Synthesis and Some Reactions of 3,4,5,6-Tetrahydro-3,6-dimethyl-2,6-methano-3-benzazocin-1(2*H*)-one (2,5-Dimethyl-8-oxo-6,7-benzomorphan)

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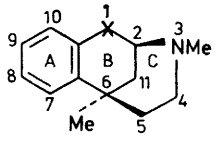
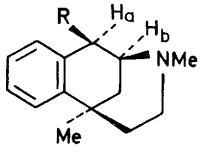
In a Beckmann rearrangement the oxime of the title compound (1) gave 1,3,4,5,6,7-hexahydro-4,7-dimethyl-3,7-methano-1,4-benzodiazonin-2-one (3). Hydrolysis of this product (3) with hydrochloric acid gave 4-(2-aminophenyl)-1,4-dimethylpiperidine-2-carboxylic acid (5) (see Scheme), which was converted into its ethyl ester (7) and cyclised in polyphosphoric acid to give back starting material (3). With tetraphosphorus decasulphide the lactam (3) gave the thiolactam (10). Whereas lactam (3) was alkylated on nitrogen with methyl iodide, to give (8), the thiolactam (10) was alkylated on sulphur, to give (11). Lactams (3) and (8) were reduced with lithium aluminium hydride. Reduction of the title compound (1) with sodium cyanohydridoborate in the presence of ammonium acetate gave a mixture containing 1-α-amino- (14) and 1-α-hydroxy-1,2,3,4,5,6-hexahydro-3,6-dimethyl-2,6-methano-3-benzazocine (15).†

ALTHOUGH compounds such as 3,4,5,6-tetrahydro-3,6-dimethyl-2,6-methano-3-benzazocin-1(2*H*)-one (2,5-dimethyl-8-oxo-6,7-benzomorphan) (1) have been known for some time as intermediates for the synthesis of clinically useful benzomorphans their chemistry has been explored very little.[1] Previously, structure–activity studies on compounds with morphine-like analgesic activity have led to some understanding of the nature of opiate receptors.[2] With these facts in mind we considered that it would be useful to expand ring B in (1) and to



(1) X = C=O
(2) X = CH_2



(14) R = NH_2
(15) R = OH
(16) R = OAc

explore the chemistry and biological properties of compounds produced in this way. In compounds such as (3) (Scheme) the tertiary N-atom offers a different spatial relationship relative to other features of the molecule, for example the aromatic ring, believed to be essential for receptor binding (*cf.* ref. 3). In this way we hoped to explore the effect of changing this relationship on the resulting biological properties of our target molecules. Ideally, such changes might result in separating the analgesic properties from the undesirable side-effects usually associated with morphine-like behaviour.[4]

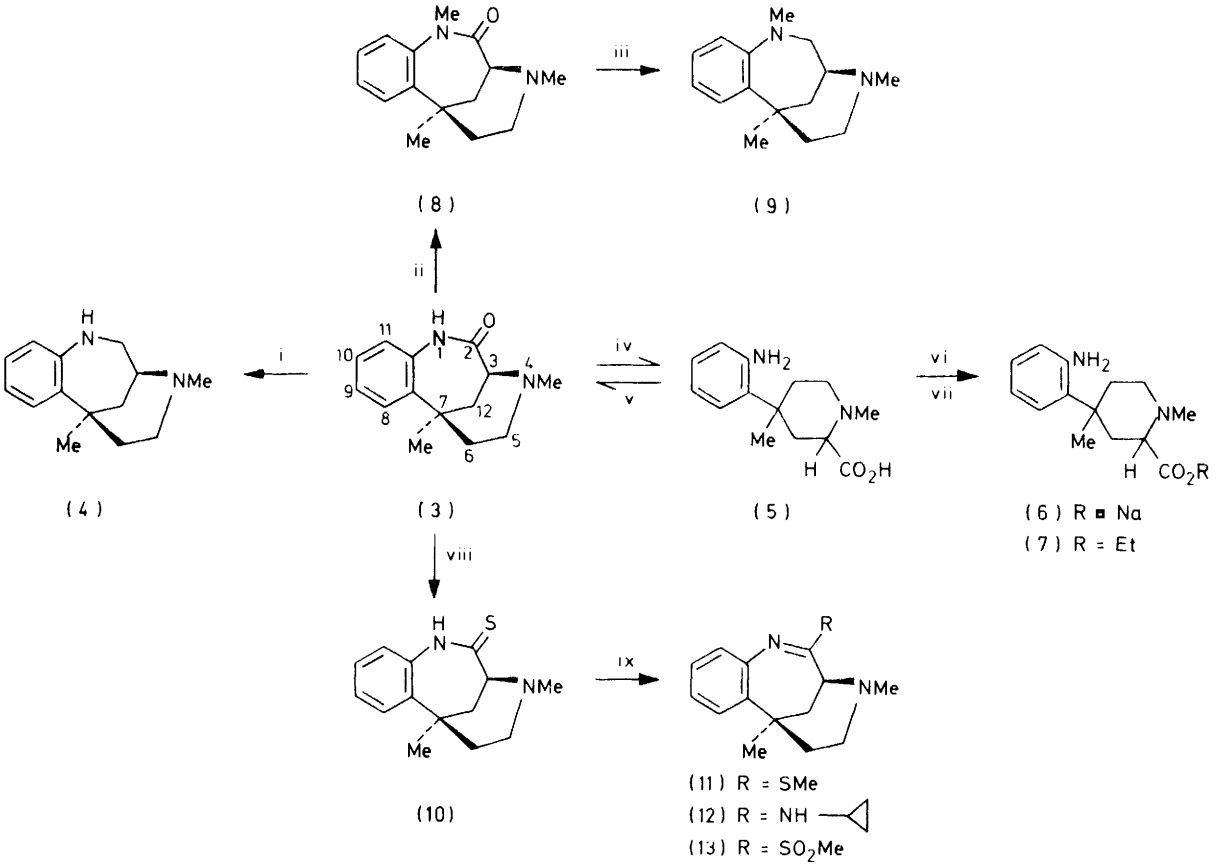
The starting material for the synthesis of (1), namely 1,2,3,4,5,6-hexahydro-3,6-dimethyl-2,6-methano-3-benzazocine (2), was prepared as an enantiomeric mixture (*cf.* refs. 5 and 6), by treatment of 4-methylpyridine methiodide with benzylmagnesium chloride,[7] reduction of the unstable product, 2-benzyl-1,2-dihydro-1,4-dimethylpyridine, with sodium borohydride,[1,8] and cyclisation of the 2-benzyl-1,2,5,6-tetrahydro-1,4-dimethylpyridine produced with 48% aqueous hydrobromic acid.[1,9]

