Synthesis and Ring-expansion of 4-(2-Dimethylaminoethyl)-4-methylnaphthalen-1(4*H*)-one and its 2,3-Dihydro-derivative and Some Reactions of the Lactam Products

By **David Carr, Brian Iddon,*** and **Hans Suschitzky,** The Ramage Laboratories, Department of Chemistry and Applied Chemistry, University of Salford, Salford M5 4WT
Robert T. Parfitt, School of Pharmacy and Pharmacology, University of Bath, Claverton Down, Bath BA2 7AY

The title compounds, (3) and (6), were prepared by subjecting the methiodides of 3,4,5,6-tetrahydro-3,6-dimethyl-2,6-methano-3-benzazocin-1(2*H*)-one (2) and 1-α-hydroxy-1,2,3,4,5,6-hexahydro-3,6-dimethyl-2,6-methano-3-benzazocine (7) to a Hofmann elimination reaction. Beckmann rearrangements of the oximes of compounds (3) and (6) gave the acylanilide-type lactam products, (13) and (8), respectively. A Schmidt ring expansion of the 4,4-disubstituted 1-tetralone (6) also gave (8) whilst a similar reaction on the 4,4-disubstituted 1-tetralone (3) gave a primary amine, probably (4). The lactam (8) was reduced to (9) and alkylated, to give (10).†

OUR interest in the biological activity of amines such as (1),[1-4] which are prepared from lactams, and the availability in our laboratories of 3,4,5,6-tetrahydro-3,6-dimethyl-2,6-methano-3-benzazocin-1(2*H*)-one (2) (2,5-dimethyl-8-oxo-6,7-benzomorphan) [5] prompted this investigation.

When the methiodide salt of 3,4,5,6-tetrahydro-3,6-dimethyl-2,6-methano-3-benzazocin-1(2*H*)-one (2) was subjected to the Hofmann elimination procedure described for related compounds [6] it gave exclusively 4-(2-dimethylaminoethyl)-4-methylnaphthalen-1(4*H*)-one (3) (91% yield). Although reduction of the 2,3-double bond in this product would yield 3,4-dihydro-4-(2-dimethylaminoethyl)-4-methylnaphthalen-1(2*H*)-one (6), we found it convenient to prepare compound (6) (99% yield) by subjecting the methiodide of 1-α-hydroxy-1,2,3,4,5,6-hexahydro-3,6-dimethyl-2,6-methano-3-benzazocine (7) to the Hofmann elimination procedure (neither of the two possible isomeric β-elimination products could be detected in the crude product). The 1-α-hydroxy-compound (7) is available in high yield by reduction of ketone (2), as described in the preceding paper.[5]

When the oxime of the 4,4-disubstituted 1-tetralone (6) was heated in polyphosphoric acid at 150 °C it gave a product (72% yield) which is assigned the acylanilide-type lactam structure (8) on the basis of its spectroscopic properties (see also preceding paper). Apart from a typical lactam carbonyl stretching frequency at 1 680 cm^{-1} [*cf.* $\nu_{max.}$ (Nujol) 1 665 cm^{-1} for (11) [5]] and an absorption at 3 200 cm^{-1} (NH) in its i.r. spectrum, the lactam (8) displayed a signal in its ^{13}C n.m.r. spectrum at δ 175.8 p.p.m. for the carbonyl C-atom [*cf.* δ 173.05 p.p.m. for (11) [5]]. Reduction of the lactam (8) with lithium aluminium hydride gave a product whose ^1H n.m.r. spectrum is consistent with structure (9); the spectrum lacks a characteristic benzylic proton signal, which would be expected if this compound had the alternative benzamide-type lactam structure. In concentrated hydrochloric acid heated under reflux for 24 h,[5] however, the lactam (8) failed to undergo hydrolysis, but resistance of lactams to hydrolysis under these conditions has been reported.[7]

