# Synthesis and Reactions of 1,2,3,4,5,6-Hexahydro-3,6-dimethyl-2,6-methano-3-benzazocin-11-one (2,5-Dimethyl-9-oxo-6,7-benzomorphan); A New Route to 3-Benzazocines [1]

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In second-order Beckmann reactions oximes of the title compound (1) and 1-[2-(*N*,*N*-dimethylamino)-ethyl]-3,4-dihydro-1-methylnaphthalen-2(1*H*)-one (14) gave 1,2,3,4-tetrahydro-3,6-dimethyl-3-benzazocine-2-carbonitrile (8) and (*E*)-2-[*o*-(2-cyanoethyl)phenyl]-4-dimethylaminobut-2-ene (15), respectively. The benzazocine-2-carbonitrile (8) was hydrolysed to the corresponding carboxylic acid (10), which was converted into its ethyl (11) and methyl esters (12) and reduced to the 2-aminomethyl-3-benzazocine (13). An attempt to prepare the ethyl ester (11) in hot 10% aqueous ethanol saturated with hydrogen chloride resulted in ring contraction, to give 1-methyl-2-(*N*-methylaminomethyl)naphthalene (17). In a Pinner reaction in ethanol the benzazocine-2-carbonitrile (8) gave the corresponding amide (9) instead of the ethyl imidate.

An evaluation of the May and Murphy synthesis of the title compound (1) is given. 1-[2-(*N*-Benzyl-*N*-methylamino)ethyl]-3,4-dihydro-1-methylnaphthalen-2(1*H*)-one (20), prepared from 1-[2-(*N*,*N*-dimethylamino)ethyl]-3,4-dihydro-1-methylnaphthalen-2(1*H*)-one and benzyl chloride, was converted into its ethylene acetal (31; R = $CH_2Ph$) and removal of the benzyl group followed by hydrolysis of the deprotected acetal gave the 2,3,5,9b-tetrahydrobenz[*e*]indole (23; R = H), a key intermediate in the Takeda-style synthesis of the title compound. 1-[2-(*N*-Chloro-*N*-methylamino)ethyl]-3,4-dihydro-1-methylnaphthalen-2(1*H*)-one ethylene acetal (31; R = Cl) was prepared but failed to cyclise under various conditions.

Under the same conditions 1-[2-(*N*-benzyl-*N*-methylamino)ethyl]-3,4-dihydro-1-methylnaphthalen-2(1*H*)-one (20; R = $CH_2Ph$) failed to brominate whilst the corresponding 1-[2-(*N*-ethoxycarbonyl-*N*-methylamino)ethyl] compound (22; $R^1$ = Et, $R^2$ = H) gave its 3,3-dibromo derivative (28).

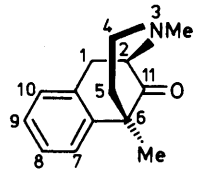
Although a variety of routes to the 3-benzazocine system have been published,[2,3] many of them tedious, none has involved conversion of a 2,6-methano-3-benzazocine into a 3-benzazocine. Recent improvements in the synthesis of the 2,6-methano-3-benzazocinone (1) [4,5] (see also later in this paper) prompted us to examine its behaviour in a Beckmann rearrangement. In an analogous reaction the isomeric cyclic ketone (2) gave, as expected, the lactam (3).[6] Like 2,6-methano-3-benzazocines,[7] *e.g.* (4), 3-benzazocines, *e.g.* (5), have been of interest as analgesics.[3,8]

When a solution of the oxime [9] of the 2,6-methano-3-benzazocine (1) in dichloromethane was added to a rapidly stirred suspension of phosphorus pentachloride in the same solvent at ambient temperature, a rearrangement occurred to give the 3-benzazocine-2-carbonitrile (8) (59% yield). In the i.r. spectrum of this product the weak nitrile stretching frequency is at 2 220 $cm^{-1}$. In addition to a 4 H multiplet for the aromatic protons at δ 7.20—7.50 in the $^1H$ n.m.r. spectrum of (8), also present are two 3 H singlets at δ 2.06 and 2.52 for the 6-methyl and the *N*-methyl groups, respectively, a 2 H doublet at δ 3.02 for the 1-methylene group, a 2 H multiplet at δ 2.30—3.30 for the 4-methylene group, a 1 H triplet at δ 4.05 for the single proton at C-2, and a 1 H multiplet at δ 5.85 for the olefinic proton at C-5. Attempts to use polyphosphoric acid [10] or methanesulphonic acid–phosphorus pentaoxide [11] only resulted in quantitative hydrolysis of the oxime to the starting ketone (1).

A possible mechanism for this Beckmann rearrangement is shown in Scheme 1. Following the initial reaction, intermediate (6) fragments and rearranges presumably because a highly stabilised benzylic carbenium ion (7) is formed. 'Abnormal' or 'second order' Beckmann rearrangements, resulting in cleavage, are well established in the literature; [12] indeed, 1,1-dimethyl- and 1,1,4,4-tetramethyl-2-tetralone oximes undergo abnormal Beckmann fragmentation.[13] Such reactions invariably proceed *via* the formation of a stabilised carbenium ion akin to (7); the rearrangement step has been shown to be the rate-determining step. We were not able to establish the geometrical configuration of the oxime of ketone (1) by its spectroscopic analysis but the rearrangement step probably involves a *trans*-migration, as shown in Scheme 1. However, *trans*-stereochemistry in Beckmann reactions must be used with caution in predicting rearrangements and assigning oxime configurations, even when oxime isomerism is unlikely.[14]

In order to show that involvement of the highly stabilised carbenium ion (7) (Scheme 1) is the major factor resulting in Beckmann cleavage of the oxime of the tricyclic ketone (1) and that the nitrogen bridge [ring c in (6)] plays little or no part, we treated the oxime of the bicyclic ketone (14) with phosphorus pentachloride using conditions identical with those used to prepare the 3-benzazocine-2-carbonitrile (8) from the ketone (1) oxime. Work-up in the same way followed by chromatographic separation of the crude product gave two fractions. The first was shown by spectroscopic analysis to be (*E*)-2-[*o*-(2-cyanoethyl)phenyl]-4-dimethylaminobut-2-ene † (15) (64%) characterised as its hydrochloride salt. In the i.r. spectrum of this salt the nitrile group appears at 2 200 $cm^{-1}$. The $^1H$ n.m.r. spectrum, recorded in deuterium oxide, displays a 4 H multiplet at δ 7.20—7.55 for the aromatic protons,

† Assigned the *E* configuration on the basis of examination of molecular models which show that the *Z* configuration is extremely unlikely to form.

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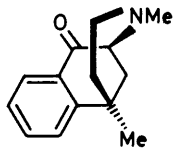


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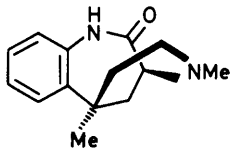


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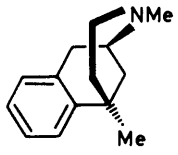


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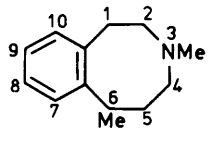


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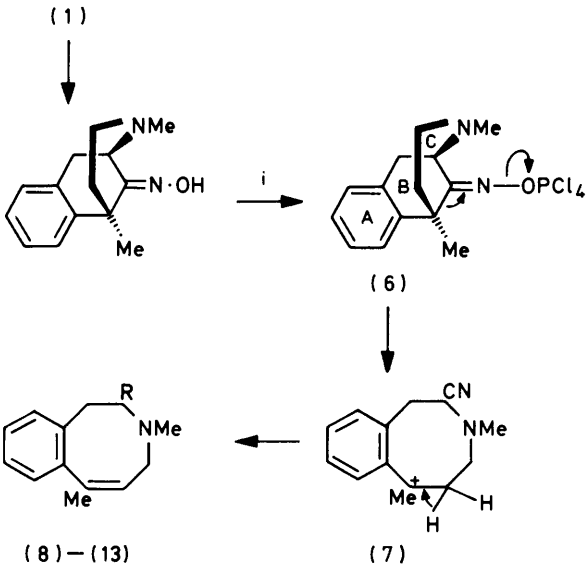
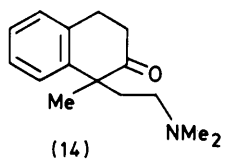



(8) R = CN
(9) R = $CONH_2$
(10) R = $CO_2H$
(11) R = $CO_2Et$
(12) R = $CO_2Me$
(13) R = $CH_2NH_2$

**Scheme 1.** *Reagents:* i, $PCl_5$, $CH_2Cl_2$

3 and 6 H singlets at δ 2.15 and 3.00, for the *C*-methyl and two *N*-methyl groups, a 1 H triplet at δ 5.53 for the olefinic proton, a 2 H doublet at δ 4.00 for the 4-methylene group, and two 2 H triplets at δ 2.70 and 3.00 for the remaining methylene groups. The second fraction collected was a mixture of three or four components (t.l.c.). In its i.r. spectrum this mixture displays a strong stretching frequency at 1 680 $cm^{-1}$, typical of that expected for the lactam carbonyl group in the benzazepinone (16), and further peaks at 3 050 and 3 150 $cm^{-1}$, typical of the NH function of a lactam. However, it was not possible to isolate this compound from the mixture by chromatographic techniques. Isolation of the nitrile (15) as the major product of

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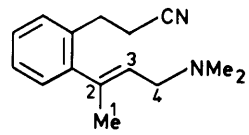


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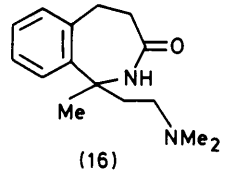


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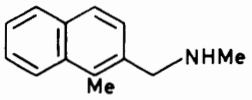
this reaction suggests, however, that the major driving force in these reactions is the generation of a benzylic carbenium ion and that the nitrogen bridge in intermediate (6) (Scheme 1) plays little or no part in its fragmentation.

We have explored the reactions of the nitrile (8) briefly with a view to providing compounds with potential analgesic activity. This compound possesses several centres of reactivity but we have studied mainly the reactivity of the nitrile group. The presence of a tertiary amino group in the 3-benzazocine (8) was advantageous in that it allowed purification of products as their hydrochloride salts but sometimes disadvantageous in that the salt of the starting material was insoluble under some literature reaction conditions.