Attempted conversion of (2) into (1) by benzylic oxidation with chromium trioxide in sulphuric acid according to procedures reported in the literature [10,11] for related systems gave only starting material. When the reaction mixtures were heated under reflux for 18 h the desired product (1) was obtained but only in low yield (<5%). Yields were increased, however, to an optimum of 42% by the use of a large excess of chromium trioxide (see Experimental section) and the product was separated from the starting material, which was re-used, by the formation of its bisulphite addition compound. Thiele's reagent [12] (chromium trioxide in acetic anhydride–concentrated sulphuric acid) gave a complex mixture (t.l.c. and i.r. spectrum) which was not examined further, whilst ceric ammonium nitrate [13] and Corey's reagent (pyridinium chlorochromate) [14] yielded only starting material. Potassium permanganate was avoided because of the likelihood of oxidation of more than one methylene group in our systems. The benzylic-type radical, the initial species involved in the oxidation of (2) to (1),[15] is expected to form only slowly due to difficulty in its stabilisation through overlap of the sp^2-hybridised C-1's *p*-orbital with the aromatic ring, a conclusion supported by examination of molecular models.

The oxime of ketone (1) was prepared by a method used to prepare the oximes of closely related ketones,[16] and a Beckmann rearrangement was carried out in polyphos-

† Throughout this paper the α-isomer is the one with the 1-substituent *cis* to the *cis*-fused piperidine ring (ring c).

phoric acid at 150 °C. This gave a single product (59% yield) whose i.r. [$\nu_{max.}$ at 1 665 (CO) and 3 210 cm^{-1} (NH)] and ^1H n.m.r. spectra suggested that, in agreement with previous literature reports,[17] it had the acylanilide-type lactam structure (3) (Scheme) rather than the alternative benzamide-type lactam structure. Confirmatory evidence for the structure (3) proposed for this lactam was obtained from its hydrolysis with acid,[18-20] which gave the deliquescent hydrochloride salt of the amino-acid (5) ($\nu_{max.}$ 1 740 cm^{-1}; free base of amino-acid). This was converted into its sodium salt (6) and into its ethyl ester (7), which had spectroscopic and other properties in agreement with the structure proposed. As relatives of the biologically active 4-arylpiperidines these compounds are interesting in their own right. With polyphosphoric acid the amino-acid (5) was recyclised to the lactam (3).



SCHEME *Reagents:* i, $LiAlH_4$–THF; ii, MeI–NaH; iii, $LiAlH_4$–Et_2O; iv, HCl; v, PPA; vi, NaOH; vii, EtOH–H_2SO_4; viii, P_4S_{10}–pyridine; ix, NaH–MeI [for (11)].

Several attempts to expand ring B of 3,4,5,6-tetrahydro-3,6-dimethyl-2,6-methano-3-benzazocin-1(2*H*)-one (1) by means of the Schmidt reaction (with hydrazoic acid prepared *in situ* from sodium azide and a concentrated acid) failed. The following acid systems were tried: polyphosphoric; sulphuric; hydrochloric; trifluoroacetic; polyphosphoric–acetic; sulphuric–acetic; sulphuric–acetic anhydride; sulphuric–chloroform. In polyphosphoric acid the starting material was not very soluble. In the other systems solubility was not a problem and the reasons for the failure of the ketone to react are not clear (see following paper).

Reduction of the lactam (3) with lithium aluminium hydride in tetrahydrofuran [21] or ether gave a high yield of compound (4) whose ^1H n.m.r. spectrum lacked the presence of benzylic methylene proton signals. Reduction of the isomeric benzamide-type lactam would produce a new benzylic methylene group exhibiting a characteristic signal in the ^1H n.m.r. spectrum. We were not able to detect the expected coupling between the newly created methylene protons and the adjacent methine proton in the ^1H n.m.r. spectrum of this product because of overlapping signals. This was attempted in order to provide further evidence of the structure of lactam (3).