With sodium azide in hot polyphosphoric acid (Schmidt reaction) the 4,4-disubstituted 1-tetralone (6) gave a product (8) (93% yield) identical in all respects with that obtained by Beckmann rearrangement of its oxime. This result is in contrast to the failure to ring-expand ketone (2) in a Schmidt reaction, whereas a Beckmann rearrangement on the oxime of this ketone (2) was successful.[5] These results suggest that the *cis*-fused piperidine ring may sterically hinder approach of certain reagents to the 1-carbonyl group in ketone (2). This conclusion is supported by the fact that an attempted reductive amination of ketone (2) with sodium cyanohydridoborate in methanol in the presence of ammonium acetate gave only a low yield (9.5%) of the desired 1-α-amino-compound.[5] Formation of the immonium intermediates in these reactions is subject to steric hindrance.[8]

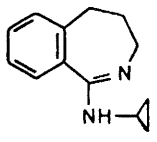
With methyl iodide in the presence of sodium hydride the lactam (8) was alkylated on the ring N-atom to give (10).

The oxime of the 4,4-disubstituted 1-tetralone (3) also undergoes a Beckmann rearrangement in polyphosphoric acid to give a product whose properties are consistent with structure (13); the olefinic proton signals appear as doublets (*J* 12.0 Hz) at τ 3.6 and 4.1, respectively, in the ^1H n.m.r. spectrum of this compound. We had hoped to confirm the identity of this lactam by an alternative synthesis involving a Hofmann elimination of the methiodide of lactam (11).[5] With hot 20% aqueous sodium hydroxide,[6] however, this methiodide gave a water-

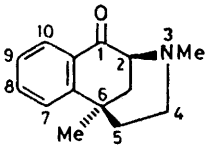
† Throughout this paper the α-isomer is the one with the 1-substituent *cis*- to the *cis*-fused piperidine ring (ring c) [in (7), for example].

soluble product, which was identified as the quaternised lactam hydrolysis product (14). In an alternative procedure, we treated the methiodide of lactam (11) with silver oxide in hot water. After distillation of the product this gave a product identified as (12) [5] and whose formation can be rationalised by initial loss of water from the quaternary hydroxide followed by alkyl group migration in the resulting resonance-stabilized ylide (15).

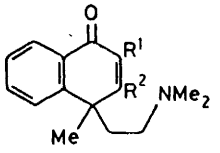
In a Schmidt reaction (sodium azide in hot polyphosphoric acid) the 4,4-disubstituted 1-tetralone (3) gave a complex mixture from which a primary amine (60% yield) was isolated as the major product. By analogy with similar reactions on related compounds [9,10] it is likely that this amine has the structure (4), although structure (5) cannot be ruled out on the evidence presented.



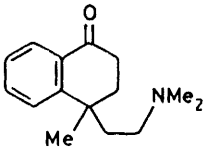
(1)



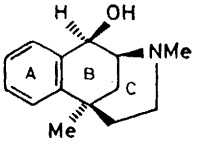
(2)



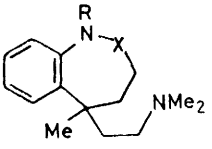
(3) $R^1 = R^2 = H$
(4) $R^1 = NH_2$, $R^2 = H$
(5) $R^1 = H$, $R^2 = NH_2$



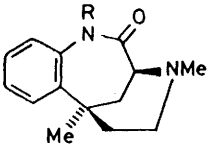
(6)



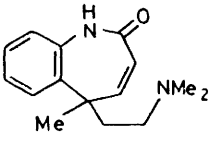
(7)



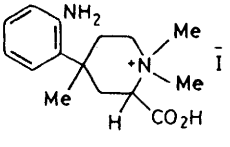
(8) X = C=O, R = H
(9) X = CH_2, R = H
(10) X = C=O, R = Me



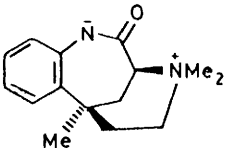
(11) R = H
(12) R = Me



(13)



(14)



(15)

EXPERIMENTAL

The instruments used and the general experimental conditions were the same as those described in the preceding paper.