Hydrolysis of the 3-benzazocine-2-carbonitrile (8) in concentrated hydrochloric acid at ambient temperature [conditions under which we expected the amide (9) to form [15]] gave the corresponding carboxylic acid (10), which was esterified with ethanol to give the ethyl ester (11). With ethereal diazomethane the acid (10) was converted into its methyl ester (12). Reduction of the nitrile (8) with lithium aluminium hydride in ether gave a high yield (69%) of 2-aminomethyl-1,2,3,4-tetrahydro-3,6-dimethyl-3-benzazocine (13), isolated as its dihydrobromide salt because the corresponding dihydrochloride salt was extremely hygroscopic.

In an attempt to prepare the ethyl imidate by a Pinner synthesis [15,16] the nitrile (8) hydrochloride was treated as a suspension in ethanol (ratio 1 : 1) saturated with anhydrous hydrogen chloride.[17-19] This gave a mixture of the amide (9) and starting material. With an excess of ethanol a higher yield (90%) of the amide (9) was obtained. The reaction between nitriles and tertiary alcohols invariably yields an amide [15,20] but amides are formed in the case of primary and secondary alcohols only when the reaction is influenced by the presence of a strong electron-withdrawing group close to the reaction site.[15,16] Presumably, in our case, protonation of the adjacent tertiary amino group alters the usual course of reaction. In compounds containing both a nitrile and an amine group it is customary to protect the amine by a tosyl group in Pinner reactions in order to prevent precipitation of the aminonitrile hydrohalide.[16,21]

In an attempt to synthesise the ethyl ester (11) a mixture of the nitrile (8) and 10% aqueous ethanol was heated under reflux whilst hydrogen chloride was bubbled through. This gave a white crystalline hydrochloride salt the free base of which lacks a carbonyl absorption in its i.r. spectrum but displays a broad NH stretching frequency at 3 300 $cm^{-1}$. In the $^1H$ n.m.r. spectrum of this compound (free base), which we suggest is the naphthalene (17), there are three singlets at δ 2.70, 2.92, and 4.45 for the C-1 and *N*-methyl groups and the methylene group, respectively. The six aromatic protons display the expected coupling pattern whilst the u.v. data for this compound correspond closely to that of 1,2-dimethyl-



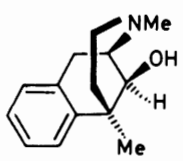
(17)

naphthalene (see Experimental section). Apparently, this is the first ring-contraction reaction of a 3-benzazocine to be reported.

Several attempts to epoxidise the alkene double bond in the nitrile (8) failed to give isolable products.

The $^1$H n.m.r. spectra of the hydrohalides of compounds (8)—(13) are complicated by protonation at the ring nitrogen atom, which produces a mixture of diastereoisomeric salts. This, together with conformational changes (see ref. 22), results in considerable broadening of the observed peaks. The 6-methyl groups appear as singlets at δ 2.17—2.20 but the *N*-methyl groups appear as two singlets between δ 2.88 and 3.07. The olefinic protons at C-5 appear either as broadened triplets or as multiplets at δ 5.90—5.97 whilst the C-2 protons appear in some cases as two multiplets and in others as two triplets between δ 3.90 and 4.58. The two methylene groups appear as complex multiplets.

*Synthesis of the Title Compound* (1).—The most widely used synthesis of compound (1) [23-25] and its derivatives [24,26-29] is that introduced by May and his co-workers. Starting from phenylacetic acid we have evaluated each stage of the eight-stage route and our experiences are summarised in the Experimental section. The major bottleneck in the procedure is the last step which involves demethobromination of the methobromide salt of the title compound (1). This has been achieved by heating the salt in octan-1-ol (20% yield), which also yields the product of Hofmann elimination (40%),[25] as well as by dry distillation [23] (an improvement to the literature procedure consists of distillation from fine sand in a Kugelrohr apparatus, the distillation bulb of which is plunged into a preheated oven at 210 °C *). Using solvents, we obtained complex mixtures (t.l.c.) whilst dry bulb-to-bulb distillation limited the yield (our maximum yield was 29% but most of our yields were considerably less than this) and scale (≤ *ca.* 1.0 g, per run). Ranus [30] has reported that the use of other high boiling alcohols, *e.g.* nonan-1-ol,[25,31] heptan-1-ol,[26] or hexan-1-ol,[26] is even less efficient than the use of octan-1-ol for this type of conversion and that the use of sodium thiophenoxide in butan-2-one [32] was unsuccessful. In order to overcome the difficulties experienced with this step we found it preferable to reduce the methobromide salt of compound (1) to its 11α-hydroxy derivative † (70%) with sodium borohydride,[5] demethobrominate this product in hot octan-1-ol (91% yield),[5] and oxidise (in 85% yield) the demethobrominated product (18) (*cf.* ref. 33). Previously we [5] used chromium trioxide in sulphuric acid for oxidation of the alcohol (18) but the optimum yield was only 62%, often less. Other chromium-based reagents, *e.g.* pyridinium chlorochromate [34] or pyridinium dichromate,[35] ‡ or Jones or Browns reagent gave considerably lower yields. It is probable that these reagents complex with the tertiary N-atom in the 11α-hydroxy compound (18). The use of acetyl bromide–dimethyl sulphoxide at −60 °C,[36] however, increased the yield of this oxidation step to 85% (*cf.* ref. 37). Compared with our maximum yield of only 29% (see comment before) for the direct demethobromination of the methobromide salt of compound (1), our preferred three-step conversion, which can be handled on a much larger scale than the direct conversion, gives an overall yield of 54% for the title compound (1). Thus, starting from phenylacetic acid, we have been able to more than double the best literature yield of compound (1) by adopting these modifications.



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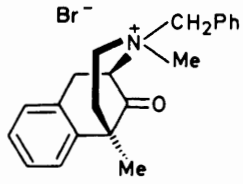

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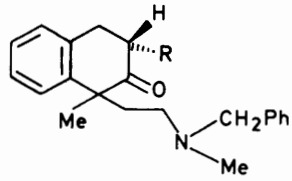


(20) R = H
(21) R = Br

In view of the relative ease of removal of benzyl groups from quaternary ammonium centres either by pyrolysis or by the use of suitable reagents,[38,39] we decided to attempt the preparation of the quaternary compound (19). 1-Methyl-2-tetralone [40] was alkylated with 2-(*N*-benzyl-*N*-methylamino)-ethyl chloride (prepared by treatment of its hydrochloride salt [41] with 50% aqueous potassium hydroxide) in toluene in the presence of sodamide as for the preparation of 1-[2-(*N*,*N*-dimethylamino)ethyl]-1-methyl-2-tetralone.[25] However, the desired product (20) was contaminated with considerable quantities of the alkylating agent, inseparable by chromatography (almost identical $R_F$ values) or distillation. The use of sodium hydride, potassium amide, or potassium t-butoxide in toluene to generate the anion gave similarly contaminated products. These procedures generate anions extremely slowly, favouring aldol-type condensations between the anions and starting material, a difficulty that can sometimes be overcome by using 1,2-dimethoxyethane.[42] Alkylation of 1-methyl-2-tetralone with 2-(*N*-benzyl-*N*-methylamino)ethyl chloride in this solvent in the presence of sodamide or sodium hydride failed to convert all the starting materials into product. Alkylation in toluene in the presence of sodamide and sodium iodide (Finkelstein conditions) was attempted also, but without significant improvement in the yield or quality of the product.

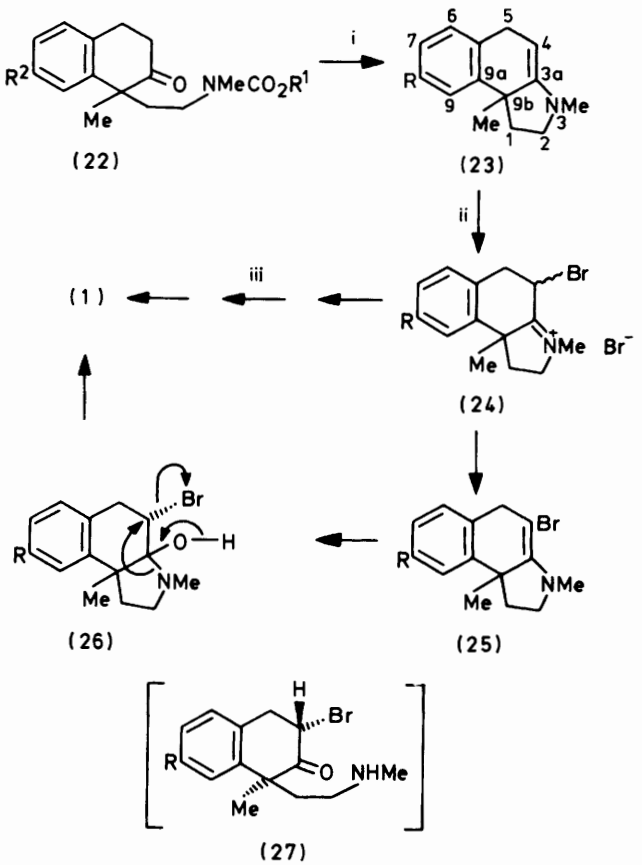
1-[2-(*N*-Benzyl-*N*-methylamino)ethyl]-1-methyl-2-tetralone (20) was prepared readily, however, in 72% yield by treating the corresponding 1-[2-(*N*,*N*-dimethylamino)ethyl] derivative with benzyl chloride in hot dimethylformamide. In benzene, toluene, or xylene the yields are lower (*ca.* 40%). Bromination of compound (20) using conditions identical with those used to brominate the 1-[2-(*N*,*N*-dimethylamino)ethyl] analogue (*i.e. via* the hydrobromide salt) [25] surprisingly gave only starting material. The use of cupric bromide,[43] *N*-bromosuccinimide,[44] or pyrrolidone hydrotribromide [33,45] similarly give only starting material and none of the desired product (21) or its diastereoisomer. Bromination of the ethylene acetal of the 2-tetralone (20) (see later) was equally unsuccessful.

In 1972, Takeda *et al.*[24,46] published a synthesis of 1,2,3,4,5,-6-hexahydro-8-methoxy-3,6-dimethyl-2,6-methano-3-benzazocin-11-one (2′-methoxy-2,5-dimethyl-9-oxo-6,7-benzomorphan) which avoids the low yield thermal demethobromination

* We thank Professor R. T. Parfitt, University of Bath, for advice on this procedure.