Attempts to *N*-alkylate lactam (3) with methyl iodide in dimethylformamide in the presence of sodium carbonate [22] or through formation of the sodium salt with sodamide in toluene [23,24] gave only starting material. With sodium hydride in a mixture of dimethylformamide and toluene,[20] however, a mixture of starting material, its methiodide salt, and an alkylated product was obtained. After chromatographic separation of the

alkylated product it was not possible to differentiate between *N*- (8) and *O*-alkylation either by i.r. ($\nu_{max.}$ 1 665 cm^{-1}) or ^1H n.m.r. spectroscopy. Examination of the ^{13}C n.m.r. spectrum of this product (8), however, revealed the presence of an amide carbonyl group C-atom at δ 176.6 p.p.m. [*cf.* δ 173.05 p.p.m. for the amide carbonyl C-atom of lactam (3)]. Reduction of this amide (8) with lithium aluminium hydride gave a product (9) (not fully characterised) whose i.r. and ^1H n.m.r. spectra lacked signals for a NH group, thus confirming the structure of the *N*-alkylated product (8). It is possible for *N*-alkylamides of type (8) to be formed by rearrangement of the initially generated *O*-alkylimidate [corresponding to (11); S = O].[25,26]

With tetraphosphorus decasulphide in pyridine [20] the lactam (3) was converted into the corresponding thiolactam (10) (78% yield). In contrast to *N*-alkylation of lactam (3), alkylation of thiolactam (10) under the same conditions yielded the *S*-alkylated product (11). The structure of this product was clear from an examination of its ^{13}C n.m.r. spectrum which exhibited a signal at δ 166.0 p.p.m. for the ring C-atom in the N=*C*(SMe) moiety [*cf.* the signal at δ 203.1 p.p.m. for the C-atom in the NH-*C*(=S) moiety of thiolactam (10)]. Unfortunately, it was not possible to purify compound (11) because of its low melting point and high solubility in most common solvents. An accurate mass measurement of its molecular ion peak in the mass spectrum was obtained and this, together with the fragmentation pattern, was in agreement with the structure (11) proposed. Whilst it formed a methiodide salt readily it was not possible to purify this derivative either. Hydrolysis of the thiolactam (10) with acid gave a product, namely (5) [isolated as its sodium salt (6)], identical with that obtained similarly from the lactam (3).

Amines such as (12) were one main type of target molecule in our project; compounds of this kind have been shown previously to have interesting biological properties.[20,25,27-29] We have prepared this type of compound previously by reaction of a *S*-alkylthioimidate, such as (11), or one of its salts with the appropriate amine or salt of the amine. Attempts to react compound (11) with various amines under different conditions [30] failed to give any of the desired products. In most cases starting material was recovered. Prop-2-ynylamine reacted in hot dimethylformamide but to give a complex mixture (t.l.c.) which was not examined further. Adoption of the technique of Fryer *et al.*[31] which, in our case, involved treatment of a cold mixture of lactam (3) and prop-2-ynylamine hydrochloride in tetrahydrofuran with a titanium tetrachloride–tetrahydrofuran complex, gave only the hydrochloride salt of the lactam (3).

An attempt to prepare compounds of type (12) by carrying out a Beckmann rearrangement of the benzenesulphonate derivative of the oxime of ketone (1) in the presence of the appropriate amine [32] failed at the oxime derivatisation stage, which yielded only the lactam (3), even at low temperatures (−5 °C).

Finally, in order to utilise the good leaving group properties of a methylsulphonyl group, we attempted a synthesis of sulphone (13) by oxidation of the parent compound (11) with potassium permanganate in acetic acid at ambient temperature. During the work-up procedure we made the reaction mixture alkaline by addition of dilute aqueous ammonium hydroxide. After extraction of the product with ether and chromatographic separation we obtained starting material (37% yield), lactam (3) (43%), and a trace of a third component (4%) which could not be purified but which ^1H n.m.r. and i.r. spectroscopy suggested was the desired sulphone (13). However, formation of the lactam (3) in this reaction confirms that the methylsulphonyl group in compound (13) is a very good leaving group since its formation can be explained by displacement of this group by water.

An attempt to prepare 1-α-amino-1,2,3,4,5,6-hexahydro-3,6-dimethyl-2,6-methano-3-benzazocine (14) by reductive amination of the ketone (1) with sodium cyanohydridoborate in methanol in the presence of ammonium acetate [33] gave a mixture of starting material (31%), 1,2,3,4,5,6-hexahydro-3,6-dimethyl-2,6-methano-3-benzazocine (2) (20%), the desired amine (14) (9.5%), and 1α-hydroxy-1,2,3,4,5,6-hexahydro-3,6-dimethyl-2,6-methano-3-benzazocine (15) (16.5%) (see following paper). In 2M-methanolic hydrogen chloride a similar reaction gave only starting material. The amine (14) was prepared unambiguously by reduction of the ketone (1) oxime with lithium aluminium hydride in ether, whilst the alcohol (15) was prepared by reduction of the parent ketone (1) with sodium borohydride in ethanol and characterised as its acetyl derivative (16). That compounds (14)—(16) have the structures shown is confirmed by an examination of their ^1H n.m.r. spectra in which proton H_a appears as a doublet with $J(H_aH_b)$ = 6.0—7.0 Hz at τ 6.05 for (14), 5.3 (15), and 3.9 (16) (lower field in this case because of the greater inductive electron-withdrawing effect of the 1-substituent). [12]

