.80 g, 9.7 mmol), conc. sulphuric acid (1.45 cm^3), and water (6.8 cm^3) were refluxed together for 24 h. The reaction mixture was allowed to cool slightly, poured onto cold water (50 cm^3), and extracted with methylene dichloride. The extracts were washed with saturated aqueous sodium hydrogen carbonate. The aqueous washings were acidified (2M-hydrochloric acid) and extracted (CH_2Cl_2). The combined methylene dichloride extracts were dried and evaporated under reduced pressure to yield the *product* (**3**; R = CO_2H) as an oil which crystallised upon trituration with diethyl ether. Recrystallisation from ether gave crystals (980 mg, 47%), m.p. 139 °C (Found: C, 70.15; H, 5.95%; M^+, 204.0785. $C_{12}H_{12}O_3$ requires C, 70.55; H, 5.9%; *M*, 204.0786); $\nu_{max.}$($CHCl_3$) 3 500—2 500 (OH), 1 710 (C=O, acid), 1 670 (C=O, ketone), and 1 595 cm^{-1} (C=C); δ_H 9.8 (1 H, br s, exch.), 7.8 (1 H, dd, ArH) 7.6—7.2 (3 H, m, ArH), 3.2—2.7 (5 H, m, aliphatic), and 2.4—2.1 (2 H, m, aliphatic).

(ii) 6,7,8,9-Tetrahydro-9-oxo-5*H*-benzocycloheptene-5-carbonitrile (**3**; R = CN) (6.0 g, 0.029 mol) and potassium hydroxide (10.0 g, 0.175 mol) were refluxed together in 50% aqueous ethanol (100 cm^3) for 24 h then the mixture was concentrated under reduced pressure and water (100 cm^3) was added. The mixture was washed with methylene dichloride, acidified (dil. hydrochloric acid), then extracted with methylene dichloride. The extracts were dried and evaporated under reduced pressure to yield a light brown oil which crystallised upon trituration with ethyl acetate. Recrystallisation from ethyl acetate yielded the product (**3**; R = CO_2H) (3.8 g, 57%), identified by comparison with previously prepared material (m.p., t.l.c., i.r., ^1H n.m.r.).

Ethyl 6,7,8,9-*Tetrahydro*-9-*oxo*-5H-*benzocycloheptene*-5-*carboxylate* (**3**; R = CO_2Et).—6,7,8,9-Tetrahydro-9-oxo-5*H*-benzocycloheptene-5-carboxylic acid (**3**; R = CO_2H) (850 mg, 4.16 mmol) and conc. sulphuric acid (0.5 cm^3) were refluxed together in ethanol (25 cm^3) for 24 h, then concentrated under reduced pressure, and water (15 cm^3) was added. The mixture was extracted (CH_2Cl_2) and the extracts were washed with saturated aqueous sodium hydrogen carbonate, dried, and evaporated under reduced pressure to yield a pale yellow oil. Kugelrohr distillation yielded the *product* (**3**; R = CO_2Et) as an oil (770 mg, 80%), b.p. 150 °C/0.05 mbar (Found: C, 71.9; H, 6.9%; M^+, 232.1074. $C_{14}H_{16}O_3$ requires C, 72.4; H, 6.95%; *M*, 232.1099); $\nu_{max.}$(film) 1 725 (C=O), ester) and 1 680 cm^{-1} (C=O, aryl ketone); δ_H 7.8—7.6 (1 H, m, ArH), 7.5—7.1 (3 H, m, ArH), 4.05 (2 H, q, *J* 7 Hz, CH_2CH_3), 3.1—2.6 (5 H, m), 2.4—1.95 (2 H, m), and 1.2 (3 H, t, *J* 7 Hz, CH_2CH_3).

N-*Benzyl*-6,7,8,9-*tetrahydro*-9-*oxo*-5H-*benzocycloheptene*-5-*carboxamide* (**3**; R = $CONHCH_2Ph$).—(i) To a stirred solution of 6,7,8,9-tetrahydro-9-oxo-5*H*-benzocycloheptene-5-carboxylic acid (**3**; R = CO_2H) (204 mg, 1.00 mmol), triethylamine (0.15 cm^3, 1.08 mmol), and 2-chloro-*N*-methylpyridinium iodide[4] (258 mg, 1.01 mmol) in acetonitrile at room temperature was added benzylamine (0.115 cm^3, 1.05 mmol) in one portion. After 5 min, a white precipitate developed. The reaction mixture was stirred for a further 20 min then the solvent was removed under reduced pressure and methylene dichloride (30 cm^3) was added. The resulting solution was washed successively with 2M-hydrochloric acid and saturated aqueous sodium hydrogen carbonate, dried, and evaporated under reduced pressure to yield a yellow oil which crystallised upon trituration with diethyl ether.

Recrystallisation from diethyl ether–light petroleum (b.p. 40—60 °C) gave the *product* (**3**; R = $CONHCH_2Ph$) as colourless needles (175 mg, 60%), m.p. 78 °C (Found: C, 77.4; H, 6.4; N, 4.55%; M^+, 293.1421. $C_{19}H_{19}NO_2$ requires C, 77.8; H, 6.55; N, 4.75%; *M*, 293.1416); $\nu_{max.}$(Nujol) 3 250 (N–H), 1 670 (C=O, aryl), and 1 630 cm^{-1} (C=O, amide); δ_H 7.65 (1 H, m, ArH), 7.4—7.15 (8 H, m, ArH), 6.5 (1 H, br s, exch., NH), 4.30 (2 H, d, *J* 6 Hz, 2 × s in D_2O, benzylic), 3.3—2.4 (5 H, m), and 2.3—1.9 (2 H, m).

(ii) 6,7,8,9-Tetrahydro-9-oxo-5*H*-benzocycloheptene-5-carboxylic acid (**3**; R = CO_2H) (1.0 g, 4.9 mmol) and excess of thionyl chloride (1.5 cm^3) were refluxed together in dry methylene dichloride (25 cm^3) for 1 h, then concentrated under reduced pressure. The crude acid chloride thus obtained was used immediately without any attempts at purification.

To a solution of the acid chloride in dry methylene dichloride (25 cm^3) at 0 °C was added dropwise an excess of benzylamine (1.0 cm^3) in dry methylene dichloride (10 cm^3). After 3 min, a voluminous white precipitate had appeared and the temperature was allowed to rise to room temperature. More methylene dichloride (25 cm^3) was added and the reaction mixture was filtered; the residue was washed with a further portion of methylene dichloride (25 cm^3). The combined filtrates were washed with saturated aqueous sodium hydrogen carbonate, dried, and evaporated under reduced pressure to yield a yellow oil which crystallised on trituration with diethyl ether. Recrystallisation from diethyl ether–light petroleum (b.p. 60—80 °C) yielded the product (**3**; R = $CONHCH_2Ph$) as needles, identified by comparison with previously prepared material (t.l.c., m.p., i.r., ^1H n.m.r.).

N-*Benzyl*-8-*bromo*-6,7,8,9-*tetrahydro*-9-*oxo*-5H-*benzocycloheptene*-5-*carboxamide* (**8**).—A solution of bromine in acetic acid (3% v/v solution; 7.75 cm^3, 4.5 mmol) was added in one portion to a stirred solution of *N*-benzyl-6,7,8,9-tetrahydro-9-oxo-5*H*-benzocycloheptene-5-carboxamide (**3**; R = $CONHCH_2Ph$) (1.33 g, 4.5 mmol) in acetic acid (75 cm^3) at room temperature. The mixture was stirred for a further 0.5 h until the solution was almost colourless. The acetic acid was removed under reduced pressure, methylene dichloride (50 cm^3) was added, and the resulting solution was washed with saturated aqueous sodium hydrogen carbonate, dried, and evaporated under reduced pressure to yield a pale yellow oil which slowly crystallised as colourless needles (1.25 g, 82%), m.p. 96—97 °C, upon being kept in diethyl ether–light petroleum (b.p. 40—60 °C) (Found: C, 61.45; H, 4.85; N, 3.6; Br, 21.1%; M^+, 373.0530, 371.0521. $C_{19}H_{18}BrNO_2$ requires C, 61.3; H, 4.85; N, 3.75; Br, 21.45%; *M*, 373.0502, 371.0521); $\nu_{max.}$ (Nujol) 3 230br (N–H), 1 675 (C=O, aryl), and 1 660 cm^{-1} (C=O, amide); δ_H 7.8—7.6 (1 H, m, ArH), 7.4—6.9 (8 H, m, ArH), 4.70 (1 H, d, *J* 7 Hz, CHBr), 4.60 (1 H, br s, exch., NH), 4.55 (1 H, d, *J* 14 Hz, C*H*H'Ph), 4.10 (1 H, d, *J* 14 Hz, CHH'Ph), and 3.0—1.8. (5 H, m).