4-(2-*Dimethylaminoethyl*)-4-*methylnaphthalen*-1(4H)-*one* (3).—A mixture of 3,4,5,6-tetrahydro-3,6-dimethyl-2,6-methano-3-benzazocin-1(2*H*)-one (2) [5] methiodide (3.57 g, 10.0 mmol) (prepared by a standard procedure and used without purification) and 20% aqueous sodium hydroxide (150 ml) was heated under reflux for 30 min and then cooled. Extraction with ether gave the *product* (3) (2.08 g, 91%), as a yellow oil, b.p. (Kugelrohr apparatus) 115—120 °C at 0.35 mmHg; $\nu_{max.}$ (liquid film) (*cf.* ref.11) 1 670 cm^{-1} (CO); τ ($CDCl_3$) 3.05 (d, 1 H, *J* 10.0 Hz, 3-H), 3.5 (d, 1 H, *J* 10.0 Hz, 2-H), 7.9 (s, 6 H, NMe_2), and 8.5 (s, 3 H, Me); δ (^{13}C n.m.r.) ($CHCl_3$) 184.3 p.p.m. (CO), characterised as its oxime (see later).

3,4-*Dihydro*-4-(2-*dimethylaminoethyl*)-4-*methylnaphthalen*-1(2H)-*one* (6).—A mixture of 1-α-hydroxy-1,2,3,4,5,6-hexahydro-3,6-dimethyl-2,6-methano-3-benzazocine (7) methiodide [5] (2.5 g, 7.0 mmol) and 20% sodium hydroxide (100 ml) was heated under reflux for 30 min and then cooled. Extraction with ether gave the product (6) (1.59 g, 99%), b.p. (Kugelrohr apparatus) 120—124 °C at 0.5 mmHg (lit.,[12] 110—120 °C at 0.5 mmHg); $\nu_{max.}$ (liquid film) 1 685 cm^{-1} (CO); τ ($CDCl_3$) 7.75 (s, 6 H, NMe_2) and 8.6 (s, 3 H, Me), characterised as its oxime (see next paragraph).

Oximes.—A mixture of 4-(2-dimethylaminoethyl)-4-methylnaphthalen-1(4*H*)-one (3) (0.27 g, 1.2 mmol), hydroxylamine hydrochloride (0.1 g, 1.4 mmol), sodium acetate (0.2 g, 2.4 mmol), and 50% aqueous ethanol (10 ml) was heated under reflux for 20 h, and then cooled and the mixture made alkaline by addition of 10% aqueous sodium hydrogen carbonate. Extraction with chloroform gave a yellow oil which was chromatographed on alumina. Chloroform eluted starting material (60 mg) and 4-(2-*dimethylaminoethyl*)-4-*methylnaphthalen*-1(4H)-*one* (3) *oxime* (90 mg, 31%), as a yellow solid, m.p. 192—194 °C (from acetone); $\nu_{max.}$ (Nujol) 970 cm^{-1} (N–O); τ ($CDCl_3$) 2.8 (d, 1 H, *J* 10.0 Hz, 3-H), 3.8 (d, 1 H, *J* 10.0 Hz, 2-H), 7.8 (s, 6 H, NMe_2), and 8.5 (s, 3 H, Me) (Found: C, 74.1; H, 8.2; N, 11.4%; M^+, 244. $C_{15}H_{20}N_2O$ requires C, 73.7; H, 8.25; N, 11.5%; *M*, 244).