EXPERIMENTAL

I.r. spectra (liquids as films and solids as Nujol mulls between sodium chloride discs) were recorded with a Perkin-Elmer 257 or 297 spectrometer, n.m.r. spectra with a Varian EM360, HA100 (^1H), or CFT20 (^{13}C) spectrometer (with $SiMe_4$ as an internal standard) and mass spectra with an AEI MS12 or MS902S instrument. Characteristic frequencies only are reported; the spectra recorded were otherwise in agreement with the structures given.

Small-scale distillations were carried out with a Kugelrohr microdistillation apparatus and the ' b.p.' temperatures recorded in these cases are strictly speaking those of the oven at the time of distillation. In all cases organic extracts were combined, dried ($MgSO_4$), and evaporated on a rotary evaporator. Light petroleum had b.p. 60—80 °C unless stated otherwise.

The following compounds were prepared by literature procedures: 4-methylpyridine methiodide [34] (88%), m.p. 154—156 °C (from ethanol) (lit.,[34] 157—158 °C); 2-benzyl-1,4-dimethyl-1,2-dihydropyridine [7] (68%); 2-benzyl-1,4-dimethyl-1,2,5,6-tetrahydropyridine [7] (94%); and 1,2,3,4,5,6-hexahydro-3,6-dimethyl-2,6-methano-3-benzazocine (2) (2,5-dimethyl-6,7-benzomorphan) [7] (51%), b.p.

115—120 °C at 0.5 mmHg (lit.,[35] 110—120 °C at 0.5 mmHg).

3,4,5,6-Tetrahydro-3,6-dimethyl-2,6-methano-3-benzazocin-1(2H)-one (1).—Concentrated sulphuric acid (18 ml) was added to sufficient ice to make up a 200 ml solution. To half of this solution (100 ml) was added 1,2,3,4,5,6-hexahydro-3,6-dimethyl-2,6-methano-3-benzazocine (2) (4.5 g, 22.4 mmol) and the mixture was heated under reflux. Chromium trioxide (5.2 g, 52.0 mmol) was added to the other half and the resulting solution was added dropwise during 8 h to the stirred reaction mixture heated under reflux. The mixture was cooled, made alkaline by addition of concentrated ammonium hydroxide, and extracted with ether to yield a dark-green oil. This was distilled, b.p. 112—117 °C at 0.01 mmHg, to give a pale-yellow oil shown by t.l.c. to be a two-component mixture. A solution of this oil in methanol was stirred at ambient temperature with saturated aqueous sodium hydrogen sulphite to form a solid adduct which was filtered off. The precipitate was washed with ether and the bisulphite adduct was decomposed by addition to 4M-hydrochloric acid. The acidic solution was made alkaline by addition of dilute ammonium hydroxide and extracted with ether to give 3,4,5,6-tetrahydro-3,6-dimethyl-2,6-methano-3-benzazocin-1(2*H*)-one (1) (2.0 g, 42%), b.p. (Kugelrohr apparatus) 113—118 °C at 0.01 mmHg, m.p. 54—57 °C (from hexane); $\nu_{max.}$ 1 690 cm^{-1} (CO); τ ($CDCl_3$) 7.7 (s, 3 H, NMe) and 8.6 (s, 3 H, Me); δ (^{13}C n.m.r.) ($CHCl_3$) 194.5 p.p.m. (CO) (Found: C, 78.15; H, 8.2; N, 6.4. $C_{14}H_{17}NO$ requires C, 78.1; H, 8.0; N, 6.5%): *hydrobromide salt* (87%), m.p. 236—238 °C (with decomp.) (from aqueous ethanol), prepared by neutralizing a dry ethereal solution of the free base with a solution of 48% aqueous hydrobromic acid in acetic acid; the oil which separated quickly solidified and was triturated with warm acetone and then cooled at −15 °C overnight: the *oxime* [16] (69%) had m.p. 133—135 °C (from ethanol); $\nu_{max.}$ 960 cm^{-1} (N–O); τ (Me_2SO) −1.1br (s, 1 H, exchangeable, OH), 7.8 (s, 3 H, NMe), and 8.7 (s, 3 H, Me); δ (^{13}C n.m.r.) (dioxan) 150.8 p.p.m. (*C*=N·OH) (Found: C, 73.0; H, 7.9; N, 12.2%; M^+, 230. $C_{14}H_{18}N_2O$ requires C, 73.0; H, 7.9; N, 12.2%; *M*, 230). The preparation of ketone (1) was scaled up without problems.