Attempted Cyclisation of N-Benzyl-8-*bromo*-6,7,8,9-*tetrahydro*-9-*oxo*-5H-*benzocycloheptene*-5-*carboxamide* (**8**).—(*a*) A solution of *N*-benzyl-8-bromo-6,7,8,9-tetrahydro-9-oxo-5*H*-benzocycloheptene-5-carboxamide (**8**) (0.31 g, 0.83 mmol) in sodium-dried diethyl ether (25 cm^3) was added to a stirred suspension of sodium hydride (60% oil dispersion; 0.045 g, 1.1 mmol) in sodium-dried diethyl ether (25 cm^3) at 0 °C, under nitrogen. The temperature of the reaction mixture was allowed to

rise to room temperature and after 1.5 h, water (25 cm^3) and 2M-hydrochloric acid (25 cm^3) were added and the mixture was extracted with ether. The extracts were washed with saturated aqueous sodium hydrogen carbonate, dried, and evaporated under reduced pressure to yield a pale yellow gum which crystallised on trituration with toluene (180 mg). Recrystallisation from toluene yielded the dehydrobromination product as colourless crystals, m.p. 156—159 °C (Found: C, 78.55; H, 5.85; N, 4.6%; M^+, 291.1260. $C_{19}H_{17}NO_2$ requires C, 78.35; H, 5.9; N, 4.8%; *M*, 291.1259); $\nu_{max.}$(Nujol) 3 300 (N–H), 1 655 (C=O, amide) with shoulder at 1 670 cm^{-1} (C=O), aryl ketone); δ_H (8.0—7.7 (1 H, m, ArH), 7.3—7.0 (8 H, m, ArH), 6.5—6.0 (2 H, m, vinylic), 5.85 (1 H, s, exch., NH), 4.25 (2 H, br s, NHCH_2Ph), 3.4 (1 H, br t), and 2.8—2.25 (2 H, m).

The product appears to be *N*-benzyl-6,9-dihydro-9-oxo-5*H*-benzocycloheptene-5-carboxamide (**9**) (see Discussion section).

(*b*) A solution of *N*-benzyl-8-bromo-6,7,8,9-tetrahydro-9-oxo-5*H*-benzocycloheptene-5-carboxamide (**8**) (0.34 g, 0.91 mmol) in methanol (25 cm^3) was added to a stirred solution of sodium methoxide [made from sodium (25 mg, 1.1 mmol) in an excess of methanol] in methanol (25 cm^3) at room temperature under nitrogen. The resulting solution was refluxed for 3.5 h, then the solvent was removed under reduced pressure and water was added. The mixture was extracted (CH_2Cl_2) and the extracts were washed with 2M-hydrochloric acid, dried, and evaporated under reduced pressure to yield a yellow gum (0.238 g) which partially crystallised when treated with toluene. This appeared to be identical with the product from (*a*) above (t.l.c., i.r.).

9-*Aminomethyl*-6,7,8,9-*tetrahydro*-5H-*benzocyclohepten*-5-*ol* (**4**; R = H).—A solution of 6,7,8,9-tetrahydro-9-oxo-5*H*-benzocycloheptene-5-carbonitrile (**3**; R = CN) (7.20 g, 39 mmol) in dry tetrahydrofuran (THF) (30 cm^3) was added dropwise during 1.5 h to a stirred suspension of lithium aluminium hydride (95%; 2.32 g, 58.1 mmol) in dry THF (70 cm^3) whilst maintaining a gentle reflux. The reaction mixture was stirred for a further 1.5 h then cooled in ice before water (2.4 cm^3), 15% aqueous sodium hydroxide (2.4 cm^3), and water (7.2 cm^3) in that order were carefully added dropwise. The resulting solution was stirred for a further 15 min, then filtered. The residue was washed with methylene dichloride (2 × 50 cm^3) and the combined filtrates were concentrated under reduced pressure to yield an off-white solid. Recrystallisation from acetone gave the title compound as crystals (4.2 g, 56%), m.p. 139—141 °C (Found: C, 75.6; H, 9.0; N, 7.3%; M^+, 191.1315. $C_{12}H_{17}NO$ requires C, 75.35; H, 8.95; N, 7.3%; *M*, 191.1310); $\nu_{max.}$(Nujol) 3 280, 3 310 (N–H), and 2 500—3 300 cm^{-1} (O–H); δ_H ([$^2H_6$]DMSO) 7.6—6.9 (4 H, m, ArH), 4.9—4.6 (1 H, br d, C*H*OH), and 3.5—0.5 (12 H, m, 3 H exch.).

9-*Acetamidomethyl*-6,7,8,9-*tetrahydro*-5H-*benzocyclohepten*-5-*ol* (**4**; R = Ac).—Acetic anhydride (0.3 cm^3, 0.325 g, 3.18 mmol) was added in one portion to a stirred solution of 9-aminomethyl-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (**4**; R = H) (485 mg, 2.54 mmol) in methanol (5 cm^3) at room temperature. After 1 h, the solution was evaporated under reduced pressure to yield a white solid which was recrystallised from ethyl acetate to yield the *product* (**4**; R = Ac) (425 mg, 72%), m.p. 164—166 °C (Found: C, 72.35; H, 8.3; N, 5.85%; M^+, 233.1421. $C_{13}H_{19}NO_2$ requires C, 72.05; H, 8.2; N, 6.0%; *M*, 233.1416); $\nu_{max.}$(Nujol) 3 290 (N–H), 2 500—3 400 (O–H), and 1 645 cm^{-1} (C=O, amide); δ_H 7.55 (1 H, d, ArH), 7.3—7.0 (3 H, m, ArH), 5.6 (1 H, br s, exch., NH), 4.95 (1 H, d, C*H*OH), 3.3—3.0 (2 H, m), 3.0—2.6 (2 H, m), 2.3—1.9 (7 H, m, including s at 2.05), 1.5—1.3 (1 H, m), and 1.15—1.0 (1 H, m).

9-*Acetamidomethyl*-6,7,8,9-*tetrahydro*-5H-*benzocyclohepten*-5-*one* (**3**; R = CH_2NHAc).—Chromium trioxide (4.04 g, 0.04 mol) was added in portions to a stirred solution of pyridine (6.6 cm^3, 0.08 mol) in dry methylene dichloride (50 cm^3) and the resulting burgundy-coloured solution was stirred for 0.5 h at room temperature. A solution of 9-acetamidomethyl-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (**4**; R = Ac) (1.57 g, 6.7 mmol) in dry methylene dichloride (35 cm^3) was added and the reaction mixture was stirred for 0.5 h, then filtered. The residue was washed (CH_2Cl_2) and the combined washings were washed successively with 2M-hydrochloric acid and saturated aqueous sodium hydrogen carbonate, dried, and evaporated under reduced pressure. Kugelrohr distillation yielded the *product* (**3**; R′ = CH_2NH Ac) (1.26 g, 81%), b.p. 220 °C/0.01 mbar, as a viscous, pale yellow gum (Found: C, 73.0; H, 7.7; N, 6.1%; M^+, 231.1257. $C_{14}H_{17}NO_2$ requires C, 72.7; H, 7.4; N, 6.05%; *M*, 231.1259); $\nu_{max.}$(film) 3 280 (N–H), 1 660v br, (C=O) and 1 595 cm^{-1} (C=C); δ_H 7.7 (1 H, dd, ArH), 7.5—7.0 (3 H, m, ArH), 6.4 (1 H, br, exch., NH), and 3.5—1.1 (12 H, m, including s at 1.95).

Attempted Preparation of 6,7,8,9-*Tetrahydro*-5-*methyl*-9-*oxo*-5H-*benzocycloheptene*-5-*carbonitrile*.—LDA was prepared by the addition of n-butyl-lithium (1.55M; 5 cm^3, 7.75 mmol) to a stirred solution of di-isopropylamine (1.09 cm^3, 7.8 mmol) in freshly distilled THF (20 cm^3) at 0 °C, and allowing reaction to continue for 15—20 min.

A solution of 6,7,8,9-tetrahydro-9-oxo-5*H*-benzocycloheptene-5-carbonitrile (**3**; R = CN) (1.44 g, 7.78 mmol) in THF (10 cm^3) was added dropwise at −78 °C and the resulting red solution was stirred for 15 min, then a solution of methyl iodide (0.49 cm^3, 7.87 mmol) in HMPA (2.90 cm^3, 23.6 mmol) was added dropwise. After 4 h at −78 °C, the solution was slowly raised to room temperature, then saturated aqueous ammonium chloride was added. The mixture was extracted ($CHCl_3$) and the extracts were washed consecutively with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium metabisulphite, then dried and evaporated under reduced pressure to yield a light brown viscous liquid (1.40 g). This was distilled (175 °C/0.015 mbar, Kugelrohr) and identified as starting material (t.l.c., i.r., ^1H n.m.r.).