3,4-*Dihydro*-4-(2-*dimethylaminoethyl*)-4-*methylnaphthalen*-1(2H)-*one* (6) *oxime* (90%) was prepared similarly; chromatographic purification of the product was not necessary in this case. It had m.p. 166—168 °C (from acetone); $\nu_{max.}$ (Nujol) 970 cm^{-1} (N–O); τ ($CDCl_3$) 7.85 (s, 6 H, NMe_2) and 8.8 (s, 3 H, Me); δ (^{13}C n.m.r.) ($CHCl_3$) 153.9 p.p.m. (CN) (Found: C, 72.95; H, 9.0; N, 11.3%; M^+, 246. $C_{15}H_{22}N_2O$ requires C, 73.1; H, 9.0; N, 11.4%; *M*, 246).

Beckmann Rearrangement of 3,4-*Dihydro*-4-(2-*dimethylaminoethyl*)-4-*methylnaphthalen*-1(2H)-*one* (6) *Oxime*.—A mixture of the oxime (1.0 g, 4.0 mmol) and polyphosphoric acid (50 g) was stirred and heated at 150 °C for 1 h and then cooled and added to water (200 ml). The resulting solution made alkaline by addition of concentrated ammonium hydroxide was extracted with chloroform to give 1,3,4,5-*tetrahydro*-5-(2-*dimethylaminoethyl*)-5-*methyl*-1-*benzazepin*-2-*one* (8) (0.71 g, 72%), m.p. 104—107 °C (from hexane); $\nu_{max.}$ (Nujol) 1 680 (CO) and 3 200 cm^{-1} (NH); τ ($CDCl_3$) 0.8br (s, 1 H, exchangeable, NH), 7.9 (s, 6 H, NMe_2), and 8.6 (s, 3 H, Me); δ (^{13}C n.m.r.) ($CHCl_3$) 175.8 p.p.m. (CO) (Found: C, 73.3; H, 9.3%; M^+, 246.173 1. $C_{15}H_{22}N_2O$ requires C, 73.1; H, 9.0%; *M*, 246.173 2).

Schmidt Rearrangement of 3,4-*Dihydro*-4-(2-*dimethylaminoethyl*)-4-*methylnaphthalen*-1(2H)-*one* (6).—A mixture of the ketone (6) (0.2 g, 0.87 mmol), sodium azide (0.10 g, 1.5 mmol), and polyphosphoric acid (100 g) was stirred and heated at 60 °C for 24 h; it was then cooled and poured on ice–water. The resulting solution was made alkaline with concentrated ammonium hydroxide and extracted with chloroform to give a product (0.20 g, 93%) with m.p. 104—107 °C (from hexane), identical in other respects with the product obtained in the preceding experiment.

Reduction of 1,3,4,5-*Tetrahydro*-5-(2-*dimethylaminoethyl*)-5-*methyl*-1-*benzazepin*-2-*one* (8).—A mixture of the lactam (8) (0.4 g, 1.6 mmol), lithium aluminium hydride (0.04 g, 1.0 mmol), and anhydrous ether (50 ml) was stirred at ambient temperature for 24 h under nitrogen. The mixture was cooled in ice while water (6 ml) and 4M-sodium hydroxide (1 ml) were added successively. The resulting mixture was filtered and the filtrate dried ($MgSO_4$) and distilled to yield 1,2,3,4-*tetrahydro*-5-(2-*dimethylaminoethyl*)-5-*methyl*-1-*benzazepine* (9) (0.28 g, 76%), b.p. (Kugelrohr apparatus) 102—107 °C at 0.03 mmHg; $\nu_{max.}$ (liquid film) 3 275 and 3 350 cm^{-1} (NH); τ ($CDCl_3$) 6.4br (s, 1 H, exchangeable, NH), 7.85 (s, 6 H, NMe_2), 8.35br (s, 2 H, CH_2-NH), and 8.65 (s, 3 H, Me); *dipicrate*, m.p. 186—189 °C (from ethanol) (Found: C, 46.7; H, 4.4; N, 16.2. $C_{27}H_{30}N_8O_{14}$ requires C, 47.0; H, 4.4; N, 16.2%).