Beckmann Rearrangement of 3,4,5,6-Tetrahydro-3,6-dimethyl-2,6-methano-3-benzazocin-1(2H)-one (1) *Oxime*.—A mixture of the oxime (0.51 g, 2.2 mmol) and polyphosphoric acid (12 g) was stirred at 150 °C for 1 h and then cooled and added carefully to water (35 ml). The resulting solution was made alkaline by addition of concentrated ammonium hydroxide, extracted with chloroform, and distilled to give a brown oil, which solidified to yield 1,3,4,5,6,7-*hexahydro-4,7-dimethyl-3,7-methano-1,4-benzodiazonin-2-one* (3) (0.3 g, 59%), m.p. 169—172 °C [from chloroform–light petroleum (b.p. 80—100 °C) with charcoal]; $\nu_{max.}$ 1 665 (CO) and 3 210 cm^{-1} (NH); τ ($CDCl_3$) 0.5br (s, 1 H, exchangeable, NH), 7.45 (s, 3 H, NMe), and 8.5 (s, 3 H, Me); δ (^{13}C n.m.r.) ($CDCl_3$) 173.05 p.p.m. (CO) (Found: C, 72.8; H, 7.6; N, 12.1%; M^+, 230. $C_{14}H_{18}N_2O$ requires C, 73.0; H, 7.9; N, 12.2%; *M*, 230): the *hydrobromide salt* (70%), prepared as described for the hydrobromide salt of (1), had m.p. 288—290 °C (with decomp.) (from 90% aqueous ethanol) (Found: C, 53.9; *H*, 6.3; N, 9.0. $C_{14}H_{19}BrN_2O$ requires C, 54.0; H, 6.15; N, 9.0%).

Hydrolysis of 1,3,4,5,6,7-Hexahydro-4,7-dimethyl-3,7-methano-1,4-benzodiazonin-2-one (3).—(*a*) A mixture of the lactam (3) (0.5 g, 2.2 mmol) and concentrated hydrochloric acid (10 ml) was heated under reflux for 30 min and then evaporated to dryness to give a pale-yellow solid, which was dissolved in ethanol and reprecipitated by addition of ether to the resulting solution. The acidic, solid product (5), $\nu_{max.}$ 1 740 cm^{-1}, was found to be highly deliquescent. Consequently, it was dissolved in water and the solution made alkaline by addition of 10% aqueous sodium hydrogen carbonate. After evaporation of the resulting solution to dryness and extraction of the residue with hot ethanol (3 × 50 ml) a white solid (6) (0.35 g, 60% overall yield) was obtained, m.p. >300 °C, $\nu_{max.}$ 1 605 cm^{-1}. It was not possible to purify this compound, nor was it possible to record its ^1H n.m.r. spectrum. Its i.r. spectrum, however, was consistent with the structure (6) proposed.

(*b*) A mixture of the sodium salt (6) (1.0 g, 3.7 mmol), ethanol (10 ml), concentrated sulphuric acid (5 ml), benzene (125 ml), and chloroform (125 ml), was heated under reflux for 24 h and then cooled, filtered, and extracted with 10% aqueous hydrochloric acid. The acidic extracts were combined, made basic by addition of concentrated ammonium hydroxide, and extracted with chloroform to give *ethyl 4-(2-aminophenyl)-1,4-dimethylpiperidine-2-carboxylate* (7) (0.95 g, 93%), m.p. 119—121 °C (from chloroform–light petroleum); $\nu_{max.}$ 1 730 (CO) and 3 350 and 3 450 cm^{-1} (NH); τ (CCl_4) 5.9 (q, 2 H, CH_2Me), 6.2br (s, 2 H, exchangeable, NH_2), 7.9 (s, 3 H, NMe), 8.7 (s, 3 H, Me), and 8.85 (t, 3 H, CH_2–CH_3); δ (^{13}C n.m.r.) ($CHCl_3$) 173.5 p.p.m. (ester CO) (Found: C, 69.25; H, 8.8; N, 10.1%; M^+, 276. $C_{16}H_{24}N_2O_2$ requires C, 69.5; H, 8.75; N, 10.1%; *M*, 276).

Cyclisation of 4-(2-Aminophenyl)-1,4-dimethylpiperidine-2-carboxylic Acid (5).—A mixture of the hydrochloride salt of the amino-acid (5) (0.2 g, 0.7 mmol) and polyphosphoric acid (300 g) was heated at 60 °C for 10 h and then poured into an ice–water mixture. The resulting solution was made alkaline by addition of concentrated ammonium hydroxide, and then extracted with chloroform to give the lactam (3) (0.14 g, 86%), m.p. 169—172 °C [from chloroform–light petroleum (b.p. 80—100 °C)], identical in other respects (i.r. and ^1H n.m.r. spectra) with the sample prepared as described before.