Ethyl α-Phenylpropionate (**14**; R = H).—A solution of ethyl phenylacetate (**13**; R = H) (32.8 g, 0.20 mol) in dry diethyl ether (50 cm^3) was added in one portion to a stirred solution of sodamide [from sodium (5 g, 0.22 mol)] in liquid ammonia (300 cm^3) at −78 °C. The resulting solution was stirred for 1 h, then a solution of methyl iodide (28.4 g, 0.20 mol) in dry diethyl ether (50 cm^3) was added in one portion. The reaction mixture was stirred for a further 1 h at −78 °C, then ammonium chloride and dry diethyl ether (300 cm^3) were added and the ammonia was allowed to evaporate off. The resulting ethereal solution was stirred with 2M-hydrochloric acid (150 cm^3) for 15 min. The layers were separated and the aqueous layer was extracted twice with diethyl ether. The combined extracts were washed successively with saturated aqueous sodium hydrogen carbonate, saturated aqueous sodium metabisulphite, and saturated aqueous sodium chloride, then dried and evaporated under reduced pressure to yield a pale brown liquid. Kugelrohr distillation yielded the product (**14**; R = H) (28.9 g, 81%) as a colourless oil, b.p. 95 °C/0.01 mbar (lit.,[18] 115—118 °C/19 mmHg) (Found: C, 74.0; H, 7.95%; M^+ 178.0994. Calc. for $C_{11}H_{14}O_2$: C, 74.1; H, 7.95%; *M*, 178.0994); $\nu_{max.}$(film) 1 735 cm^{-1} (C=O, ester); δ_H 7.3 (5 H, d, Ph), 4.1 (2 H, q, CH_2CH$_3$), 3.7 (1 H, q, 2-H), 1.5 (3 H, d, Me), and 1.2 (3 H, t, CH$_2$CH_3).

Diethyl 2-*Methyl*-2-*phenylhexanedioate* (**15**; R = H).—LDA was prepared by the addition of n-butyl-lithium (1.55M; 10 cm^3, 15.5 mmol) to a stirred solution of di-isopropylamine (2.18 cm^3, 15.6 mmol) in freshly distilled THF (20 cm^3) at 0 °C under nitrogen which was then stirred at 0 °C for 15—20 min.

A solution of ethyl α-phenylpropionate (2.52 g, 14.1 mmol) in THF (10 cm^3) was added dropwise to this solution of LDA at −78 °C and the mixture was stirred at that temperature for a further 1 h; then a solution of ethyl γ-iodobutyrate * (3.41 g, 14.1 mmol) in THF (10 cm^3) was added dropwise during 15 min. The resulting solution was allowed to rise to room temperature overnight then saturated aqueous ammonium chloride was added. 2M-Hydrochloric acid was added and the mixture was extracted (Et_2O). The extracts were washed successively with saturated aqueous sodium hydrogen carbonate, saturated aqueous sodium metabisulphite, and saturated aqueous sodium chloride, and was then dried and evaporated under reduced pressure to yield a yellow liquid. Kugelrohr distillation yielded the *product* (**15**; R = H) (3.3 g, 80%) as a pale yellow liquid, b.p. 195 °C/0.05 mbar (Found: C, 70.1; H, 8.4%; M^+, 292.1668. $C_{17}H_{24}O_4$ requires C, 69.85; H, 8.25%; *M*, 292.1674); $\nu_{max.}$(film) 1 725 (C=O, ester) and 1 600 cm^{-1} (C=C); δ_H 7.8 (5 H, m, Ph), 4.12 (2 H, q, CH_2CH_3), 4.10 (2 H, q, CH_2CH_3), 2.28 (2 H, t, CH_2CO_2Et), 2.15—1.85 (2 H, m, CH_2), 1.80—1.40 (5 H, m, CH_2, and s at 1.57, Me), 1.22 (3 H, t, CH_2CH_3), and 1.18 (3 H, t, CH_2CH_3).

1-*Ethyl Hydrogen* 2-*Methyl*-2-*phenylhexanedioate* (**16**; R = H).—Diethyl 2-methyl-2-phenylhexanedioate (**15**; R = H) (1.00 g, 3.42 mmol) and sodium hydroxide (154 mg, 3.85 mmol) were refluxed together in aqueous ethanol (50%; 20 cm^3) for 18 h, then the mixture was concentrated under reduced pressure and water (20 cm^3) was added. The aqueous solution was washed with methylene dichloride then acidified with 2M-hydrochloric acid and extracted (CH_2Cl_2). The extracts were dried, then evaporated under reduced pressure to yield a yellow oil. Kugelrohr distillation yielded the *product* (**16**; R = H) (595 mq, 66%) as a pale yellow viscous oil, b.p. 220 °C/0.01 mbar (Found: C, 67.95; H, 7.45%; M^+, 264.1349. $C_{15}H_{20}O_4$ requires C, 68.15; H, 7.65%; *M*, 264.1361); $\nu_{max.}$(film) 3 500—2 500 (OH), 1 725 (C=O, ester), 1 710 (C=O, acid), and 1 600 cm^{-1} (C=C); δ_H 10.67 (1 H, s, OH, exch.), 7.28 (5 H, m, Ph), 4.11 (2 H, q, CH_2CH_3), 2.2 (2 H, t, CH_2CO_2H), 2.2—1.8 (2 H, m, CH_2), 1.75—1.40 (5 H, m, CH_2, and s, Me, at 1.57), and 1.17 (3 H, t, CH_2CH_3).

Attempted Cyclisation of 1-*Ethyl Hydrogen* 2-*Methyl*-2-*phenylhexanedioate* (**16**; R = H).—(i) *Polyphosphoric acid (PPA).* 1-Ethyl hydrogen 2-methyl-2-phenylhexanedioate (1.80 g, 6.8 mmol) was stirred with PPA (20 g) at 60—70 °C for 16 h, then allowed to cool to room temperature. The reaction mixture was poured on to ice (100 cm^3) and extracted (CH_2Cl_2). The extracts were washed with saturated aqueous sodium hydrogen carbonate, dried, and evaporated under reduced pressure to yield a light brown oil which crystallised with time. Recrystallisation from diethyl ether gave colourless crystals, identified as 3-phenylcyclohex-2-enone (0.85 g, 73%), m.p. 58—60 °C (lit.,[19] 61—62 °C) (Found: C, 83.35; H, 6.95%; M^+, 172.0850. Calc. for $C_{12}H_{12}O$; C, 83.7; H, 7.0%; *M*, 172.0888); $\nu_{max.}$(Nujol) 1 655w cm^{-1} (C=O, unsaturated ketone); δ_H (7.6—7.2 (5 H, m, Ph), 6.4 (1 H, t, *J* 1 Hz, vinylic), 2.9—2.65 (2 H, m), 2.55—2.35 (2 H, m), and 2.3—2.0 (2 H, m).

(ii) *Thionyl chloride–aluminium chloride.* Thionyl chloride (3.5 cm^3) was added in one portion to a stirred solution of 1-ethyl hydrogen 2-methyl-2-phenylhexanedioate (**16**; R = H) (1.95 g, 7.38 mmol) in dry methylene dichloride (40 cm^3) at room temperature. The resulting solution was stirred at room temperature for 0.5 h, then the excess of thionyl chloride and methylene dichloride were removed under reduced pressure to yield the crude acid chloride as a pale yellow oil [$\nu_{max.}$(film) 1 780 cm^{-1} (C=O].