N-Alkylation of 1,3,4,5-*Tetrahydro*-5-(2-*dimethylaminoethyl*)-5-*methyl*-1-*benzazepin*-2-*one* (8).—Sodium hydride (0.3 g, 12.5 mmol) was added in pieces to a stirred solution of the lactam (8) (0.6 g, 2.4 mmol) in a mixture of toluene (7.5 ml) and dimethylformamide (15 ml) at ambient temperature and the mixture was stirred at this temperature for 2 h. Methyl iodide (0.42 g, 2.96 mmol) in toluene (7.5 ml) was added dropwise during 30 min and the mixture was stirred for a further 20 h at ambient temperature. It was then filtered and the filtrate washed with water, dried ($MgSO_4$), and evaporated to dryness under reduced pressure. The residue (0.52 g) was chromatographed on alumina. Chloroform eluted 1,3,4,5-*tetrahydro*-5-(2-*dimethylaminoethyl*)-1,5-*dimethyl*-1-*benzazepin*-2-*one* (10) (0.45 g, 73%), b.p. (Kugelrohr apparatus) 146—150 °C at 0.05 mmHg; $\nu_{max.}$ (liquid film) 1 660 cm^{-1} (CO); τ ($CDCl_3$) 6.6 (s, 3 H, NMe), 7.9 (s, 6 H, NMe_2), and 8.6 (s, 3 H, Me) (Found: C, 73.3; H, 9.3; N, 10.7%; M^+, 260. $C_{16}H_{24}N_2O$ requires C, 73.8; H, 9.3; N, 10.8%; *M*, 260).

Beckmann Rearrangement of 4-(2-*Dimethylaminoethyl*)-4-*methylnaphthalen*-1(4H)-*one* (3) *Oxime*.—A mixture of the oxime (0.18 g, 0.74 mmol) and polyphosphoric acid (10 g) was stirred and heated at 150 °C for 1 h and then cooled and poured into water. The resulting solution was made basic with concentrated ammonium hydroxide and extracted with chloroform to yield a brown oil (160 mg) which was chromatographed on alumina. Chloroform–ethanol (95 : 5) eluted a product which we believe (see Discussion) to be 5-(2-*dimethylaminoethyl*)-5-*methyl*-5H-1-*benzazepin*-2(1H)-*one* (13) (80 mg, 44%), b.p. (Kugelrohr apparatus) 135—140 °C at 0.05 mmHg; $\nu_{max.}$ (liquid film) 1 670 (CO) and 3 200 cm^{-1} (NH); τ ($CDCl_3$) 3.6 (d, 1 H, *J* 12.0 Hz, 4-H), 4.1 (d, 1 H, *J* 12.0 Hz, 3-H), 7.9 (s, 6 H, NMe_2), and 8.45 (s, 3 H, Me).

Attempted Schmidt Rearrangement of 4-(2-*Dimethylaminoethyl*)-4-*methylnaphthalen*-1(4H)-*one* (3).—A mixture of the ketone (3) (0.2 g, 0.87 mmol), sodium azide (0.10 g, 1.5 mmol), and polyphosphoric acid (100 g) was stirred and heated at 60 °C for 20 h and then cooled and poured into ice–water. The resulting solution was made alkaline with concentrated ammonium hydroxide and extracted with chloroform to give a solid (0.18 g) which was chromatographed on alumina. Ethyl acetate eluted: (i) 2-*amino*-4-(2-*dimethylaminoethyl*)-4-*methylnaphthalen*-1(4H)-*one* (4) (0.13 g, 62%), m.p. 118—121 °C (from chloroform–light petroleum); $\nu_{max.}$ (Nujol) 1 650 (CO) and 3 420 and 3 440 cm^{-1} (NH_2); τ ($CDCl_3$) 4.15 (s, 1 H, olefinic CH), 6.15br (s, 2 H, exchangeable, NH_2), 7.9 (s, 6 H, NMe_2), and 8.5 (s, 3 H, Me) (Found: C, 73.6; H, 8.2; N, 11.2%; M^+, 244. $C_{15}H_{20}N_2O$ requires C, 73.7; H, 8.25; N, 11.5%; *M*, 244): (ii) a brown oil (10 mg), $\nu_{max.}$ 2 100 cm^{-1} (N_3): and (iii) a three-component (t.l.c.) dark-red, viscous, oil (40 mg).