† The α-isomer is the one with the hydroxy group *cis* to the *cis*-fused piperidine ring (ring C).

‡ **CARE**: see J. Salmon, letter in *Chem. Br.*, 1982, 703.

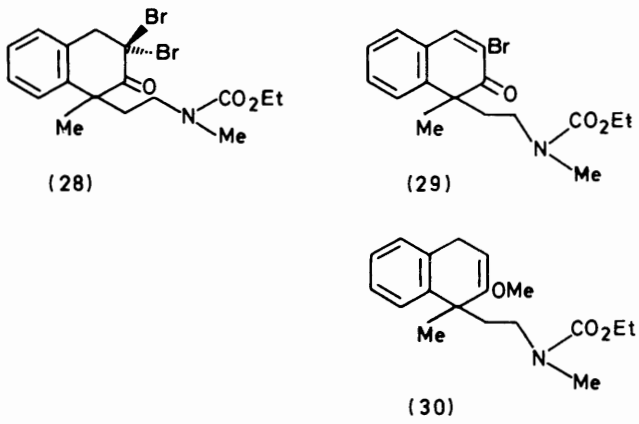


**Scheme 2.** *Reagents:* i, KOH–Bu$^t$OH; ii, $Br_2$; iii, $NH_4OH$

step of the ' May and Murphy procedure '. This involves (see Scheme 2) treatment of 1-[2-(*N*,*N*-dimethylamino)ethyl]-7-methoxy-1-methyl-2-tetralone with ethyl chloroformate in hot benzene, hydrolysis of the resulting carbamate (22; $R^1$ = Et, $R^2$ = OMe) with potassium hydroxide in hot t-butyl alcohol, bromination of the 2,3,5,9b-tetrahydrobenz[*e*]indole (23; R = OMe) produced, and rearrangement of the brominated product (24; R = OMe) with ammonium hydroxide. Using the same procedure we prepared the carbamate (22; $R^1$ = Et, $R^2$ = H) but its treatment with potassium hydroxide in t-butyl alcohol gave a complex mixture (t.l.c.). Variations in base, solvent, temperature, and concentration also gave complex mixtures (t.l.c.). Attempted cleavage of the carbamate (22; $R^1$ = Et, $R^2$ = H), with iodotrimethylsilane [47] obtained commercially or generated *in situ* [48] from chlorotrimethylsilane gave only starting material. Belleau's group [4] have found also that the Takeda procedure is not generally applicable and gives low yields of products.

In the Takeda procedure rearrangement of the bromoiminium salts (24) in the presence of base into the desired products [*e.g.* (1)] is postulated to proceed *via* intermediates (25) and (26); the final step is usually written as a concerted rearrangement of (26) but intermediates (27) have not been ruled out on the evidence available to date.[4,24,46] It occurred to us that it might be possible to prepare compound (27; R = H) by bromination of the carbamate (22; $R^1$ = Et, $R^2$ = H) and cleavage of the carbamate group in the resulting product. This would provide an alternative synthesis of the desired product (1) from the carbamate (22; $R^1$ = Et, $R^2$ = H) which avoids isolation of the extremely air-sensitive [4] 2,3,5,9b-tetrahydrobenz[*e*]indole (23; R = H).

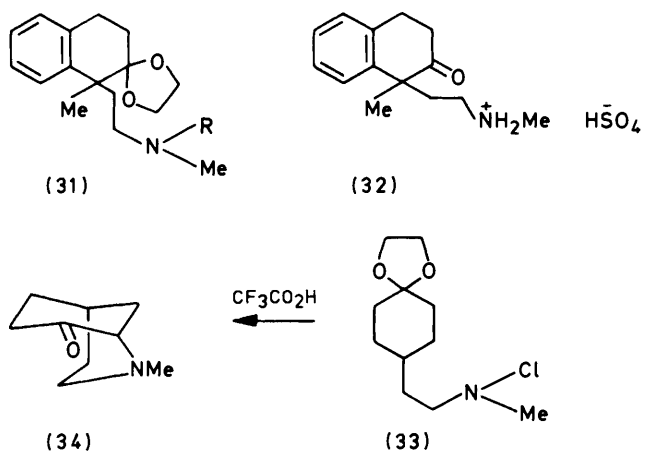
Acid-catalysed bromination of the carbamate (22; $R^1$ = Et, $R^2$ = H) using an identical procedure (bromine in acetic acid) with that used for monobromination of the hydrobromide salt of 1-[2-(*N*,*N*-dimethylamino)ethyl]-1-methyl-2-tetralone gave only the dibromo derivative (28). This was confirmed by spectroscopic analysis and by heating the product at 90 °C in dimethyl sulphoxide in the $^1$H n.m.r. probe when elimination of hydrogen bromide was observed, to give the elimination product (29). In the $^1$H n.m.r. spectrum of compound (28) the methylene protons at C-4 appear as a 2 H singlet at δ 4.10. After elimination this signal is replaced by a 1 H singlet at δ 8.33 for the C-4 proton in compound (29). An optimum yield (75%) of the dibromo compound (28) was obtained by bromination of the carbamate (22; $R^1$ = Et, $R^2$ = H) with a large excess of bromine in chloroform containing sulphuric acid. Cupric bromide,[43] *N*-bromosuccinimide,[44] or pyrrolidone hydrotribromide [33,45] gave only the dibromo compound (no trace of the monobromo derivative). It is not clear why bromination of the carbamate (22; $R^1$ = Et, $R^2$ = H) yields its dibromo derivative (28) so readily whilst, under identical conditions, 1-[2-(*N*,*N*-dimethylamino)ethyl]-1-methyl-2-tetralone gives the 3-monobromo derivative together with its diastereoisomer and compound (20) fails to react.

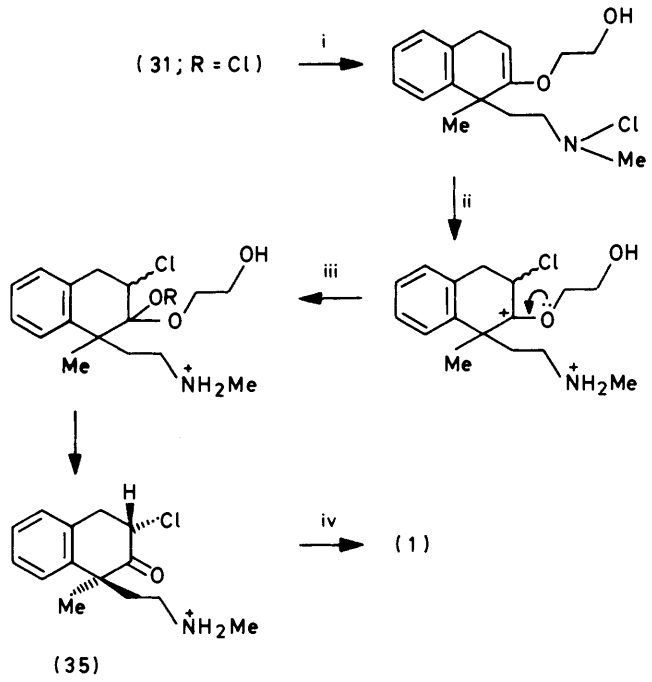


The enol-ether (30) was prepared in 85% yield from the carbamate (22; $R^1$ = Et, $R^2$ = H) and trimethyl orthoformate, but its bromination with bromine, cupric bromide, *N*-bromosuccinimide, or pyrrolidone hydrotribromide similarly gave only the dibromo derivative (28).

Failure to prepare the 2,3,5,9b-tetrahydrobenz[*e*]indole (23; R = H) by hydrolysis of the carbamate (22; $R^1$ = Et, $R^2$ = H) prompted us to examine deprotection [49] of the corresponding benzyl carbamate (22; $R^1$ = $CH_2Ph$, $R^2$ = H). However, unfortunately a reaction between 1-[2-(*N*,*N*-dimethylamino)ethyl]-1-methyl-2-tetralone and benzyl chloroformate gave only starting materials.

The availability of 1-[2-(*N*-benzyl-*N*-methylamino)ethyl]-1-methyl-2-tetralone (20) suggested two further routes to the title compound (1) using this starting material in addition to the unsuccessful route already described. The first of these involved the synthesis of the ethylene acetal (31; R = $CH_2Ph$) (75% yield), removal of its benzyl group (90% yield), and hydrolysis of the resulting ethylene acetal (31; R = H) with concomitant cyclisation to the 2,3,5,9b-tetrahydrobenz[*e*]indole (23; R = H) (90% yield). Acetalisation of the 2-tetralone (20) was carried out by a standard procedure using toluene-4-sulphonic acid. However, to obtain the optimum yield of the ethylene acetal (31; R = $CH_2Ph$) it was necessary to add the sulphonic acid in aliquots each 30 min during 3 h (see Experimental section). Similar acetalisation of 1-[2-(*N*,*N*-dimethylamino)ethyl]-1-methyl-2-tetralone occurred without difficulty. Removal of the benzyl group in the ethylene acetal (31;




Scheme 3. *Reagents:* i, $CF_3CO_2H$; ii, $2\,H^+$; iii, $CF_3CO_2^-$ or MeOH (R in intermediate Me or $CF_3CO_2$); iv, $OH^-$

R = $CH_2Ph$) was achieved by hydrogenolysis at ambient temperature in 20% aqueous ethanol over 10% palladium–charcoal,[50] and hydrolysis of the resulting deprotected acetal (31; R = H) occurred at ambient temperature in aqueous acetonitrile containing 2M-sulphuric acid. Cyclisation of the product (32) of hydrolysis occurs on addition of base to the reaction mixture during its work-up, to give the extremely air-sensitive 2,3,5,9b-tetrahydrobenz[*e*]indole (23; R = H). This can be converted into the title compound (1) using the further improvements to the Takeda procedure already reported by Belleau's group.[4] This improved route to 1,2,3,4,5,6-hexahydro-3,6-dimethyl-2,6-methano-3-benzazocin-11-one (1) may be summarised as follows: 1-[2-(*N*,*N*-dimethylamino)ethyl]-1-methyl-2-tetralone ⟶ (20) (72%) ⟶ (31; R = $CH_2Ph$) (75%) ⟶ (31; R = H) (90%) ⟶ (23; R = H) (90% yield) ⟶ (1) (as shown in Scheme 2).