Anhydrous aluminium chloride (2.65 g, 19.9 mmol) was added in small portions to a solution of the crude acid chloride in dry methylene dichloride (50 cm^3) at 0 °C. The reaction mixture was allowed to rise to room temperature and was then stirred overnight. 2M-Hydrochloric acid was added and the mixture was treated with methylene dichloride. The organic phase was washed with saturated aqueous sodium hydrogen carbonate, dried, and evaporated under reduced pressure to yield a brown gum. Kugelrohr distillation gave a pale yellow oil (1.5 g), b.p. 150 °C/0.05 mbar, which appeared by t.l.c. (5% ethyl acetate–toluene) and g.l.c. (200 °C) to be one component [Found: C, 73.75; H, 6.65%, molecular weight determination, 225; M^+, 246.1254 (area 45.6), M^+, 200.0840 (area 62.7). $C_{15}H_{18}O_3$ requires C, 73.1; H, 7.35%; *M*, 246.1256; and $C_{13}H_{12}O_2$ requires C, 78.0; H, 6.05%; *M*, 200.0837]; $\nu_{max.}$(film) 1 755 (C=O, cyclopentanone), 1 720 (C=O, ester), and 1 680 cm^{-1} (C=O, aryl ketone); δ_H 8.2—8.0 (1 H, m), 7.75—7.2 (7 H, m, ArH), 4.05 (2 H, q, CH_2, ester), 3.75 (1 H, d), 2.8—1.5 (16 H, m, including s at 1.65 and s at 1.60), and 1.1 (3 H, t). These data suggest that the product isolated was probably a mixture of ethyl 6,7,8,9-tetrahydro-5-methyl-9-oxo-5*H*-benzocycloheptene-5-carboxylate (**18**; R = H) and 5,6,7,8-tetrahydro-5-methyl-5,8-methano-9*H*-benzocycloheptene-9,10-dione (**17**; R = H).

Ethyl 3-*Methoxyphenylacetate* (**13**; R = OMe).—3-Methoxyphenylacetic acid (5.00 g, 0.03 mol), ethanol (50 cm^3), and conc. sulphuric acid (0.25 cm^3) were refluxed together for 2.5 h; the ethanol was then removed under reduced pressure and water (150 cm^3) was added. The mixture was extracted (CH_2Cl_2) and the extracts were washed with saturated aqueous sodium hydrogen carbonate, dried, and evaporated under reduced pressure to yield a pale yellow oil. Kugelrohr distillation yielded the title ester as a colourless liquid (4.75 g, 80%), b.p. 100 °C/0.04 mbar (lit.,[20] b.p. 146—147 °C/14 mmHg) (Found: C, 67.7; H, 7.45%; M^+, 194.0952. Calc. for $C_{11}H_{14}O_3$: C, 68.0; H, 7.25%; *M*, 194.0943); $\nu_{max.}$(film) 1 730 cm^{-1} (C=O, ester); δ_H 7.35—6.7 (4 H, m, ArH), 4.15 (2 H, q, CH_2CH_3), 3.8 (3 H, s, OCH_3), 3.55 (2 H, s, CH_2), and 1.25 (3 H, t, CH_2CH_3).

Ethyl 2-(3-*Methoxyphenyl*)*propionate* (**14**; R = OMe).—Sodamide was prepared by dissolving sodium metal (668 mg, 29.0 mmol) in liquid ammonia (80 cm^3), with a catalytic amount of iron(III) nitrate, at −78 °C. A solution of ethyl 3-methoxyphenylacetate (**13**; R = OMe) (5.034 g, 25.9 mmol) in dry diethyl ether (10 cm^3) was added dropwise and the resulting solution was stirred for 0.5 h at −78 °C. A solution of methyl iodide (1.62 cm^3, 3.690 g, 26.0 mmol) in dry diethyl ether (10 cm^3) was added dropwise and the reaction mixture was stirred for a further 2.5 h at −78 °C, then ammonium chloride (1 g) and diethyl ether (100 cm^3) were added and the ammonia was allowed to evaporate off. 2M-Hydrochloric acid (40 cm^3) was added and the solution was stirred for 15 min. The mixture was treated with ether and the ethereal phase was washed successively with 2M-hydrochloric acid, saturated aqueous sodium hydrogen carbonate, saturated sodium metabisulphite, and saturated aqueous sodium chloride, dried, and evaporated under reduced pressure to yield a yellow oil. Kugelrohr distillation yielded a colourless liquid (4.35 g 81%), b.p. 110 °C/0.05 mbar (Found: C, 69.2; H, 7.95%; M^+, 208.1085. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.75%; *M*, 208.1099); $\nu_{max.}$(film) 1 725 cm^{-1} (C=O); δ_H 7.3—6.7 (4 H, m, ArH), 4.1 (2 H, q, CH_2CH_3), 3.75 (3 H, s, OCH_3), 3.65 (1 H, q, *J* 7 Hz), 1.45 (3 H, d, *J* 7 Hz CH_3), and 1.20 (3 H, t, CH_2CH_3).

Diethyl 2-(3-*Methoxyphenyl*)-2-*methylhexanedioate* (**15**; R =

* Prepared by stirring ethyl γ-bromobutyrate with excess of sodium iodide in acetone overnight at room temperature.

OMe).—(*a*) LDA was prepared by the addition of n-butyllithium (1.55M; 5.0 cm^3, 7.75 mmol) to a stirred solution of diisopropylamine (1.09 cm^3, 0.784 g, 7.75 mmol) in dry THF (15 cm^3) at 0 °C under nitrogen. After 15 min the temperature of the bath was lowered to −72 °C (ethanol–solid CO_2) and a solution of ethyl 2-(3-methoxyphenylpropionate (**14**; R = OMe) (1.375 g, 6.60 mmol) in dry THF (10 cm^3) was added dropwise. The resulting solution was stirred at −72 °C for 1 h after which a white precipitate had formed. A solution of ethyl γ-iodobutyrate (1.876 g, 7.75 mmol) in dry THF (10 cm^3) was added dropwise and the resulting solution was stirred at −72 °C for 1 h. The temperature was allowed to rise slowly to room temperature during 2 h, after which saturated aqueous ammonium chloride then 2M-hydrochloric acid were added. The mixture was extracted with ether and the extracts were washed successively with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium metabisulphite, dried, and evaporated under reduced pressure to yield a pale yellow oil. Kugelrohr distillation yielded the title diester as an almost colourless oil, b.p. 200 °C/0.05 mbar (0.895 g, 42%) (Found: C, 67.4; H, 8.25%; M^+, 322.1780. $C_{18}H_{26}O_5$ requires C, 67.05; H, 8.15%; *M*, 322.1779); $\nu_{max.}$(film) 1 725 cm^{-1} (C=O, ester); δ_H 7.35—6.70 (4-H, m, ArH), 4.14 (2 H, q, $CO_2CH_2CH_3$), 4.12 (2 H, q, $CO_2CH_2CH_3$), 3.80 (3 H, s, OCH_3), 2.30 (2 H, t, CH_2), 2.20—1.40 (4 H, m, 2 × CH_2), 1.75 (3 H, s, Me), 1.25 (3 H, t, $CO_2CH_2CH_3$), and 1.20 (3 H, t, $CO_2CH_2CH_3$).

(b) *In the presence of HMPA.*—Procedure was as above with 2 mol equiv. of HMPA (2.82 cm^3, 15.5 mmol) added neat to the reaction mixture before the addition of ethyl γ-iodobutyrate. When the mixture had been stirred for 15 min at −72 °C, the lithium enolate salt had dissolved to yield a yellow solution. Reaction as above gave an improved yield (70%) of the title diester with identical characteristics.

1-*Ethyl Hydrogen* 2-(3-*Methoxyphenyl*)-2-*methylhexanedioate* (**16**; R = OMe).—Diethyl 2-(3-methoxyphenyl)-2-methylhexanedioate (**15**; R = OMe) (1.02 g, 3.16 mmol), sodium hydroxide (180 mg, 4.50 mmol), ethanol (5 cm^3), and water (5 cm^3) were refluxed for 18 h. The ethanol was removed under reduced pressure, water (25 cm^3) was added, and the solution was extracted with methylene dichloride. The aqueous layer was acidified (2M-hydrochloric acid) and extracted with methylene dichloride. The continued extracts were dried and evaporated under reduced pressure to yield a pale yellow oil (0.59 g). Kugelrohr distillation yielded a colourless oil (0.55 g, 60%), b.p. 220 °C/0.03 mbar, which slowly crystallised (Found: C, 65.9; H, 7.7%; M^+, 294.1477. $C_{16}H_{22}O_5$ requires C, 65.3; H, 7.55%; *M*, 294.1467); $\nu_{max.}$(film) 2 500—3 500 (OH) and 1 700—1 725 cm^{-1} (C=O, ester and acid); δ_H 10.65 (1 H, br s, exch., CO_2H), 7.35—6.65 (4 H, m, ArH), 4.12 (2 H, q, $CO_2CH_2CH_3$), 3.80 (3 H, s, OCH_3), 2.32 (2 H, t, *J* 7 Hz, CH_2), 2.15—1.30 (4 H, m, CH_2CH_2), 1.55 (3 H, s, Me), and 1.18 (3 H, t, $CO_2CH_2CH_3$).