Reduction of 1,3,4,5,6,7-Hexahydro-4,7-dimethyl-3,7-methano-1,4-benzodiazonin-2-one (3).—A mixture of the lactam (3) (1.28 g, 5.56 mmol), lithium aluminium hydride (1.0 g, 26.3 mmol), and anhydrous tetrahydrofuran (70 ml) was stirred and heated under reflux under nitrogen for 20 h. Then the mixture was cooled in ice, and water (6 ml) was added carefully followed by 15% aqueous sodium hydroxide (1 ml). The precipitate was filtered off, washed with ether, and the filtrate was dried ($MgSO_4$). Distillation gave 2,3,4,5,6,7-*hexahydro-4,7-dimethyl-3,7-methano-1H-1,4-benzodiazonine* (4) (1.10 g, 91%), as an oil, b.p. (Kugelrohr apparatus) 146—150 °C at 0.04 mmHg; $\nu_{max.}$ 3 350 cm^{-1} (NH); τ ($CDCl_3$) 4.5br (s, 1 H, exchangeable, NH), 7.8 (s, 3 H, NMe), and 8.7 (s, 3 H, Me); M^+, 216: the *hydrobromide salt* (52%), prepared as described before for the hydrobromide salt of (1), had m.p. 269—271 °C (from ethanol) (Found: C, 56.3; H, 7.2; N, 9.4. $C_{14}H_{21}BrN_2$ requires C, 56.6; H, 7.1; N, 9.4%).

Alkylation of 1,3,4,5,6,7-Hexahydro-4,7-dimethyl-3,7-methano-1,4-benzodiazonin-2-one (3).—(*a*) Sodium hydride (0.01 g, 4.2 mmol) was added in portions to a stirred solution of the lactam (3) (0.46 g, 2.0 mmol) in a mixture of dimethylformamide (5 ml) and toluene (2.5 ml) at ambient temperature. When hydrogen evolution ceased, a solution of methyl iodide (0.28 g, 2.0 mmol) in toluene (2.5 ml) was added dropwise during 15 min. The resulting mixture was

stirred overnight at ambient temperature, then washed with water (see later), and dried ($MgSO_4$). Distillation of the solvents gave an oil (0.25 g), containing (t.l.c.) two major components, which was chromatographed on an alumina column. Chloroform eluted starting material (0.08 g, 17% recovery) and 1,3,4,5,6,7-*hexahydro*-1,4,7-*trimethyl*-3,7-*methano*-1,4-*benzodiazonin*-2-*one* (8) (0.14 g, 29%), m.p. 90—92 °C (from hexane); $\nu_{max.}$ 1 665 cm^{-1} (CO); τ ($CDCl_3$) 6.65 (s, 3 H, NMe), 7.8 (s, 3 H, NMe), and 8.6 (s, 3 H, Me); δ (^{13}C n.m.r.) ($CHCl_3$) 176.6 p.p.m. (CO) (Found: C, 73.6; H, 8.4; N, 11.35%; M^+, 244. $C_{15}H_{20}N_2O$ requires C, 73.7; H, 8.25; N, 11.5%; *M*, 244). The aqueous washings (see before) were combined and evaporated to dryness and the residue was extracted with hot ethanol. Distillation of the ethanol from the combined, dried ($MgSO_4$) extracts gave the *methiodide salt* of the lactam (3) as a white solid (0.14 g, 18%), m.p. 266—268 °C (with decomp.) (from ethanol) (Found: C, 48.1; H, 5.7; N, 7.5. $C_{15}H_{21}IN_2O$ requires C, 48.4; H, 5.7; N, 7.5%).

(*b*) A mixture of 1,3,4,5,6,7-hexahydro-1,4,7-trimethyl-3,7-methano-1,4-benzodiazonin-2-one (8) (100 mg, 0.4 mmol), lithium aluminium hydride (19 mg, 0.5 mmol), and anhydrous ether (25 ml) was stirred at ambient temperature for 20 h. The mixture was cooled in an ice-bath and water (1 ml) was added carefully. The precipitate was filtered off, washed with ether, and the filtrate and washings were combined and dried ($MgSO_4$). Distillation of the solvent gave 2,3,4,5,6,7-hexahydro-1,4,7-trimethyl-3,7-methano-1*H*-1,4-benzodiazonine (9) (90 mg, 98%), b.p. (Kugelrohr apparatus) 125—130 °C at 0.5 mmHg; τ ($CDCl_3$) 7.2 (s, 3 H, NMe), 7.8 (s, 3 H, NMe), and 8.7 (s, 3 H, Me) (no benzylic proton signals).

1,3,4,5,6,7-*Hexahydro*-4,7-*dimethyl*-3,7-*methano*-1,4-*benzodiazonine*-2-*thione* (10).—A mixture of the lactam (3) (0.17 g, 0.74 mmol) and tetraphosphorus decasulphide (0.17 g, 0.38 mmol) in pyridine (10 ml) was heated under reflux for 2 h; the volume of the mixture was then reduced by half by distillation of the solvent, and the residual mixture was heated under reflux for a further 1 h. The mixture was poured portionwise into boiling water (10 ml) and extracted with chloroform to give a dark-brown solid, which was chromatographed on alumina (50 g). Ethyl acetate–light petroleum (50 : 50) eluted the *thione* (10) (0.14 g, 78%), as a brown solid, m.p. 140—142 °C [from light petroleum (b.p. 80—100 °C)]; τ ($CDCl_3$) −0.2br (s, 1 H, exchangeable, NH), 7.4 (s, 3 H, NMe), and 8.5 (s, 3 H, Me); δ (^{13}C n.m.r.) ($CHCl_3$) 203.1 p.p.m. (CS) (Found: C, 68.2; H, 7.5; N, 11.3%; M^+, 246. $C_{14}H_{18}N_2S$ requires C, 68.25; H, 7.4; N, 11.4%; *M*, 246).