Based on a synthesis of 2-azabicyclo-[2.2.2] and -[3.2.1]-octanes and -[3.3.1]nonanes reported by Furstoss *et al.*,[51] *e.g.* (33) ⟶ (34), we prepared the *N*-chloroamine (31; R = Cl) by treatment of the secondary amine (31; R = H) with 0.25M-sodium hypochlorite and attempted its cyclisation in trifluoroacetic acid, trifluoroacetic acid–methanol, and trifluoroacetic acid–dichloromethane. These reactions gave only the 2,3,5,9b-tetrahydrobenz[*e*]indole (23; R = H) (optimum yield of 65%) and none of the desired compound (1). The proposed mechanism [51] for this type of process is shown in Scheme 3 adapted for our system. It involves an intermediate (35) similar to that [(27) Scheme 2] proposed in the Takeda process. Belleau's group [52] have used a *N*-chloroamine solvolysis for the synthesis of D-normorphinans whilst Stella *et al.*[53] have prepared 2-methyl-6,7-benzomorphan in a similar way.

## Experimental

I.r. spectra (liquids as films and solids as Nujol mulls between sodium chloride plates unless stated otherwise) were recorded with a Perkin-Elmer 257, 297, or 357 spectrometer or with a Pye Unicam SP 20 instrument, n.m.r. spectra with a Varian EM 360 (60 MHz), a Perkin-Elmer R 32, or a Varian EM 390 (90 MHz) ($^1H$), or a Varian CFT 20 (20 MHz) ($^{13}C$) spectrometer (with $SiMe_4$ as an internal standard), and mass spectra with an AEI MS 12 or MS 902S instrument unless stated otherwise. Microanalytical (C, H, N) results were provided by Butterworth Laboratories Ltd., Teddington, and Glaxo Group Research Ltd., Ware.

Small-scale distillations were carried out with a Kugelrohr micro-distillation apparatus and the ' b.p.' temperatures recorded in these cases are the oven temperatures at the time of distillation. In all cases organic extracts were combined, dried ($MgSO_4$), and evaporated on a rotary evaporator. Light petroleum with b.p. 40—60 °C was used unless stated otherwise. For column chromatography silica MFC from BDH or alumina Type H from Merck was used. Ether refers to diethyl ether.

The following compounds were prepared by literature procedures: 1,2,3,4,5,6-hexahydro-11α-hydroxy-3,6-dimethyl-2,6-methano-3-benzazocine methobromide (70%),[5] m.p. 223—225 °C (from acetone) (lit.,[5] 89% and 222—225 °C); 1,2,3,4,5,6-hexahydro-11α-hydroxy-3,6-dimethyl-2,6-methano-3-benzazocine (18) (91%),[5] m.p. 113—115 °C (from ethanol) (lit.,[25] 60% and 112—114 °C); 2-(*N*-benzyl-*N*-methylamino)-ethanol (85%); [54] and 2-(*N*-benzyl-*N*-methylamino)ethyl chloride hydrochloride (87%),[41] m.p. 135—138 °C (from methanol) (lit.,[41] 135—138 °C).

1,2,3,4,5,6-*Hexahydro*-3,6-*dimethyl*-2,6-*methano*-3-*benzazocin*-11-*one* (1).—The following summarises our evaluation of the literature route to this compound: phenacetyl chloride (90%),[55] b.p. 95—96 °C at 12.0 mmHg (lit.,[55] 94% and 122 °C at 70.0 mmHg), $\nu_{max.}$ 1 800 $cm^{-1}$ (CO) ⟶ 3,4-dihydronaphthalen-2(1*H*)-one (2-tetralone) (70%) (prepared by our [5] improved large scale synthesis but on double the previous scale) ⟶ 3,4-dihydro-1-methylnaphthalen-2(1*H*)-one (1-methyl-2-tetralone) [40] (70% overall) [toluene used instead of benzene to prepare the enamine (80%). This enamine quickly darkens on exposure to air during change of the solvent from toluene to dioxane prior to addition of methyl iodide; it is possible to store it under nitrogen at −10 °C for considerable periods without affecting the overall yield],* b.p. 142—144 °C at 19.00 mmHg (lit.,[40] 138—142 °C at 20.0 mmHg), $\nu_{max.}$ 1 710 $cm^{-1}$ (CO) ⟶ 1-[2-(*N*,*N*-dimethylamino)ethyl]-3,4-dihydro-1-methylnaphthalen-2(1*H*)-one {1-[2-(*N*,*N*-dimethylamino)-ethyl]-1-methyl-2-tetralone} (68%) [toluene used instead of

* Ranus [30] prepared an enamine from 7-methoxy-2-tetralone using cyclohexylamine and alkylated it with methyl iodide and lithium amide but this procedure failed in our hands with 2-tetralone.

benzene;[23,25] we have increased our earlier yield of 38%[5] to 68% by distilling the very volatile 2-(*N*,*N*-dimethylamino)-ethyl chloride prior to its immediate use (commercial hydrochloride salt treated in a separating funnel with 50% aqueous potassium hydroxide, the free base run off and dried over potassium hydroxide pellets prior to its distillation from calcium hydride), b.p. 108—110 °C at 760 mmHg], $\nu_{max.}$ 1 710 $cm^{-1}$ (CO), hydrobromide (95%),[25] m.p. 187—190 °C (from ethanol) (lit.,[25] 94% and 187—189 °C), $\nu_{max.}$ 1 740 $cm^{-1}$ (CO) ⟶ 3-bromo-1-[2-(*N*,*N*-dimethylamino)ethyl)-3,4-dihydro-1-methylnaphthalen-2(1*H*)-one (70%)[25] (it is essential in this preparation to remove the excess of hydrogen bromide in a rapid stream of nitrogen before addition of anhydrous ether, otherwise a black oil is obtained rather than the desired solid product) as a mixture of the required compound (A) with the bromo and methyl groups *cis* with respect to one another, m.p. 147—148 °C (from acetone) (lit.,[23] 84.5% and 147—148.5 °C) and its diastereoisomer (B) (in one experiment, ratio 3 : 2) (there is no mention of this problem in the literature[23,25]), $\nu_{max.}$ (mixture) 1 720 and 1 735sh $cm^{-1}$ (CO); δ (mixture) [$CDCl_3$–$(CD_3)_2SO$] 1.55 [s, 1-Me of (B)], 1.70 [s, 1-Me of (A)], 2.00—3.30 [m, $(CH_2)_2NMe_2$], 3.20—4.00 (m, 4-$CH_2$), 4.93 [dd, 3-H of (B)], 5.17 [dd, 3-H of (A)], and 7.10—7.50 (m, aromatic) ⟶ methobromide of title compound (1) (60%),[25] m.p. 198—200 °C [from methanol after removal of diastereoisomer (B) by digestion of the crude product in hot acetone followed by filtration, to give the uncontaminated quaternary salt] (lit.,[23,25] 66 and 77% and m.p. 192—194 and 198—200 °C, respectively), $\nu_{max.}$ 1 730 $cm^{-1}$ (CO) ⟶ title compound (1) (29%) [1.0 g of the methobromide salt heated in 1.0 g of fine sand (see Discussion section) gave an oil containing three components (t.l.c.) which were separated by chromatography on a silica plate; ethyl acetate–ethanol (10 : 1) eluted 0.2 g (29% was the highest yield obtained; most yields were considerably less than this) of the product], identical with the sample prepared as described later.

*Oxidation of* 1,2,3,4,5,6-*Hexahydro*-11α-*hydroxy*-3,6-*dimethyl*-2,6-*methano*-3-*benzazocine* (18).—(*a*) *With acetyl bromide–dimethyl sulphoxide.* A mixture of dimethyl sulphoxide (2.9 g, 37.0 mmol) and dichloromethane (20 ml) at −60 °C was added dropwise by syringe to a stirred solution of acetyl bromide (2.27 g, 18.4 mmol) in dichloromethane (20 ml), kept under nitrogen at −60 °C, at such a rate that the temperature did not rise above −60 °C. The mixture was stirred for a further 30 min at this temperature, then a solution of 1,2,-3,4,5,6-hexahydro-11α-hydroxy-3,6-dimethyl-2,6-methano-3-benzazocine (18) (2.0 g, 9.2 mmol) in dichloromethane (30 ml) was added dropwise at such a rate that the temperature did not rise above −60 °C. The mixture was allowed to warm up to ambient temperature, water (40 ml) was added, and the mixture was stirred for 30 min. The organic layer was separated and the aqueous layer extracted with dichloromethane. Evaporation of the combined organic layer and extracts gave a product which was chromatographed on alumina. Dichloromethane–ethanol (400 : 1) eluted 1,2,3,4,5,6-hexahydro-3,6-dimethyl-2,6-methano-3-benzazocin-11-one (1) (1.68 g, 85%) as a pale yellow solid, m.p. 62—64 °C (from dichloromethane–ethanol), $\nu_{max.}$ 1 736 $cm^{-1}$ (CO), identical in all other respects with the sample prepared as described previously;[5] hydrochloride (a hemihydrate), m.p. 227—229 °C (from acetone) (lit.,[25] 228—230 °C).

(*b*) *With chromium trioxide–sulphuric acid.* Using the procedure described previously[5] the alcohol (18) (1.0 g, 4.6 mmol) gave an oily product (0.66 g), which was chromatographed as described in (*a*) to give the ketone (1) (0.45 g, 46%).

(*c*) *With pyridinium chlorochromate.* A solution of the alcohol (18) (0.1 g, 0.46 mmol) in dichloromethane (10 ml) was added to a stirred suspension of the reagent (0.15 g, 0.69 mmol) in dichloromethane (10 ml) at ambient temperature and the resulting mixture was stirred for a further 5.0 h. Ether (20 ml) was added, the fine precipitate was filtered off with the help of a filter aid, and distillation of the solvent from the filtrate gave a product (0.035 g) which was chromatographed as described in (*a*), to give the product (1) (0.021 g, 21%).

(*d*) *With pyridinium dichromate* (**CARE**: see J. Salmon, letter in *Chem. Br.*, 1982, 703). A solution of the alcohol (18) (0.1 g, 0.46 mmol) in dimethylformamide (5.0 ml) was added to a stirred solution of pyridinium dichromate[35] (0.216 g, 0.57 mmol) in dimethylformamide (10 ml) at 0°C and the resulting mixture was stirred at 0 °C for 8 h. Ether (20 ml) was added and the precipitate was filtered off using a filter aid. Distillation of the solvent from the filtrate (under reduced pressure) gave an oil which was chromatographed as described in (*a*), to give the product (1) (0.043 g, 44%).