5,6,7,8-*Tetrahydro*-3-*methoxy*-5-*methyl*-5,8-*methano*-5H-*benzocycloheptene*-9,10(8H)-*dione* (**17**; R = OMe).—(*a*) 1-Ethyl hydrogen 2-(3-methoxyphenyl)-2-methylhexanedioate (**16**; R = OMe) (0.420 g, 1.43 mmol) and PPA (10 cm^3) were mechanically stirred and slowly heated to 45 °C. The bright yellow reaction mixture was stirred at 45 °C for 24 h, then poured onto ice. The mixture was extracted (CH_2Cl_2) and the extracts were washed with saturated aqueous sodium hydrogen carbonate, dried, and evaporated under reduced pressure to yield a pale yellow oil which recrystallised on trituration with diethyl ether. Recrystallisation from ethyl acetate gave the *product* (**17**; R = OMe) as colourless plates (250 mg, 76%), m.p. 99 °C (Found: C, 72.7; H, 6.05%; M^+, 230.0962. $C_{14}H_{14}O_3$ requires C, 73.05; H, 6.15%; *M*, 230.0943); $\nu_{max.}$(Nujol) 1 755 (C=O, 5-membered ring), 1 675 (C=O, aryl ketone), and 1 600 cm^{-1} (C=C); δ_H 8.10 (1 H, m, ArH), 7.00—6.95 (2 H, m, ArH), 3.90 (3 H, s, OCH_3) 3.70 (1 H, d, 8-H), 2.50—2.35 (1 H, m), 2.20—2.10 (1 H, m), 2.05—1.90 (1 H, m), 1.85—1.70 (1 H, m), and 1.60 (3 H, s, Me); δ_C 206.883 (s), 195.361 (s), (d), 124.739 (s), 113.576 (d), 109.266 (d), 61.945 (d), 55.817 (q), 51.994 (s), 34.703 (t), 21.416 (t), and 15.895 p.p.m. (q)

(*b*) 1-Ethyl hydrogen 2-(3-methoxyphenyl)-2-methylhexanedioate (**16**; R = OMe) (1.30 g, 4.4 mmol) and phosphorus pentaoxide (3.25 g, 23 mmol) were stirred in methanesulphonic acid (98%; 22 cm^3, 0.33 mol) at 70 °C for 24 h. The cooled reaction mixture was poured onto cold water (50 cm^3) and extracted with methylene dichloride. The extracts were washed successively with water and saturated aqueous sodium hydrogen carbonate, then dried and evaporated under reduced pressure to yield a dark brown oil which crystallised on trituration with diethyl ether. Recrystallisation from ethyl acetate yielded the title product as white plates (690 mg, 68%), identical on comparison (m.p., t.l.c., i.r.) with a genuine sample.

(*c*) 1-Ethyl hydrogen 2-(3-methoxyphenyl)-2-methylhexanedioate (**16**; R = OMe) (1.50 g, 5.08 mmol) and conc. sulphuric acid (98%; 25 cm^3) were stirred together at room temperature for 5 h. The reaction mixture was poured onto ice and extracted with methylene dichloride. The extracts were washed with saturated aqueous sodium hydrogen carbonate, dried, and evaporated under reduced pressure to yield an oil which crystallised (50 mg) and appeared by comparison (m.p., t.l.c., i.r.) to be 5,6,7,8-tetrahydro-3-methoxy-5-methyl-5,8-methano-5*H*-benzocycloheptene-9,10(8*H*)-dione (**17**; R = OMe).

Starting material (500 mg) was recovered from the sodium hydrogen carbonate washings.

Prolonged reaction time (18 h) gave a slightly higher yield of diketone (100 mg) but no starting material could be recovered.

(*d*) Thionyl chloride (3.0 cm^3, 0.04 mol) was added in one portion to a stirred solution of 1-ethyl hydrogen 2-(3-methoxyphenyl)-2-methylhexanedioate (**16**; R = OMe) (2.00 g, 6.77 mmol) in dry methylene dichloride (20 cm^3) at room temperature. The resulting solution was stirred at room temperature for 0.5 h then the excess of thionyl chloride and methylene dichloride were removed under reduced pressure to yield the crude acid chloride, $\nu_{max.}$(film) 1 780 cm^{-1} (C=O.

Anhydrous aluminium chloride (2.55 g, 19.1 mmol) was added in portions to a stirred solution of the crude acid chloride in dry methylene dichloride (50 cm^3) at 0 °C. After 0.5 h, 2M-hydrochloric acid (50 cm^3) was added and the organic layer was washed with saturated aqueous sodium hydrogen carbonate, dried, and evaporated under reduced pressure to yield a light yellow oil, $\nu_{max.}$(film) 1 725 (C=O, ester) and 1 680 cm^{-1} (C=O, aryl ketone).

After 15 min, the oil rapidly discoloured and eventually crystallised, to yield 5,6,7,8-tetrahydro-3-methoxy-5-methyl-5,8-methano-9*H*-benzocycloheptene-9,10-dione (**17**; R = OMe) (1.05 g, 67%), identified by comparison with a genuine sample (m.p., t.l.c., i.r.).

6,7,8,9-*Tetrahydro*-3-*methoxy*-5-*methyl*-9-*oxo*-5H-*benzocycloheptene*-5-*carboxylic Acid* (**21**).—(*a*) 5,6,7,8-Tetrahydro-3-methoxy-5-methyl-5,8-methanobenzocycloheptene-9,10-dione (**17**; R = OMe) (200 mg, 0.87 mmol) and dil. aqueous sodium hydroxide (2% w/v; 19 cm^3) were stirred at room temperature for 1 h until all material had dissolved. The reaction mixture was then acidified and extracted (CH_2Cl_2), and the extracts were dried and evaporated under reduced pressure to yield a white solid (195 mg, 90%), m.p. 148 °C, which recrystallised from methanol (Found: C, 67.65; H, 6.55%; M^+, 248.1036. $C_{14}H_{16}O_4$ requires C, (67.75; H, 6.05%; *M*, 248.1049); $\nu_{max.}$(Nujol) 3 240 (O–H), 1 700 (C=O), and 1 600 cm^{-1} (C=C); δ_H 7.5 1 H, d, ArH), 6.95—6.85 (2 H, m, ArH), 3.85 (3 H, s, OCH_3), 3.2 (1 H, br s,

exch.), 2.6—2.15 (3 H, m), 1.9—1.6 (5 H, m, with s at 1.65), and 1.5—1.25 (1 H, m).

(*b*) Reaction as above using saturated aqueous sodium hydrogen carbonate (20 cm^3) in place of sodium hydroxide solution for 24 h at room temperature yielded the same product (87%), identified by comparison (m.p., i.r., t.l.c.).

N-*Benzyl*-6,7,8,9-*tetrahydro*-3-*methoxy*-5-*methyl*-9-*oxo*-5H-*benzocycloheptene*-5-*carboxamide* (**22**).—(*a*) To a stirred suspension of sodium hydride (60% oil dispersion; 0.30 g, 0.075 mol) in sodium-dried toluene (100 cm^3) under nitrogen at room temperature was added benzylamine (8.1 cm^3, 0.074 mol). The resulting solution was stirred at room temperature for 1.5 h, then a solution of 5,6,7,8-tetrahydro-3-methoxy-5-methyl-5,8-methanobenzocycloheptene-9,10-dione (**17**; R = OMe) (17.1 g, 0.074 mol) in sodium-dried toluene (100 cm^3) was added dropwise. The reaction mixture was heated at 75 °C for 3 h then allowed to cool to room temperature before water (100 cm^3) and 2M-hydrochloric acid (100 cm^3) were added. After 0.5 h, a white precipitate developed and this was filtered off (18.5 g). The filtrate was extracted with diethyl ether and the extracts were washed with saturated aqueous sodium hydrogen carbonate, dried, and evaporated under reduced pressure to yield a yellow oil which crystallised on being cooled (2.5 g). The combined material was recrystallised from 10% aqueous ethanol to give the *title product* (19.0 g, 76%), m.p. 168—170 °C (Found: C, 75.05; H, 6.95; N, 3.95%; M^+, 337.1672. $C_{21}H_{23}NO_3$ requires C, 74.75; H, 6.9; N, 4.15%; *M*, 337.1678); $\nu_{max.}$(Nujol) 3 370 (N–H), 1 630 (C=O), [shoulder at 1 635 (C=O], and 1 605 cm^{-1} (C=C); δ_H 7.3—6.6 (8 H, m, ArH), 5.0 (1 H, d, *J* 15 Hz, NHC*H*H′), 4.6 (1 H, d, *J* 15 Hz, NHCH*H*′), 3.8 (3 H, s, OCH_3), 3.25 (1 H, br, exch., NH), and 2.1—0.9 (9 H, m, $[CH_2]_3$, s at 1.6, Me); δ_C 175.577 (s), 160.588 (s), 140.514 (s), 140.028 (s), 134.204 (s), 128.865 (2 C, d), 127.894 (2 C, d), 127.166 (d), 122.555 (d), 111.149 (d), 110.479 (d), 87.487 (s), 55.453 (q), 46.595 (s), 44.411 (t), 35.188 (t), 34.521 (t), 22.023 (t), and 21.113 p.p.m. (q).