Attempted Hofmann Elimination Reaction of 1,3,4,5,6,7-*Hexahydro*-4,7-*dimethyl*-3,7-*methano*-1,4-*benzodiazonin*-2-*one* (11) *Methiodide*.[5]—A mixture of the methiodide (0.22 g, 0.6 mmol), freshly prepared silver oxide (0.28 g, 1.2 mmol), and water (40 ml) was stirred and heated overnight at 60 °C; it was then cooled, filtered, and evaporated to dryness to leave a red oil. Attempts to distil the oil caused decomposition but, as decomposition occurred, a colourless oil (0.11 g, 78%) distilled over, b.p. (Kugelrohr apparatus) 120—125 °C at 0.09 mmHg. This was identified as 1,3,4,5,6,7-*hexahydro*-1,4,7-trimethyl-3,7-methano-1,4-benzodiazonin-2-one (12), m.p. 89—92 °C (from hexane), identical (^1H n.m.r. and i.r. spectra) with the sample prepared as described previously.[5]

We thank the S.C.R. (CASE award to D. C.) and the Nicholas Research Institute Limited for financial support.

[0/049 *Received*, 9*th January*, 1980]

REFERENCES

[1] M. W. Gittos, M. D. Robinson, J. P. Verge, R. V. Davies, B. Iddon, and H. Suschitzky, *J.C.S. Perkin I*, 1976, 33.
[2] R. V. Davies, B. Iddon, T. McC. Paterson, M. W. Pickering, H. Suschitzky, and M. W. Gittos, *J.C.S. Perkin I*, 1976, 138.
[3] R. V. Davies, B. Iddon, M. W. Pickering, H. Suschitzky, P. T. Gallagher, M. W. Gittos, and M. D. Robinson, *J.C.S. Perkin I*, 1977, 2357.
[4] M. W. Gittos, J. W. James, and J. P. Verge, Ger. P. Offen. 1,911,519/1969 (*Chem. Abs.*, 1970, **72**, 12601); M. W. Gittos, Ger. P. Offen. 2,318,399/1973 (*Chem. Abs.*, 1974, **80**, 14857); M. W. Gittos, J. W. James, and J. P. Verge, B.P. 1,244,501/1971.
[5] D. Carr, B. Iddon, H. Suschitzky, and R. T. Parfitt, preceding paper.
[6] E. L. May and H. Kugita, *J. Org. Chem.*, 1961, **26**, 188.
[7] T. Fujii and S. Yoshifuji, *Tetrahedron*, 1970, **26**, 5953.
[8] P. S. Portoghese, D. L. Larson, J. B. Jiang, T. P. Caruso, and A. E. Takemori, *J. Medicin. Chem.* 1978, **21**, 598; 1979, **22**, 168.
[9] K. Mitsuhashi and K. Nomura, *Chem. and Pharm. Bull.* (*Japan*), 1965, **13**, 951.
[10] K. Mitsuhashi, K. Nomura, N. Minami, and M. Hatsuyama, *Chem. and Pharm. Bull.* (*Japan*), 1969, **17**, 1578.
[11] E. L. May, H. Kugita, and J. H. Ager, *J. Org. Chem.*, 1961, **26**, 1621.
[12] E. L. May and J. G. Murphy, *J. Org. Chem.*, 1955, **20**, 257.