1,2,3,4,5,6-*Hexahydro*-3,6-*dimethyl*-2,6-*methano*-3-*benzazocin*-11-*one* (1) *Oxime.*—A stirred mixture of 1,2,3,4,5,6-hexahydro-3,6-dimethyl-2,6-methano-3-benzazocin-11-one (1)[5] (0.5 g, 2.3 mmol), hydroxylamine hydrochloride (0.24 g, 3.5 mmol), sodium acetate (0.57 g, 7.0 mmol), and 50% aqueous ethanol (20 ml) was heated under reflux under nitrogen for 20 h, then cooled, and made alkaline by addition of 10% aqueous sodium hydrogen carbonate. Extraction with chloroform (2 × 20 ml) gave the oxime (0.43 g, 81%), m.p. 173—175 °C (from ethanol) (lit.,[9] m.p. 175—176 °C), $\nu_{max.}$ ($CHBr_3$) 930 (N–O), 3 290, and 3 565 $cm^{-1}$ (OH); δ ($CDCl_3$) 1.20—2.80 (2 × m, 4 H, *ax* and *eq* 4- and 5-$CH_2$), 1.56 (s, 3 H, Me), 2.47 (s, 3 H, NMe), 2.98 (dd, 1 H, *J* 6.0 and 18.0 Hz, 1-H), 3.32 (dd, 1 H, *J* 18.0 Hz, 1-H), 4.63 (d, 1 H, *J* 6.0 Hz, 2-H) (ABX system), 7.00—7.50 (m, 4 H, aromatic), and 9.30br (s, 1 H, OH). This experiment gave the same yield when repeated on four times the scale described here.

1-[2-(N,N-*Dimethylamino*)*ethyl*]-1-*methyl*-2-*tetralone* (14) *oxime* (92%) was prepared similarly, m.p. 106—108 °C (from chloroform–light petroleum (Found: C, 73.2; H, 8.8; N, 11.4%; $M^+$, 246.1729. $C_{15}H_{22}N_2O$ requires C, 73.1; H, 9.0; N, 11.4%; *M*, 246.1731): *hydrochloride*, m.p. 207—209 °C (from chloroform–ethanol) (Found: C, 63.4; H, 8.0; N, 10.0. $C_{15}H_{23}ClN_2O$ requires C, 63.7; H, 8.2; N, 9.9%).

1,2,3,4-*Tetrahydro*-3,6-*dimethyl*-3-*benzazocine*-2-*carbonitrile* (8).—A solution of 1,2,3,4,5,6-hexahydro-3,6-dimethyl-2,6-methano-3-benzazocin-11-one (1) oxime (1.0 g, 4.4 mmol) in anhydrous dichloromethane (40 ml) was added rapidly to a vigorously stirred suspension of phosphorus pentachloride (1.8 g, 8.6 mmol) in anhydrous dichloromethane (40 ml) at ambient temperature and the resulting mixture was stirred at this temperature for 5 min. 10% Aqueous ammonium hydroxide (50 ml) was added, the mixture was stirred for a further 5 min, then the organic layer was separated, washed with water (2 × 40 ml), dried ($MgSO_4$), and the solvent distilled off under reduced pressure to leave a residue which was chromatographed on silica. Ethyl acetate–benzene (1 : 7) eluted the *product* (8) (0.55 g, 59%), m.p. 75—77 °C (from ethyl acetate–chloroform), $\nu_{max.}$ ($CHBr_3$) 2 220w $cm^{-1}$ (CN); δ ($CDCl_3$) 2.06 (s, 3 H, Me), 2.30—3.30 (m, 2 H, 4-$CH_2$), 2.52 (s, 3 H, NMe), 3.02 (d, 2 H, 1-$CH_2$), 4.05 (t, 1 H, 2-H), 5.85 (m, 1 H, 5-H), and 7.20—7.50 (m, 4 H, aromatic); δ ($^{13}C$) ($CDCl_3$) 23.8 (q, Me), 35.5 (t, $CH_2$), 44.2 [q and d, NMe and CH(CN)], 49.6 (t, $CH_2$), 55.3 (d, olefinic CH), 115.4 (s, C), 124.2 (s, aromatic C), 126.6, 127.0, 131.2, and 133.2 (all d, 4 aromatic C), 138.0 (s, aromatic C), and 139.9 p.p.m. (s, CN): *hydrochloride*, m.p. 159—161 °C (from chloroform–

light petroleum) (Found: C, 67.2; H, 6.8; N, 11.2. $C_{14}H_{17}ClN_2$ requires C, 67.6; H, 6.9; N, 11.3%).

*Beckmann Rearrangement of* 1-[2-(N,N-*Dimethylamino*)-*ethyl*]-1-*methyl*-2-*tetralone* (14) *Oxime*.—The title compound (2.0 g, 8.0 mmol) in anhydrous dichloromethane (80 ml) was added rapidly to a vigorously stirred suspension of phosphorus pentachloride (3.7 g, 18.0 mmol) in anhydrous dichloromethane (80 ml) at ambient temperature, the resulting mixture was stirred at this temperature for 5 min, then 10% aqueous ammonium hydroxide (100 ml) was added. The organic layer was separated, washed with water (2 × 100 ml), dried ($MgSO_4$), and the solvent evaporated under reduced pressure to give a residue (1.82 g) which was chromatographed on alumina. Ether eluted: (i) (E)-2-[o-(2-*cyanoethyl*)*phenyl*]-4-*dimethylaminobut*-2-*ene* (15) (1.15 g, 64%), colourless oil: *hydrochloride*, m.p. 160—162 °C (from chloroform–light petroleum); $\nu_{max.}$ (Nujol) 2 200 $cm^{-1}$ (CN); δ ($D_2O$) 2.15 (s, 3 H, Me), 2.70 and 3.00 (2 × t, 4 H, 2 × $CH_2$), 3.00 (s, 6 H, $NMe_2$), 4.00 (d, 2 H, 4-$CH_2$), 5.53 (t, 1 H, 3-H), and 7.20—7.55 (m, 4 H, aromatic) (Found: C, 68.1; H, 7.9; N, 10.4. $C_{15}H_{21}ClN_2$ requires C, 68.0; H, 8.0; N, 10.6%); and (ii) a colourless oil (0.48 g) whose i.r. spectrum displayed the probable presence of a lactam moiety, $\nu_{max.}$ (film) 3 050, 3 150 (NH), and 1 680 $cm^{-1}$ (CO). The $^1H$ n.m.r. spectrum of this oil showed it to be a mixture. However, further chromatographic separation could not be achieved and an attempt to prepare hydrochlorides (for fractional crystallisation) resulted in the formation of a hygroscopic oil.

1,2,3,4-*Tetrahydro*-3,6-*dimethyl*-3-*benzazocine*-2-*carboxylic Acid Hydrochloride* (10).—Anhydrous hydrogen chloride was bubbled continuously and vigorously for 3 h through a mixture of 1,2,3,4-tetrahydro-3,6-dimethyl-3-benzazocine-2-carbonitrile (8) (0.1 g, 0.47 mmol) and concentrated hydrochloric acid (20 ml) heated under reflux. The resulting mixture was cooled and evaporated to dryness under reduced pressure to give a white crystalline solid. Chloroform (50 ml) was added to this solid and the mixture was heated under reflux for 30 min, then filtered and the solvent evaporated from the filtrate, to give the *product* (10) (0.082 g, 65%), as a slightly hygroscopic white solid, m.p. 238—240 °C (with decomp.) (from chloroform–ethanol); $\nu_{max.}$ (Nujol) 1 740 $cm^{-1}$ (CO); δ ($D_2O$) 2.20 (s, 3 H, Me), 2.80—4.00 (m, 4 H, 1- and 4-$CH_2$), 2.90 and 3.00 (2 × s, 3 H, $\overset{+}{>}NHMe$), 4.40 (m, H, 2-H), 5.97br (t, 1 H, 5-H), and 7.30—7.70 (m, 4 H, aromatic) (Found: $M^+$, 231.1257. $C_{14}H_{17}NO_2$ requires $M$, 231.1258).

*Ethyl* 1,2,3,4-*Tetrahydro*-3,6-*dimethyl*-3-*benzazocine*-2-*carboxylate* (11) *Hydrochloride*.—A solution of 1,2,3,4-tetrahydro-3,6-dimethyl-3-benzazocine-2-carboxylic acid hydrochloride (10) (0.1 g, 0.37 mmol) in dry ethanol (10 ml) was heated under reflux for 24 h during which time anhydrous hydrogen chloride was bubbled through continuously. The reaction mixture was cooled and the solvent distilled off under reduced pressure to give a white solid. To this was added chloroform (100 ml) and the mixture was heated under reflux for 30 min, then filtered to remove traces of insoluble material. Evaporation of the solvent from the filtrate gave the *ester* (11) *hydrochloride* (0.05 g, 45%), m.p. 168—170 °C (from chloroform–light petroleum), $\nu_{max.}$ (Nujol) 1 735 $cm^{-1}$ (CO); δ ($D_2O$) 1.38 (t, 3 H, Me), 2.18 (s, 3 H, 6-Me), 2.88 and 2.95 (2 × s, 3 H, $\overset{+}{>}NHMe$), 3.10—3.90 (m, 4 H, 1- and 4-$CH_2$), 4.34 (q, 2 H, $OCH_2$), 4.50 (m, 1 H, 2-H), 5.97 (t, 1 H, 5-H), and 7.40—7.70 (m, 4 H, aromatic) (Found: $M^+$, 259.1564. $C_{16}H_{21}NO_2$ requires $M$, 259.1572).