(*b*) To a stirred solution of 6,7,8,9-tetrahydro-3-methoxy-5-methyl-9-oxo-5*H*-benzocycloheptene-5-carboxylic acid (**21**) (0.500 g, 2.01 mmol), triethylamine (0.30 cm^3, 2.15 mmol), and 2-chloro-*N*-methylpyridinium iodide (0.515 g, 2.02 mmol) in acetonitrile (20 cm^3) at room temperature was added benzylamine (0.23 cm^3, 2.11 mmol). After 5 min, a white precipitate developed. The reaction mixture was stirred for a further 15 min then the solvent removed under reduced pressure and methylene dichloride (50 cm^3) was added. The resulting solution was washed successively with 2M-hydrochloric acid and saturated aqueous sodium hydrogen carbonate, dried, and evaporated under reduced pressure to yield a light brown viscous oil which was distilled at 200 °C/0.05 mbar (Kugelrohr) and crystallised after 1 week. This product was identified as *N*-benzyl-6,7,8,9-tetrahydro-3-methoxy-5-methyl-9-oxo-5*H*-benzocycloheptene-5-carboxamide (**22**) (80%) by comparison with an authentic sample (t.l.c., i.r., n.m.r., m.s.) from method (*a*).

N-*Benzyl*-8-*bromo*-6,7,8,9-*tetrahydro*-3-*methoxy*-5-*methyl*-9-*oxo*-5H-*benzocycloheptene*-5-*carboxamide* (**23**).—(*a*) To a stirred solution of *N*-benzyl-6,7,8,9-tetrahydro-3-methoxy-5-methyl-9-oxo-5*H*-benzocycloheptene-5-carboxamide (**22**) (4.00 g, 11.8 mmol) in dry THF (50 cm^3) at 0 °C was added dropwise a solution of phenyltrimethylammonium perbromide (4.45 g, 11.8 mmol) in THF (50 cm^3). The reaction mixture was stirred at 0 °C for 1 h, then allowed to rise to room temperature and poured into saturated aqueous sodium hydrogen carbonate (100 cm^3). The mixture was extracted with ether and the extracts were washed with water then dried and evaporated under reduced pressure to yield a pale yellow oil which crystallised upon trituration. Recrystallisation from ethyl acetate gave the title *bromo compound* as colourless crystals (4.10 g, 83%), m.p. 130 °C (Found: C, 61.05; H, 5.45; N, 3.25; Br, 18.85%; M^+, 417.0744, 415.0775. $C_{21}H_{22}BrNO_3$ requires C, 60.6; H, 5.35; N, 3.35; Br, 19.2%; *M*, 417.0764, 415.0783); $\nu_{max.}$ (Nujol) 3 320 (N–H), 1 635 (C=O) [shoulder at 1 630 (C=O)], and 1 605 cm^{-1} (C=C); δ_H 7.45 (1 H, d, ArH_a), 7.4—7.15 (5 H, m, ArH), 6.95—6.8 (2 H, m, ArH), 4.95 (1 H, d, *J* 13 Hz, NHC*H*H′), 4.5 (1 H, d, *J* 13 Hz, NHCH*H*′), 4.2 (1 H, dd, CHBr), 3.85 (3 H, s, OCH_3), 3.5 (1 H, br s, exch., NH), 2.25—2.1 (1 H, m), 2.05—1.8 (1 H, m), and 1.7—1.4 [5 H, m, including s (Me) at 1.65]; δ_C 175.091 (s), 161.258 (s), 139.722 (s), 139.543 (s), [129.530, 128.923 (2 C), 128.438 (2 C), 127.530, and 125.768, together *m*], 111.086 (d), 110.600 (d), 87.002 (s), 55.695 (q), 55.513 (d), 46.231 (s), 44.471 (t), 36.463 (t), 34.400 (t), and 20.627 p.p.m. (q).

(*b*) A solution of bromine in acetic acid (3% v/v solution; 5.06 cm^3, 2.94 mmol) was added in one portion to a stirred solution of the keto amide (**22**) (1.00 g, 2.96 mmol) in acetic acid (25 cm^3) at room temperature. After 15 min, the solution was almost colourless and the acetic acid was evaporated off under reduced pressure to leave a white powder (1.15 g, 94%), m.p. 118—121 °C (Found: C, 61.05; H, 5.4; N, 3.15; Br, 19.15%; M^+, 417.0743, 415.0752); $\nu_{max.}$(Nujol) 3 130 (N–H), 1 625v br (C=O), and 1 605 cm^{-1} (C=C); δ_H 7.7—6.7 (8 H, m, ArH), 5.1—4.6 (2 H, m), 4.2—3.8 (5 H, m, including s at 3.9 and s at 3.8), and 2.4—1.4 (7 H, m, including s at 1.59 and s at 1.61). This product was a mixture of compounds (**23**) and (**23a**).

3-*Benzyl*-3,4-*dihydro*-8-*methoxy*-1-*methyl*-1,4-*ethano*-1H-3-*benzazepine*-2,5-*dione* (**24**).—A solution of *N*-benzyl-8-bromo-6,7,8,9-tetrahydro-3-methoxy-5-methyl-9-oxo-5*H*-benzocycloheptene-5-carboxamide (**23**) (3.00 g, 7.2 mmol) in sodium-dried toluene (50 cm^3) was added dropwise to a stirred suspension of sodium hydride (60% oil dispersion; 0.45 g, 11.2 mmol) and 15-crown-5 ether (0.15 cm^3, 0.75 mmol) in sodium-dried toluene (100 cm^3) at room temperature under nitrogen. The reaction mixture was stirred overnight at room temperature, then water and 2M-hydrochloric acid were added. The mixture was extracted with more toluene and the extracts were washed with saturated aqueous sodium hydrogen carbonate, dried, and evaporated under reduced pressure to yield a colourless gum which crystallised on trituration. Recrystallisation from ethyl acetate–light petroleum (b.p. 60—80 °C) yielded the *title compound* as crystals (1.84 g, 76%), m.p. 144 °C (Found: C, 75.2; H, 6.3; N, 4.05%; M^+, 335.1517. $C_{21}H_{21}NO_3$ requires C, 75.2; H, 6.3; N, 4.2%; M^+, 335.1521); $\nu_{max.}$(Nujol) 1 665 (C=O, aryl), 1 630 (C=O, lactam), and 1 600 cm^{-1} (C=C); δ_H 8.10 (1 H, d, *J* 8 Hz, ArH_a), 7.3—7.15 (5 H, m, ArH), 7.05 (1 H, d, *J* 3 Hz, ArH), 6.90 (1 H, dd, *J* 3 and 8 Hz, ArH), 4.85 (1 H, d, *J* 14 Hz, NC*H*H′Ph), 4.4 (1 H, d, *J* 14 Hz, NCH*H*′Ph), 4.2 (1 H, m, bridgehead), 3.9 (3 H, s, OCH_3), 2.3—1.9 (4 H, m, $[CH_2)_2$), and 1.8 (3 H, s, Me); δ_C 193.963 (s), 173.878 (s), 164.539 (s), 149.129 (s), 137.053 (s), 133.534 (d), [129.044 (2 C), 128.680 (2 C), 128.137, and 126.254, together m], 112.605 (d), 112.056 (d), 65.767 (d), 60.489 (s), 55.635 (q), 50.356 (t), 47.687 (t), 34.460 (t), and 23.479 p.p.m. (q).

Analogous attempted reactions in the absence of 15-crown-5 ether gave no apparent reaction.