Alkylation of 1,3,4,5,6,7-*Hexahydro*-4,7-*dimethyl*-3,7-*methano*-1,4-*benzodiazonine*-2-*thione* (10).—Sodium hydride (0.1 g, 4.3 mmol) was added portionwise to a stirred solution of the thiolactam (10) (0.49 g, 2.0 mmol) in a mixture of dimethylformamide (5 ml) and toluene (2.5 ml) at ambient temperature. When hydrogen evolution ceased, a solution of methyl iodide (0.28 g, 2.0 mmol) in toluene (2.5 ml) was added dropwise during 15 min. Then, the mixture was stirred overnight at ambient temperature, washed with water, and the organic layer was dried ($MgSO_4$). Distillation of the solvents gave 3,4,5,6-*tetrahydro*-4,7-*dimethyl*-2-*methylthio*-3,7-*methano*-7H-1,4-*benzodiazonine* (11) (0.39 g, 75%), b.p. (Kugelrohr apparatus) 140—145 °C at 0.5 mmHg; m.p. 55—58 °C (after distillation); $\nu_{max.}$ 1 650 cm^{-1} (C=N); τ ($CDCl_3$) 7.3 (s, 3 H, NMe), 7.5 (s, 3 H, SMe), and 8.5 (s, 3 H, Me); δ (^{13}C n.m.r.) ($CHCl_3$) 166.0 p.p.m. (C=N) (Found: M^+, 260.134 7. $C_{15}H_{20}N_2S$ requires *M*, 260.134 7; the *methiodide salt* (45%) had m.p. 218—220 °C (with decomp.) [from chloroform–light petroleum (b.p. 80—100 °C)].

Hydrolysis of 1,3,4,5,6,7-*Hexahydro*-4,7-*dimethyl*-2-*methylthio*-3,7-*methano*-1,4-*benzodiazonine*-2-*thione* (10).—A mixture of the thiolactam (10) (0.5 g, 2.0 mmol) and concentrated hydrochloric acid (10 ml) was heated under reflux for 30 min and then evaporated to dryness. The residue was treated with 10% aqueous sodium hydrogen carbonate and the resulting solution was evaporated to dryness; extraction of the residue with hot ethanol gave the sodium salt (6) (0.31 g, 57%) of 4-(2-aminophenyl)-1,4-dimethylpiperidine-2-carboxylic acid (5), identical with the sample prepared as described before by hydrolysis of lactam (3).

Attempted Preparation of the Benzenesulphonate Derivative of 3,4,5,6-*Tetrahydro*-3,6-*dimethyl*-2,6-*methano*-3-*benzazocin*-1(2H)-*one* (1) *Oxime*.—A solution of the oxime (0.23 g, 1.0 mmol) in 10% aqueous sodium hydroxide (5 ml) was added to a solution of benzenesulphonyl chloride (0.17 g, 1.0 mmol) in acetone (5 ml) at ambient temperature and the resulting mixture was stirred for 1 h. Extraction of the resulting orange solution with ether gave a solid shown by t.l.c. to be a two-component mixture, which was chromatographed on alumina. Chloroform eluted starting material (0.04 g, 17%) and 1,3,4,5,6,7-hexahydro-4,7-dimethyl-3,7-methano-1,4-benzodiazonin-2-one (3) (0.12 g, 52%), identical in all respects with the sample prepared as described before.

Attempted Synthesis of 3,4,5,6-*Tetrahydro*-4,7-*dimethyl*-2-*methylsulphonyl*-3,7-*methano*-7H-1,4-*benzodiazonine* (13).—A solution of potassium permanganate (0.7 g, 4.4 mmol) in water (50 ml) was added dropwise during 1 h to a stirred solution of 3,4,5,6-tetrahydro-4,7-dimethyl-2-methylthio-3,7-methano-7*H*-1,4-benzodiazonine (11) (1.4 g, 5.4 mmol) in acetic acid (40 ml) at ambient temperature and the resulting mixture was stirred for a further 1 h. Water (200 ml) was added and sulphur dioxide was bubbled through the mixture until it was decolourised and until the precipitated manganese dioxide had all reacted. The mixture was made alkaline with concentrated ammonium hydroxide and a strong sulphurous odour was detected. Extraction of the aqueous layer (see later) with ether gave a three-component (t.l.c.) brown oil which was chromatographed on alumina. Chloroform eluted the lactam (3) (0.53 g, 43%), starting material (11) (0.52 g, 37%), and a trace (0.07 g, 4%) of an oil whose i.r. and ^1H n.m.r. spectra indicated that it may have been the desired sulphone (13); $\nu_{max.}$ (liquid film) 1 650 cm^{-1} (C=N); τ ($CDCl_3$) 6.6 (s, 3 H, SO_2Me), 7.7 (s, 3 H, NMe), and 8.5 (s, 3 H, Me).

The aqueous layer remaining after ether extraction was evaporated to dryness and the residue was extracted with chloroform. Distillation of the solvent gave an oil containing some acetic acid. This was treated with 10% aqueous sodium hydrogen carbonate and re-extraction with chloroform yielded a mixture (t.l.c.) of the lactam (3) (0.10 g, 8%) and starting material (11) (0.04 g, 3%).