*Methyl* 1,2,3,4-*Tetrahydro*-3,6-*dimethyl*-3-*benzazocine*-2-*carboxylate* (12) *Hydrochloride*.—An ethereal solution of diazomethane was added dropwise to a vigorously stirred solution of 1,2,3,4-tetrahydro-3,6-dimethyl-3-benzazocine-2-carboxylic acid (10) hydrochloride (0.1 g, 0.37 mmol) in methanol (20 ml) at 0 °C until the yellow colour of an excess of diazomethane persisted; then the mixture was allowed to warm up to room temperature and stirred until the colour of diazomethane was discharged. Evaporation of the mixture to dryness gave a viscous oil which was dissolved in anhydrous ether (50 ml). Treatment of this solution with anhydrous hydrogen chloride precipitated the *ester* (12) *hydrochloride* (0.08 g, 76%), m.p. 189—191 °C (dried in a vacuum desiccator and recrystallised from chloroform–ether); $\nu_{max.}$ (Nujol) 1 730 $cm^{-1}$ (CO); δ ($D_2O$) 2.20 (s, 3 H, 6-Me), 2.90 and 3.00 (2 × s, 3 H, $\overset{+}{>}NHMe$), 3.90 (s, 3 H, OMe), 2.80—4.00 (m, 4 H, 1- and 4-$CH_2$), 4.25 and 4.58 (2 × m, 1 H, 2-H), 5.97 (t, 1 H, 5-H), and 7.30—7.70 (m, 4 H, aromatic) (Found: $M^+$, 245.1413. $C_{15}H_{19}NO_2$ requires $M$, 245.1415).

2-*Aminomethyl*-1,2,3,4-*tetrahydro*-3,6-*dimethyl*-3-*benzazocine* (13) *Dihydrobromide*.—To a stirred suspension of lithium aluminium hydride (0.16 g, 4.2 mmol) in anhydrous ether (50 ml) at ambient temperature was added dropwise a solution of 1,2,3,4-tetrahydro-3,6-dimethyl-3-benzazocine-2-carbonitrile (8) (0.3 g, 1.4 mmol) in anhydrous ether (50 ml), the resulting mixture was heated under reflux for 2 h, then cooled in an ice-bath, and 10% aqueous sodium hydroxide (30 ml) was added slowly. The mixture was stirred for a further 30 min and the ethereal layer was separated, washed with water (2 × 20 ml), and dried ($MgSO_4$). Distillation of the solvent gave an oil which dissolved in anhydrous ether (100 ml). Anhydrous hydrogen bromide was bubbled through this solution, to give 2-*aminomethyl*-1,2,3,4-*tetrahydro*-3,6-*dimethyl*-3-*benzazocine* (13) *dihydrobromide* (0.38 g, 69%), m.p. 156 °C (with decomp.) (hygroscopic) (dried in a vacuum desiccator, then recrystallised from ethanol–light petroleum), $\nu_{max.}$ ($CHBr_3$) 3 300—3 600br and 2 500—2 700br $cm^{-1}$ ($\overset{+}{NH_3}$ + $\overset{+}{>}NHMe$); δ ($D_2O$) 2.20 (s, 3 H, Me), 2.97 and 3.07 (2 × s, 3 H, $\overset{+}{>}NHMe$), 2.90—4.00 (m, 7 H, 1- and 4-$CH_2$, $CH_2N$, and 2-H), 5.94 (t, 1 H, 5-H), and 7.52 (s, 4 H, aromatic) (Found: C, 42.2; H, 5.8; N, 6.7. $C_{14}H_{22}Br_2N_2 \cdot H_2O$ requires C, 42.4; H, 6.1; N, 7.0%) (Found: $M^+$, 216.1625. $C_{14}H_{20}N_2$ requires $M$, 216.1625).

1,2,3,4-*Tetrahydro*-3,6-*dimethyl*-3-*benzazocine*-2-*carboxamide* (9) *Hydrochloride*.—(*a*) Anhydrous hydrogen chloride was bubbled for 12 h through a solution of 1,2,3,4-tetrahydro-3,6-dimethyl-3-benzazocine-2-carbonitrile (8) hydrochloride (0.1 g, 0.4 mmol) in anhydrous ethanol (20 ml) at ambient temperature. Then the mixture was evaporated to dryness under reduced pressure, to give 1,2,3,4-*tetrahydro*-3,6-*dimethyl*-3-*benzazocine*-2-*carboxamide* (9) *hydrochloride* (0.097 g, 90%), m.p. 266—268 °C (from ethanol–light petroleum), $\nu_{max.}$ (Nujol) 1 700 (CO) and 3 100 and 3 250 $cm^{-1}$ ($NH_2$); δ ($D_2O$) 2.17 (s, 3 H, Me), 2.82 and 2.98 (2 × s, 3 H, $\overset{+}{>}NHMe$), 3.00—3.80 (m, 4 H, 1- and 4-$CH_2$), 3.90 and 4.30 (2 × t, 1 H, 2-H), 5.90 (m, 1 H, 5-H), and 7.30—7.60 (m, 4 H, aromatic) (Found: C, 61.0; H, 7.0; N, 10.0. $C_{14}H_{19}ClN_2O \cdot 0.5H_2O$ requires C, 61.0; H, 6.9; N, 10.2%) (Found: $M^+$, 230.1417. $C_{14}H_{18}N_2O$ requires $M$, 230.1418).

(*b*) A solution of 1,2,3,4-tetrahydro-3,6-dimethyl-3-benzazocine-2-carbonitrile (8) (0.1 g, 0.47 mmol) in anhydrous ethanol (5 ml) at 0 °C was saturated with anhydrous hydrogen chloride and the resulting mixture was stirred at 0 °C for 3 h. The solvent was distilled off under reduced pressure to give a

white crystalline solid which was identified as a two component mixture (t.l.c.) containing the hydrochloride of the starting material and 1,2,3,4-tetrahydro-3,6-dimethyl-3-benzazocine-2-carboxamide hydrochloride (ratio 2 : 3).

1-*Methyl*-2-(N-*methylaminomethyl*)*naphthalene* (17) *Hydrochloride*.—Anhydrous hydrogen chloride was bubbled for 3.5 h through a solution of 1,2,3,4-tetrahydro-3,6-dimethyl-3-benzazocine-2-carbonitrile (8) hydrochloride (0.5 g, 2.0 mmol) in 10% aqueous ethanol (30 ml) heated under reflux, then the solution was cooled and the solvent distilled off to give a white crystalline solid. Chloroform (100 ml) was added to this solid and the mixture was heated under reflux for 1 h, then filtered to remove traces of insoluble material. Distillation of the solvent gave 1-*methyl*-2-(N-*methylaminomethyl*)*naphthalene* (17) *hydrochloride* (0.24 g, 55%), m.p. 249—251 °C (from chloroform–light petroleum); $\nu_{max.}$ (free base) (film) 3 300br cm$^{-1}$ (NH); $\lambda_{max.}$ (EtOH) (HCl salt) 228 (ε 87 100), 275sh, 283 (5 550), 292sh, 308, 317, and 322.5 nm (460) (similar to the data for 1,2-dimethylnaphthalene [56]); δ (HCl salt in $D_2O$) 2.70 (s, 3 H, Me), 2.92 (s, 3 H, NMe), 4.45 (s, 2 H, $CH_2$), 7.50 (d, 1 H, 3-H), 7.60—7.90 (m, 2 H, 6- and 7-H), 7.90 (d, 1 H, 4-H), and 7.90—8.27 (m, 2 H, 5- and 8-H) (Found: C, 70.2; H, 7.2; Cl, 16.3; N, 6.2. $C_{13}H_{16}ClN$ requires C, 70.4; H, 7.3; Cl. 16.0; N, 6.3%) (Found: $M^+$, 185.268. $C_{13}H_{15}N$ requires *M*, 185.269).

1-[2-(N-*Benzyl*-N-*methylamino*)*ethyl*]-1-*methyl*-2-*tetralone* (20).—(*a*) A stirred mixture of 1-[2-(*N*,*N*-dimethylamino)-ethyl]-1-methyl-2-tetralone (40.0 g, 173.0 mmol), benzyl chloride (24.2 g, 191.0 mmol), and dimethylformamide (300 ml) was heated under reflux under nitrogen for 24 h, then cooled, and the solvent distilled off under reduced pressure. The residue was dissolved in ether (200 ml), the ethereal solution extracted with 10% hydrochloric acid (2 × 100 ml), and the combined acidic extracts made alkaline by addition of 4M-ammonium hydroxide. Extraction with ether (2 × 10 ml) gave an oil which was chromatographed on alumina. Ether–light petroleum (1 : 4) eluted the *product* (20) (38.3 g, 72%), b.p. 159—161 °C at 5.0 mmHg; $\nu_{max.}$ 1 700 cm$^{-1}$ (CO); δ ($CDCl_3$) 1.40 (s, 3 H, 1-Me), 1.94—2.30 (m, 5 H, $CH_2$ and NMe), 2.34—2.80 (m, 4 H, 3-$CH_2$ and N$CH_2$), 3.00 (m, 2 H, 4-$CH_2$), 3.30 (s, 2 H, benzylic $CH_2$), and 6.95—7.37 (m, 9 H, aromatic); δ($^{13}$C)·($CDCl_3$) 28.2 (q and t, 1-Me and $CH_2$), 37.6 (t, 2 × $CH_2$), 41.6 (q, NMe), 49.9 (s, C-1), 53.6 (t, $CH_2$), 61.5 (t, benzylic $CH_2$), 126.0, 126.2, 126.5, 126.7, 127.8 [probably a C(3)-atom signal], 128.8 [probably a C(2)-atom signal] (all doublets), 135.7 (s, C-4a or -8a), 138.4 (s, C-4a or -8a), 141.3 (s, C-1 of phenyl group), and 213.2 p.p.m. (s, CO) (Found: C, 81.7; H, 8.4; N, 4.5%; $M^+$, 307.1935. $C_{21}H_{25}NO$ requires C, 82.05; H, 8.2; N, 4.6%; *M*, 307.1935); *hydrochloride*, m.p. 177—179 °C (from chloroform–light petroleum) (hygroscopic).

(*b*) A solution of 1-methyl-2-tetralone (1.60 g, 10.0 mmol) in anhydrous toluene (10 ml) was added to a stirred mixture of sodamide (0.39 g, 10.0 mmol) in anhydrous toluene (10 ml) heated under reflux and the mixture was heated under reflux for a further 3 h. Then a solution of 2-(*N*-benzyl-*N*-methylamino)ethyl chloride (1.84 g, 10.0 mmol) in anhydrous toluene (10 ml) was added during 1 h and the mixture was heated under reflux for a further 12 h. The mixture was washed with water and extracted with 10% hydrochloric acid (2 × 20 ml). The combined acidic extracts were made alkaline by addition of 4M-ammonium hydroxide and the crude product (1.24 g) extracted with ether. T.l.c. analysis suggested that it was a single compound but $^1$H n.m.r. analysis showed the product to be a mixture of 1-[2-(*N*-benzyl-*N*-methylamino)ethyl]-1-methyl-2-tetralone (20) and 2-(*N*-benzyl-*N*-methylamino)-ethyl chloride (ratio *ca.* 6 : 1). Chromatography of this product either on silica or alumina using a series of solvent systems failed to achieve a separation of these compounds, whilst distillation under reduced pressure gave only 2-(*N*-benzyl-*N*-methylamino)ethyl chloride and residual tar.