3-*Benzyl*-4,5-*dihydro*-8-*hydroxy*-1-*methyl*-1,4-*ethano*-1H-3-*benzazepin*-2(3*H*)-*one* (**25**).—3-Benzyl-3,4-dihydro-8-methoxy-1-methyl-1,4-ethano-1*H*-3-benzazepine-2,5-dione (**24**) (4.17 g, 12.4 mmol), potassium hydroxide (18.35 g), and hydrazine hydrate (31.5 cm^3, 100%) were stirred in digol (250 cm^3) for 2.5 h at 120 °C; the condenser then was removed and the reaction mixture was slowly heated to 180 °C during 4 h. The condenser was replaced and the mixture was maintained at that temperature for a further 3 h. After having cooled, the mixture was poured onto ice and extracted with chloroform. The extracts were washed with 2M-sodium hydroxide and these

washings were added to the alkaline aqueous mother liquor. The combined alkaline solutions were acidified and extracted ($CHCl_3$), and the extracts were dried and evaporated under reduced pressure to yield an off-white solid. Recrystallisation from methanol–acetone yielded the *title product* as needles (3.13 g, 82%), m.p. 196—199 °C (Found: C, 77.8; H, 6.95; N, 4.4%; M^+, 307.1551. $C_{20}H_{21}NO_2$ requires C, 78.15; H, 6.9; N, 4.4%; *M*, 307.1572); $\nu_{max.}$($CHCl_3$) 3 280 (O–H), 1 635 (C=O), and 1 605 cm^{-1} (C=C); δ_H[$^2H_6$]DMSO) 9.15 (1 H, s, exch., OH), 7.3 (5 H, s, ArH), 7.0—6.5 (3 H, m, ArH), 4.8 (1 H, d, *J* 15 Hz, NC*H*H'Ph), 4.35 (1 H, d, *J* 15 Hz, NCH*H'*Ph), 3.9—3.6 (1 H, m, bridgehead), 3.1—2.85 (2 H, m, benzylic), 2.3—1.7 (4 H, m, $[CH_2]_2$), and 1.5 (3 H, s, Me); δ_C([$^2H_6$]DMSO) 174.121 (s), 155.560 (s), 141.727 (s), 138.509 (s), 132.262 (d), 128.622 (2 C, d), 127.831 (2 C, d), 127.287 (d), 125.526 (s), 113.877 (d), 111.814 (d), 52.359 (d), 48.172 (t), 44.653 (s), 37.494 (t), 36.584 (t), 26.270 (t), and 23.722 p.p.m. (q).

From the initial chloroform washings, a neutral product could be isolated in varying but minor amounts and was identified as 3-benzyl-4,5-dihydro-8-methoxy-1-methyl-1,4-ethano-1*H*-3-benzazepin-2(3*H*)-one (**26**) by comparison (i.r., n.m.r., t.l.c.), with authentic material (see below).

3-*Benzyl*-4,5-*dihydro*-8-*methoxy*-1-*methyl*-1,4-*ethano*-1H-3-*benzazepin*-(2(3H)-*one* (**26**).—3-Benzyl-3,4-dihydro-8-hydroxy-1-methyl-1,4-ethano-1*H*-3-benzazepin(2(5*H*)-one (**25**) (0.50 g, 1.6 mmol), potassium hydroxide (0.175 g), methyl iodide (1.5 cm^3, excess), ethanol (10 cm^3), and water (10 cm^3) were heated together at 60 °C for 8 h then allowed to cool slightly and concentrated under reduced pressure. Methylene dichloride and water were added and the organic phase was washed successively with 2M-sodium hydroxide and saturated aqueous sodium metabisulphite, then dried and evaporated under reduced pressure to yield a pale yellow viscous oil. Kugelrohr distillation yielded a colourless viscous oil (395 mg, 77%), b.p. 200 °C/0.02 mbar (Found: C, 78.6; H, 7.3; N, 4.35%; M^+, 321.1730. $C_{21}H_{23}NO_2$ requires C, 78.45; H, 7.2; N, 4.35%; *M*, 321.1729); $\nu_{max.}$(film) 1 650br (C=O, lactam) and 1 605 cm^{-1} (C=C); δ_H 7.4—7.2 (5 H, m, ArH), 6.95 (2 H, m, ArH), 6.70 (1 H, dd, ArH), 4.95 (1 H, d, *J* 17 Hz, NC*H*H'Ph), 4.40 (1 H, d, *J* 17 Hz, NCH*H'*Ph), 3.80 (3 H, s, OCH_3), 3.75 (1 H, m, bridgehead), 3.15 (1 H, dd, benzylic), 2.90 (1 H, dd, benzylic), 2.30—1.75 (4 H, m, $[CH_2)_2$), and 1.70 (3 H, s, Me); δ_C 175.334 (s), 158.351 (s), 142.455 (s), 138.266 (s), 132.384 (d), [128.923 (2 C), 128.438 (2 C), 127.773, and 127.467, together m], 112.241 (d), 111.693 (d), 55.392 (q), 52.722 (d), 49.143 (t), 45.624 (s), 38.101 (t), 37.191 (t), 27.119 (t), and 23.904 p.p.m. (q).

3-*Benzyl*-2,3,4,5-*tetrahydro*-1-*methyl*-1,4-*ethano*-1H-3-*benzazepin-8-ol* (**27**).—A solution of 3-benzyl-4,5-dihydro-8-hydroxy-1-methyl-1,4-ethano-1*H*-3-benzazepin-2(3*H*)-one (**25**) (1.12 g, 3.6 mmol) in dry THF (50 cm^3) was added dropwise to a stirred suspension of lithium aluminium hydride (90%; 0.29 g, 6.9 mmol) in dry THF (75 cm^3) at room temperature under nitrogen. The resulting solution was refluxed for 3 h and allowed to cool. Water (0.3 cm^3), 15% aqueous sodium hydroxide (0.3 cm^3), and water (0.9 cm^3) were cautiously added in that order. After 0.5 h, the resulting suspension was filtered and the residue was washed twice with methylene dichloride. The combined filtrates were evaporated under reduced pressure to yield a pale yellow gum, which was dissolved in methylene dichloride and the solution was then washed three times with 2M-hydrochloric acid. The acid washings were basified with sodium hydrogen carbonate, extracted (CH_2Cl_2), and the extracts were dried and evaporated under reduced pressure to yield a light brown oil. Kugelrohr distillation yielded a colourless viscous oil (420 mg, 40%), b.p. 220 °C/0.02 mbar. (Found: C, 81.65; H, 7.9; N, 4.5%; M^+, 293.1779. $C_{20}H_{23}NO$ requires C, 81.85; H, 7.9; N, 4.75%; *M*, 293.1780); $\nu_{max.}$(film) 3 400 (OH) and 1 605 cm^{-1} (C=C); δ_H (7.4—7.15 (5 H, m, ArH), 6.95 (1 H, d, ArH), 6.65—6.5 (2 H, m, ArH), 5.0 (H, v br s, exch., OH), 3.70 (1 H, d, *J* 15 Hz, NC*H*H'Ph), 3.60 (1 H, d, *J* 15 Hz, NCH*H'*Ph), 3.40 (1 H, br d, *J* 18 Hz, 5-*H*H'), 3.05 (1 H, br s, 4-H), 2.80 (1 H, d, *J* 11 Hz, 2-*H*H'), 2.70 (1 H, d, *J* 11 Hz, 2-H*H'*), 2.60 (1 H, dd, *J* 18 and 6 Hz, 5-H*H'*), 2.05—1.8 (2 H, m), 1.60—1.45 (2 H, m), and 1.20 (3 H, s, Me); δ_C 153.5068 (s), 149.0373 (s), 139.3485 (s), 131.4092 (d), 129.8949 (s), 128.8363 (2 C, d), 128.2041 (2 C, d), 126.8662 (d), 112.4138 (d), 111.6199 (d), 62.8083 (t), 59.2503 (t), 51.3993 (d), 36.6823 (s), 35.2855 (t), 34.1094 (t), 28.1843 (q), and 25.0968 p.p.m. (t).

3-*Benzyl*-2,3,4,5-*tetrahydro*-8-*methoxy*-1-*methyl*-1,4-*ethano*-1H-3-*benzazepine* (**28**).—A solution of 3-benzyl-3,4-dihydro-8-methoxy-1-methyl-1,4-ethano-1*H*-3-benzazepin-2(5*H*)-one (**26**) (1.08 g, 3,4 mmol) in dry THF (75 cm^3) was added dropwise to a stirred suspension of lithium aluminium hydride (90%; 0.45 g, 10.7 mmol) in dry THF (75 cm^3) at room temperature under nitrogen. The resulting mixture was refluxed for 5 h and allowed to cool. Water (0.45 cm^3), 15% aqueous sodium hydroxide (0.45 cm^3), and water (1.35 cm^3) were cautiously added in that order. After 0.5 h, the resulting suspension was filtered and the residue was washed twice with methylene dichloride. The combined filtrates were evaporated under reduced pressure to yield a pale yellow gum, which was dissolved in methylene dichloride; the solution was washed twice with water, dried, and evaporated under reduced pressure to yield a colourless oil. Kugelrohr distillation yielded the *title product* (605 mg, 58%), b.p. 180 °C/0.05 mbar (Found: C, 81.75; H, 8.25; N, 4.95%; M^+, 307.1921. $C_{21}H_{25}NO$ requires C, 82.05; H, 8.2; N, 4.55%; *M*, 307.1936); $\nu_{max.}$ (film) 1 610 cm^{-1} (C=C); δ_H 7.4—7.2 (5 H, m, ArH), 7.1 (1 H, d, ArH), 6.8 (1 H, d, ArH), 6.7 (1 H, dd, ArH), 3.8 (3 H, s, OCH_3), 3.75 (1 H, d, *J* 14 Hz, NC*H*H'Ph), 3.65 (1 H, d, *J* 14 Hz, NCH*H'*Ph), 3.4 (1 H, br d, *J* 18 Hz, 5-H), 3.1 (1 H, br s, 4-H), 2.85 (1 H, d, *J* 11 Hz, 2-H), 2.75 (1 H, d, *J* 11 Hz, 2-H), 2.7 (1 H, dd, *J* 18 and 6 Hz, 5-H), 2.1—1.9 (2 H, m, CH_2), and 1.8—1.2 (5 H, m, including s at 1.35, CH_2 and Me); δ_C 157.5205 (s), 148.9932 (s), 139.9219 (s), 131.1740 (d), 130.3212 (s), 128.5717 (2 C, d), 128.1600 (2 C, d), 126.7192 (d), 111.1053 (d), 109.8409 (d), 62.9112 (t), 59.2650 (t), 55.2072 (q), 51.4140 (d), 36.8734 (s), 35.4326 (t), 34.2417 (t), 28.2137 (q), and 25.2292 p.p.m. (t).