1-α-*Amino*-1,2,3,4,5,6-*hexahydro*-3,6-*dimethyl*-2,6-*methano*-3-*benzazocine* (14).—(*a*) A mixture of 3,4,5,6-tetrahydro-3,6-dimethyl-2,6-methano-3-benzazocin-1(2*H*)-one (1) oxime (0.5 g, 2.1 mmol), lithium aluminium hydride (0.4 g, 10.0 mmol), and ether (20 ml) was stirred under nitrogen overnight at ambient temperature. The mixture was cooled in an ice-salt bath and water (4 ml) was added carefully. The precipitate was filtered off, washed with ether, and the filtrate and washings were combined, dried ($MgSO_4$), and evaporated to give the *product* (14) (0.37 g, 80%), b.p.

(Kugelrohr apparatus) 115—120 °C at 0.5 mmHg; $\nu_{max.}$ 3 350 cm^{-1} (NH_2): τ ($CDCl_3$) 6.05 (d, 1 H, $J_{H_aH_b}$ 6.0 Hz, H_a), 7.1br (m, 1 H, H_b), 7.35 (s, 3 H, NMe), 7.55br (s, 2 H, exchangeable, NH_2), and 8.55 (s, 3 H, Me) (Found: M^+, 216.162 7. $C_{14}H_{20}N_2$ requires M, 216.162 6).

(*b*) A mixture of the ketone (1) (0.43 g, 2.0 mmol), sodium cyanohydridoborate (0.66 g, 10.4 mmol), ammonium acetate (15.4 g), and anhydrous methanol (60 ml) was stirred at ambient temperature for 48 h, concentrated hydrochloric acid was then added until the pH was reduced to below 2 after which the methanol was distilled off under reduced pressure. The residue was dissolved in water and the aqueous solution extracted with ether. The pH of the aqueous phase was adjusted to 10 by addition of solid potassium hydroxide and the resulting solution saturated with sodium chloride. Extraction with ether gave a pale-yellow oil (0.36 g) which was chromatographed on alumina. Chloroform eluted: (i) starting material (0.13 g, 31%); (ii) 1,2,3,4,5,6-hexahydro-3,6-dimethyl-2,6-methano-3-benzazocine (2) (0.08 g, 20%); (iii) 1-α-hydroxy-1,2,3,4,5,6-hexahydro-3,6-dimethyl-2,6-methano-3-benzazocine (15) (0.07 g, 16.5%), identical with a sample prepared as described later; and (iv) 1-α-amino-1,2,3,4,5,6-hexahydro-3,6-dimethyl-2,6-methano-3-benzazocine (14) (0.04 g, 9.5%), b.p. (Kugelrohr apparatus) 115—120 °C at 0.05 mmHg, identical (i.r. and ^1H n.m.r. spectra) with the sample prepared as described in (*a*).

1-α-*Hydroxy*-1,2,3,4,5,6-*hexahydro*-3,6-*dimethyl*-2,6-*methano*-3-*benzazocine* (15).—A mixture of the ketone (1) (2.15 g, 10.0 mmol), sodium borohydride (0.76 g, 20.0 mmol), and ethanol (30 ml) was stirred at ambient temperature for 20 h, then evaporated to dryness. Water was added to the residue and extraction of the resulting aqueous solution with chloroform gave the *product* (15) (2.17 g, 100%), m.p. 88—90 °C (from ethanol); $\nu_{max.}$ 3 350 cm^{-1} (OH); τ ($CDCl_3$) 5.3 (d, 1 H, *J* 7.0 Hz, H_a), 5.6br (s, 1 H, exchangeable, OH), 6.7 (m, 1 H, H_b), 7.4 (s, 3 H, NMe), and 8.65 (s, 3 H, Me); the *methiodide* (94%) had m.p. 201—203 °C (from ethanol); the *hydrobromide* had m.p. 155—160 °C (from ethanol). The *acetyl derivative* (16) (88%), a pale-yellow oil having b.p. (Kugelrohr apparatus) 131—136 °C at 0.04 mmHg; $\nu_{max.}$ 1 745 cm^{-1} (CO); τ ($CDCl_3$) 3.9 (d, 1 H, $J_{H_aH_b}$ 6.0 Hz, H_a), 6.7 (m, 1 H, H_b), 7.3 (s, 3 H, NMe), 7.85 (s, 3 H, COMe), and 8.7 (s, 3 H, Me), was prepared as follows. A mixture of the alcohol (15) (0.18 g, 0.83 mmol) and a 50 : 50 mixture (10 ml) of acetic acid and acetic anhydride was heated under reflux for 3 h, then poured into water. The aqueous solution was made alkaline by addition of concentrated ammonium hydroxide and extraction with chloroform gave (16) (0.19 g). The acetyl derivative (16) was characterised as its *hydrobromide salt*, m.p. 235—238 °C (from 95% aqueous ethanol) (Found: C, 56.25; H, 6.6; N, 4.0%; M^+ — HBr, 259. $C_{16}H_{22}BrNO_2$ requires C, 56.5; H, 6.5; N, 4.1%; M — HBr, 259).

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