(*c*) The reaction described in (*b*) was repeated with the sodamide replaced by sodium hydride, potassium amide, or potassium t-butoxide. A similar mixture to that obtained in (*b*) was obtained in each case.

(*d*) The reaction described in (*b*) was repeated with 1,2-dimethoxyethane as the solvent instead of toluene. Work-up as described in (*b*) gave a similar crude product (1.38 g) though containing more unidentified impurities (t.l.c.).

(*e*) The reaction described in (*b*) was repeated but with addition of sodium iodide (3.0 g, 20.0 mmol). Work-up as described in (*b*) gave a similar product.

1-[2-(N-*Ethoxycarbonyl*-N-*methylamino*)*ethyl*]-1-*methyl*-2-*tetralone* (22; $R^1$ = Et, $R^2$ = H).—1-[2-(*N*,*N*-Dimethylamino)-ethyl]-1-methyl-2-tetralone (15.0 g, 65.0 mmol) in benzene (100 ml) was added dropwise to a stirred solution of ethyl chloroformate (14.1 g, 130.0 mmol) in benzene (100 ml) at ambient temperature, and the resulting mixture was heated under reflux for 2 h. Then it was washed successively with 5% hydrochloric acid (2 × 50 ml) and water (2 × 50 ml), and dried ($MgSO_4$). Distillation gave the *product* (22; $R^1$ = Et, $R^2$ = H) (14.1 g, 75%), b.p. 169—171 °C at 760.0 mmHg; $\nu_{max.}$ 1 680 cm$^{-1}$ (both CO groups); δ 1.20 (t, 3 H, *J* 7.0 Hz, Me), 1.41 (s, 3 H, 1-Me), 2.78 (s, 3 H, NMe), 1.70—3.70 (m, 8 H, 4 × $CH_2$), 4.05 (q, 2 H, *J* 7.0 Hz, $CH_2$), and 7.00—7.50 (m, 4 H, aromatic) (Found: C, 70.7; H, 8.0; N, 4.8. $C_{17}H_{23}NO_3$ requires C, 70.6; H, 8.0; N, 4.8%).

A similar attempt (reflux time 24 h) to prepare 1-[2-(*N*-benzyloxycarbonyl-*N*-methylamino)ethyl]-1-methyl-2-tetralone (22; $R^1$ = $CH_2Ph$, $R^2$ = H) gave only starting materials (t.l.c.).

*Attempts to Cleave* 1-[2-(N-*Ethoxycarbonyl*-N-*methylamino*)*ethyl*]-1-*methyl*-2-*tetralone* (22; $R^1$ = Et, $R^2$ = H).—(*a*) A stirred mixture of the carbamate (22; $R^1$ = Et, $R^2$ = H) (1.5 g, 5.2 mmol), potassium hydroxide (2.0 g, 50.0 mmol), and t-butyl alcohol (30 ml) was heated under reflux under nitrogen for 8 h, then cooled and the solvent distilled off under reduced pressure. The residue was dissolved in ether and the ethereal solution was extracted with 10% hydrochloric acid (2 × 20 ml). The combined acidic extracts were made alkaline by addition of 4M-ammonium hydroxide, and extraction with ether gave a complex mixture (at least 15 components by t.l.c.) which was not examined further.

(*b*) The reaction described in (*a*) was repeated at 25 and 0 °C and with ethanol or methanol as the solvent (instead of t-butyl alcohol) containing varying amounts (0.1—2.0 g) of potassium hydroxide. Complex mixtures (t.l.c.) were obtained in all cases.

(*c*) Iodotrimethylsilane (1.4 g, 7.0 mmol) was syringed into a stirred solution of the carbamate (22; $R^1$ = Et, $R^2$ = H) (1.0 g, 3.5 mmol) in anhydrous chloroform (20 ml) under nitrogen at ambient temperature; then the mixture was warmed up to 60 °C and stirred at this temperature for 18 h. Methanol (4.0 ml) was added and the mixture was evaporated to dryness under reduced pressure. The residue was dissolved in methanol (20 ml) and sodium methoxide (0.2 g, 3.7 mmol) was added. Distillation of the solvent and other volatiles under reduced pressure gave only starting material (0.6 g, 60% recovery), b.p. 169—171 °C at 760.0 mmHg.

(*d*) A mixture of the carbamate (22; $R^1$ = Et, $R^2$ = H) (1.0 g, 3.5 mmol), chlorotrimethylsilane (0.76 g, 7.0 mmol), sodium iodide (1.50 g, 10.0 mmol), and anhydrous aceto-

nitrile (30 ml) was heated under reflux under nitrogen for 18 h, then cooled, and methanol (2.0 ml) added. The mixture was stirred for a further 30 min, then evaporated to dryness. The residue was dissolved in methanol (20 ml), sodium methoxide (0.2 g, 3.7 mmol) added, and the solvent distilled off. The second residue was shaken with a mixture of ether (20 ml) and water (20 ml), and the ethereal layer was separated, washed successively with water (20 ml) and 10% aqueous sodium thiosulphate (20 ml), dried ($MgSO_4$), and the solvent distilled; only starting material (0.45 g, 45% recovery) was obtained.

*Bromination of* 1-[2-(N-*Ethoxycarbonyl*-N-*methylamino*)-*ethyl*]-1-*methyl*-2-*tetralone* (22; $R^1$ = Et, $R^2$ = H).—(*a*) Bromine (0.62 g, 38.75 mmol) in chloroform (30 ml) was added during 1.5 h to a stirred solution of the carbamate (22; $R^1$ = Et, $R^2$ = H) (1.0 g, 3.5 mmol) in chloroform (20 ml) containing concentrated sulphuric acid (0.5 ml) heated under reflux. The resulting mixture was heated under reflux for a further 1 h, then cooled, and made alkaline by addition of 2M-sodium hydrogen carbonate. The organic layer was separated, washed with water (2 × 50 ml), dried ($MgSO_4$), and the solvent distilled to give 3,3-*dibromo*-1-[2-(N-*ethoxycarbonyl*-N-*methylamino*)*ethyl*]-1-*methyl*-2-*tetralone* (28) (1.18 g, 75%), m.p. 131—133 °C (from aqueous acetone); $\nu_{max.}$ ($CHBr_3$) 1 680 and 1 720 $cm^{-1}$ (carbamate and ketone CO); δ ($CDCl_3$) 1.23 (t, 3 H, $CO_2CH_2CH_3$), 1.64 (s, 3 H, 1-Me), 1.90—3.50 (m, 4 H, $-CH_2CH_2-$), 2.82 (s 3 H, NMe), 4.10 (q and s, 4 H, $CO_2CH_2CH_3$ and 4-$CH_2$) (in $C_6D_6$ the singlet separated at δ 3.8 from the quartet), and 7.10—7.60 (m, 4 H, aromatic) (Found: C, 45.9; H, 4.8; N, 3.0. $C_{17}H_{21}Br_2NO_3$ requires C, 45.7; H, 4.7; N, 3.1%): at 90 °C in dimethyl sulphoxide the $^1H$ n.m.r. spectrum of (28) changed to that of the elimination product (29); δ 1.30 (t, 3 H, Me), 1.62 (s, 3 H, 1-Me), 2.30—2.60 (m, 2 H, $CH_2$), 2.78 (s, 3 H, NMe), 2.95 (m, 2 H, $CH_2N$), 4.00 (q, 2 H, $CH_2$), 7.40—7.70 (m, 4 H, aromatic), and 8.33 (s, 1 H, 4-H).

(*b*) Bromination of the carbamate (1.5 g, 5.2 mmol) using the same procedure as that used to prepare 3-bromo-1-[2-(*N*,*N*-dimethylamino)ethyl]-1-methyl-2-tetralone also gave only the 3,3-dibromo derivative (28) (0.57 g, 25%).

(*c*) A mixture of the carbamate (1.0 g, 3.5 mmol) and copper(II) bromide (0.78 g, 3.5 mmol) in tetrahydrofuran (50 ml) was heated under reflux for 2 h, then cooled, and water (100 ml) added. Extraction with chloroform (2 × 100 ml) gave only the 3,3-dibromo derivative (28) (0.46 g, 30%).

(*d*) A mixture of the carbamate (1.0 g, 3.5 mmol), *N*-bromosuccinimide (0.93 g, 5.23 mmol), and tetrachloromethane (20 ml) was stirred at ambient temperature for 5 h, then filtered, the filtrate washed with water (3 × 50 ml), dried ($MgSO_4$), and the solvent distilled to give the 3,3-dibromo derivative (28) (0.48 g, 32%).

(*e*) Pyrrolidone hydrotribromide (1.60 g, 3.5 mmol) in chloroform (100 ml) was added during 1 h to a solution of the carbamate (1.0 g, 3.5 mmol) in chloroform (100 ml) at ambient temperature, then the mixture was heated under reflux for 30 min, cooled, washed with water (3 × 150 ml), dried ($MgSO_4$), and the solvent distilled to give the 3,3-dibromo derivative (28) (0.53 g, 35%).

1-[2-(N-*Ethoxycarbonyl*-N-*methylamino*)*ethyl*]-2-*methoxy*-1-*methyl*-1,4-*dihydronaphthalene* (30).—A mixture of 1-[2-(*N*-ethoxycarbonyl-*N*-methylamino)ethyl]-1-methyl-2-tetralone (22; $R^1$ = Et, $R^2$ = H) (5.0 g, 17.3 mmol), trimethyl orthoformate (2.0 g, 18.9 mmol), toluene-4-sulphonic acid (0.1 g), and methanol (20 ml) was heated under reflux for 20 h, then cooled and the solvent distilled off. A solution of the residue in chloroform (50 ml) was washed with water (2 × 50 ml), dried ($MgSO_4$), and distillation gave the *product* (30) (4.41 g, 85%), b.p 150 °C at 100 mmHg; $\nu_{max.}$ 1 680 $cm^{-1}$ (CO); δ ($CDCl_3$) 1.22 (t, 3 H, *J* 7.0 Hz, Me), 1.50 (s, 3 H, 1-Me), 1.81—3.17 (m, 5 H, five $CH_2$ protons), 2.65 (s, 3 H, NMe), 3.41—3.84 (m, 1 H, one $CH_2$ proton), 3.55 (s, 3 H, OMe), 4.12 (q, 2 H, *J* 7.0 Hz, $CH_2$), 4.95 (t, 1 H, 3-H), and 7.04—7.68 (m, 4 H, aromatic) (Found: $M^+$, 303.4020. $C_{18}H_{25}NO_3$ requires *M*, 303.4022).