3-*Benzyl*-2,3,4,5-*tetrahydro*-8-*methoxy*-1-*methyl*-1,4-*ethano*-1H-3-*benzazepin-5-ol* (**29**).—A solution of 3-benzyl-3,4-dihydro-8-methoxy-1-methyl-1,4-ethano-1*H*-3-benzazepine-2,5-dione (**24**) (1.68 g, 5.0 mmol) in dry THF (75 cm^3) was added dropwise to a stirred suspension of lithium aluminium hydride (90%; 0.63 g, 15.0 mmol) in dry THF (75 cm^3) at room temperature under nitrogen. The resulting mixture was refluxed for 4 h, then allowed to cool. Water (0.63 cm^3), 15% aqueous sodium hydroxide (0.63 cm^3), and water (1.89 cm^3) were cautiously added in that order. After 0.5 h, the resulting suspension was filtered and the residue was washed twice with methylene dichloride. The combined filtrates were evaporated under reduced pressure to yield a pale yellow oil which was dissolved in methylene dichloride and the solution was washed with 2M-hydrochloric acid (× 3). The acid washings were basified (2M-sodium hydroxide) and extracted (CH_2Cl_2). These extracts were dried and evaporated under reduced pressure to yield the product (**29**) as a light brown oil (750 mg, 46%) (Found: N, 4.35%; M^+, 323.1894. $C_{21}H_{25}NO_2$ requires N, 4.2%; *M*, 323.1885. Carbon analyses were consistently 2% in error); $\nu_{max.}$($CHCl_3$) 3 400 (OH) and 1 605 cm^{-1} (C=C); δ_H 7.6—7.1 (6 H, m, ArH), 6.9—6.7 (2 H, m, ArH), 4.95 (1 H, br d, *J* 6 Hz, C*H*OH), 3.9—3.6 (5 H, m, including s at 3.8, OCH_3 and

NCH_2Ph), 3.2—2.9 (1 H, m, bridgehead), 2.7 (2 H, br s, NCH_2), 2.55 (1 H, br s, exch., OH), 2.1—1.5 (4 H, m, $[CH_2]_2$), and 1.35 (3 H, s, Me).

3-Benzyl-3,4-dihydro-8-methoxy-1-methyl-1,4-ethano-1H-3-benzazepin-5(2H)-one (**30**).—Chromium trioxide (1.29 g), dry pyridine (2.1 cm^3), and dry methylene dichloride were stirred for 0.5 h at 20 °C. To this solution was then added dropwise a solution of 3-benzyl-2,3,4,5-tetrahydro-8-methoxy-1-methyl-1,4-ethano-1*H*-3-benzazepin-5-ol (**29**); 0.5 g) in methylene dichloride (12.5 cm^3). After 0.5 h, the mixture was filtered and the residue was washed with methylene dichloride. Evaporation of the filtrate yielded a brown gum (0.5 g) which gave the *product* (**30**) (0.4 g) as a gum on flash chromatography with ethyl-acetate–light petroleum (b.p. 60—80 °C) 3:7) as eluant (Found: C, 78.15; H, 7.45; N, 4.45%; M^+ 321.1720. $C_{21}H_{23}NO_2$ requires C, 78.5; H, 7.15; N, 4.35%; *M*, 321.19); $\nu_{max.}$(film) 1 660 cm^{-1} (C=O); δ_H 8.18 (1 H, d, *J* 9 Hz, 6-H), 7.2 (5 H, s, Ph), 6.75—6.9 (2 H, m, 7- and 9-H), 3.8 (3 H, s, OMe), 3.4—3.7 (3 H, m, 2-H_2 + 4-H) 2.96 (1 H, d, *J* 11 Hz, NC*H*HPh), 2.43 (1 H, d, *J* 11 Hz, NCH*H*Ph), 1.4 (3 H, s, Me), and 1.2—2.2 (4-H, m, CH_2CH_2).

6,7-Dihydro-10-hydroxyimino-5,8-methano-3-methoxy-5-methyl-5H-benzocyclohepten-9(8H)-one (**31**).—6,7-Dihydro-3-methoxy-5-methyl-5,8-methano-5*H*-benzocycloheptene-9,10-(8*H*)-dione (**17**; R = OMe) (0.5 g, 2.17 mmol) and hydroxylamine hydrochloride (0.160 g, 2.30 mmol) were refluxed together with pyridine (0.5 cm^3) in ethanol (10 cm^3) for 1 h. Ethanol was removed under reduced pressure, then methylene dichloride (50 cm^3) was added and the resulting solution was washed with water, dried, and evaporated under reduced pressure to yield an oil which crystallised on trituration with diethyl ether. Recrystallisation from 50% aqueous ethanol yielded the *mono-oxime* (**31**) as crystals (0.45 g, 84%), m.p. 196 °C (Found: C, 68.9; H, 6.4; N, 5.45%; M^+, 245.1037. $C_{14}H_{15}NO_3$ requires C, 68.55; H, 6.15; N, 5.7%; *M*, 245.1052); $\nu_{max.}$(Nujol) 3 330 (O–H, oxime), 1 680 (C=O, aryl ketone), and 1 655 cm^{-1} (C=N, oxime); δ_H 8.60 (1 H, s, exch.), 8.05—7.95 (1 H, m, ArH), 6.90—6.70 (2 H, m, ArH), 4.40 (1 H, d, *J* 7 Hz), 3.85 (3 H, s, OCH_3), and 2.50—1.50 [7 H, m, including s (Me) at 1.65].

Attempted Beckmann Rearrangement of 6,7-Dihydro-10-hydroxyimino-3-methoxy-5-methyl-5,8-methano-5H-benzocyclohepten-9(8H)-one (**31**).—Phosphorus pentachloride (1.66 g, 8.0 mmol) was added in portions to a stirred solution of the oxime (**31**) (1.00 g, 4.1 mmol) in dry methylene dichloride (70 cm^3) at room temperature. After 45 min, dil. aqueous ammonium hydroxide (25 cm^3) was added and the mixture was stirred for 10 min. The organic layer was washed successively with 2M-hydrochloric acid and water, dried, and evaporated under reduced pressure to yield a yellow oil (760 mg). Attempted distillation resulted in decomposition (Found: M^+, 227.0943. $C_{14}H_{13}NO_2$ requires *M*, 227.0946); $\nu_{max.}$(film) 2 240 (C≡N), 2 190, 1 750 (C=O, ketone), 1 675 (C=O, aryl ketone), and 1 595 cm^{-1} (C=C); δ_H 7.95 (1 H, d, ArH), 7.1—6.8 (2 H, m, ArH), 5.45 (1 H, d, *J* 15 Hz), 4.1—3.8 (4 H, m, including s at 3.9, OCH_3 and CHCN), and 3.01—1.5 (5 H, m, including s at 1.65, Me and CH_2). Traces of starting material (**17**; R = OMe) were also apparent in ^1H n.m.r. and i.r. spectra). These data suggest that the product was 5,7-dihydro-2-methoxy-9-methyl-5-oxo-6*H*-benzocycloheptene-6-carbonitrile (**33**) (see Discussion section).

Some measure of purification could be obtained by extraction of the major product (**33**) into 2M-sodium hydroxide and subsequent isolation: $\nu_{max.}$(film) 2 240 (C≡N), 1 675 (C=O, aryl), and 1 595 cm^{-1} (C=C). However, attempted chromatography and distillation resulted in decomposition.

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