*Attempted Bromination of* 1-[2-(N-*Ethoxycarbonyl*-N-*methylamino*)*ethyl*]-2-*methoxy*-1-*methyl*-1,4-*dihydronaphthalene* (30).—This compound (1.0 g, 3.3 mmol) was brominated using the five methods, (*a*)—(*e*), used to brominate 1-[2-(*N*-ethoxycarbonyl-*N*-methylamino)ethyl]-1-methyl-2-tetralone (22; $R^1$ = Et, $R^2$ = H) (see before) with the only exception that, with method (*a*), concentrated sulphuric acid was not added. In each case 3,3-dibromo-1-[2-(*N*-ethoxycarbonyl-*N*-methylamino)ethyl]-1-methyl-2-tetralone (28) (20—40%) was the only isolable product.

1-[2-(N-*Benzyl*-N-*methylamino*)*ethyl*]-1-*methyl*-2-*tetralone Ethylene Acetal* (31; R = $CH_2Ph$).—A mixture of 1-[2-(*N*-benzyl-*N*-methylamino)ethyl]-1-methyl-2-tetralone (20) (20 g, 65.0 mmol), ethylene glycol (50 ml, large excess), toluene-4-sulphonic acid (0.5 g), and toluene (300 ml) was heated under reflux for 6 h with azeotropic removal of water (Dean–Stark apparatus) and addition of further quantities (1.0 g) of toluene-4-sulphonic acid each 30 min. The resulting mixture was cooled, washed with water (3 × 200 ml), dried ($MgSO_4$), and the solvent distilled off to give a residue which was chromatographed on alumina. Ether–light petroleum (1 : 4) eluted the *product* (31; R = $CH_2Ph$) (17.1 g, 75%) as a colourless oil, b.p. 165—167 °C at 5.0 mmHg; δ ($CDCl_3$) 1.30 (s, 3 H, 1-Me), 1.60—2.54 (m, 6 H, 3 × $CH_2$), 2.00 (s, 3 H, NMe), 2.87 (t, 2 H, 4-$CH_2$), 3.34 (s, 2 H, benzylic $CH_2$), 3.84 (s, 4 H, acetal $CH_2$ groups), and 6.87—7.34 (m, 9 H, aromatic); δ ($^{13}C$) ($CDCl_3$) 21.7 (q, 1-Me), 26.9 (t, $CH_2$), 27.2 (t, $CH_2$), 36.5 (t, $CH_2$), 41.9 (q, NMe), 44.7 (s, C-1), 53.5 (t, $CH_2$), 61.8 (t, benzylic $CH_2$), 64.1 (t, $CH_2O$), 64.4 (t, $CH_2O$), 111.9 (s, C-2), 125.2, 126.4, 127.7, 128.3, 128.5 (all d, overlapping peaks in aromatic region), 134.0 (s, C-4a or -8a), 138.9 (s, C-4a or -8a), and 142.6 p.p.m. (s, C-1 of phenyl group) (Found: $M^+$, 351.487. $C_{23}H_{29}NO_2$ requires *M*, 351.489).

1-[2-(N-*Methylamino*)*ethyl*]-1-*methyl*-2-*tetralone Ethylene Acetal* (31; R = H).—10% Palladium–charcoal (0.5 g) was added to a solution of 1-[2-(*N*-benzyl-*N*-methylamino)ethyl]-1-methyl-2-tetralone ethylene acetal (31; R = $CH_2Ph$) (10.0 g, 28.5 mmol) in 20% aqueous ethanol (50 ml) and the mixture was shaken overnight under hydrogen at atmospheric pressure. The palladium–charcoal was filtered off, the filtrate evaporated to dryness, and the residue chromatographed on alumina. Ether eluted the *product* (31; R = H) (6.7 g, 90%), b.p. 119—121 °C at 5.0 mmHg; $\nu_{max.}$ 3 320 $cm^{-1}$ (NH); δ ($CDCl_3$) 1.27 (s, 3 H, 1-Me), 1.64—2.10 (m, 4 H, 2 × $CH_2$), 2.14—2.70 (m, 2 H, $CH_2$), 2.25 (s, 3 H, NMe), 2.90 (t, 2 H, 4-$CH_2$), 3.94 (s, 4 H, acetal $CH_2$ groups), and 6.90—7.27 (m, 5 H, NH and aromatic); δ ($^{13}C$) ($CDCl_3$) 21.2 (q, 1-Me), 27.2 (t, $CH_2$), 27.4 (t, $CH_2$), 36.1 (q, NMe), 40.0 (t, $CH_2$), 45.0 (s, C-1), 48.4 (t, $CH_2$), 64.4, (t, $CH_2O$), 64.8 (t, $CH_2O$), 112.3 (s, C-2), 125.5, 126.6, 128.5 (all d, overlapping peaks in aromatic region), 134.5 (s, C-4a or -8a), and 143.2 p.p.m. (s, C-4a or -8a) (Found: $M^+$, 261.1727. $C_{16}H_{23}NO_2$ requires *M*, 261.1728): *hydrochloride*, m.p. 184—186 °C (from chloroform–light petroleum) (Found: C, 64.6; H, 8.0; N, 4.7. $C_{16}H_{24}ClNO_2$ requires C, 64.5; H, 8.1; N, 4.7%).

*Hydrolysis of* 1-[2-(N-*Methylamino*)*ethyl*]-1-*methyl*-2-*tetralone Ethylene Acetal* (31; R = H).—The acetal (31; R = H) (1.5 g, 5.7 mmol) was added to a mixture (20 ml) of acetonitrile, water, and 2M-sulphuric acid (ratio 6 : 2 : 1) under nitrogen and the mixture was stirred at ambient temperature for 18 h. The solvent was distilled off and the residue made alkaline by addition of saturated aqueous sodium hydrogen carbonate. Extraction with ether (2 × 20 ml) gave 3,9b-dimethyl-2,3,5,9b-tetrahydro-1*H*-benz[*e*]indole (23; R = H) (1.03 g, 90%); extremely air-sensitive: $\nu_{max.}$ 1 660 $cm^{-1}$ (C=C); δ ($CDCl_3$) 1.34 (s, 3 H, 9b-Me), 2.10—2.44 (m, 2 H, 1-$CH_2$), 2.80 (s, 3 H, NMe), 3.00—3.67 (m, 4 H, 2- and 5-$CH_2$), 4.40 (m, 1 H, 4-H), and 7.24 (s, 4 H, aromatic) (Found: $M^+$, 199.1360. $C_{14}H_{17}N$ requires *M*, 199.1360).

1-[2-(N-*Chloro*-N-*methylamino*)*ethyl*]-1-*methyl*-2-*tetralone Ethylene Acetal* (31; R = Cl).—0.25M-Sodium hypochlorite (40 ml) was added dropwise to a stirred solution of 1-(2-*N*-methylaminoethyl)-1-methyl-2-tetralone ethylene acetal (31; R = H) (0.5 g, 1.9 mmol) in dichloromethane (20 ml) under nitrogen at ambient temperature in the dark and the resulting mixture was stirred vigorously for a further 3 h. The separated organic layer was washed with water (3 × 20 ml), dried ($MgSO_4$), and distilled to give the *product* (31; R = Cl) (0.53 g, 95%), b.p. 126—128 °C at 5.0 mmHg; δ ($CDCl_3$) 1.50 (s, 3 H, 1-Me), 1.94—2.44 (m, 4 H, 2 × $CH_2$), 2.84—3.34 (m, 4 H, 2 × $CH_2$), 2.95 (s, 3 H, NMe), 4.17 (s, 4 H, acetal $CH_2$ groups), and 7.20—7.64 (m, 4 H, aromatic) (Found: $M^+$, 295.1339. $C_{16}H_{22}ClNO_2$ requires *M*, 295.1338).

*Attempted Conversion of* 1-[2-(N-*Chloro*-N-*methylamino*)-*ethyl*]-1-*methyl*-2-*tetralone Ethylene Acetal* (31; R = Cl) *into the Title Compound* (1).—(*a*) A mixture of anhydrous trifluoroacetic acid (1.45 g, 13.0 mmol) and anhydrous methanol (10 ml) was added to a stirred solution of the ethylene acetal (31; R = Cl) (0.5 g, 1.7 mmol) in anhydrous methanol (10 ml) at 0 °C. The mixture was allowed to warm up slowly to ambient temperature, then heated under reflux for 3 h. Potassium carbonate (10.0 g) was added, the mixture was heated under reflux for a further 1 h, then cooled, the solvent distilled off, and the residue dissolved in water (20 ml). Extraction with ether (2 × 20 ml) gave a light brown oil (0.22 g, 65%) which darkened on exposure to air. $^1H$ N.m.r. spectroscopic analysis of this oil showed it to be 3,9b-dimethyl-2,3,5,9b-tetrahydro-1*H*-benz[*e*]indole (23; R = H), identical with the sample prepared as described before.

(*b*) The reaction described in (*a*) was repeated but the methanol was replaced by anhydrous dichloromethane; the same product (23; R = H) was obtained in the same yield.

(*c*) The ethylene acetal (31; R = Cl) (0.5 g, 1.7 mmol) was added to trifluoroacetic acid (5 ml) at 0 °C under nitrogen and the resulting mixture was allowed to warm up to ambient temperature. Distillation of the solvent under reduced pressure gave a residue which was dissolved in methanol (10 ml). Potassium hydrogen carbonate (2.0 g) was added to the methanolic solution which was heated under reflux for 1 h. The solvent was distilled off and the residue dissolved in water (20 ml). Extraction with dichloromethane (2 × 20 ml) also gave 3,9b-dimethyl-2,3,5,9b-tetrahydro-1*H*-benz[*e*]indole (23; R = H) (0.2 g, 59%).

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