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BECKMANN CLEAVAGE OF 1,2,3,4,5,6-HEXAHYDRO-3,6-DIMETHYL-2,6-METHANO-3-BENZAZOCIN-11-ONE OXIME (2,5-DIMETHYL-9-OXO-6,7-BENZOMORPHAN OXIME); A NEW ROUTE TO 3-BENZAZOCINES

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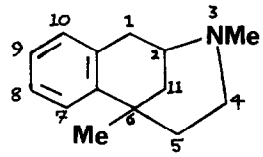
Summary: The title reaction gave 1,2,3,4-tetrahydro-3,6-dimethyl-3-benzazocine-2-carbonitrile (8) which showed some expected and some unexpected properties.

Many 2,6-methano-3-benzazocines, e.g. (1), possess analgesic activity[1] as do analogous 3-benzazocines, e.g. (2).[2,3] Published[3,4] routes to 3-benzazocines are tedious and none involve direct conversion of a 2,6-methano-3-benzazocine into a 3-benzazocine. Recent improvements[5,6] in the synthesis of the 2,6-methano-3-benzazocinone (3) prompted us to submit its oxime to a Beckmann rearrangement. The oxime of the isomeric ketone (4) gives the lactam (5).[7]



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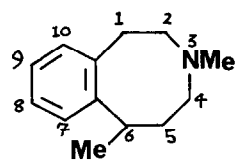

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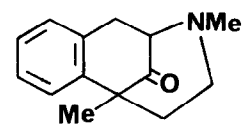

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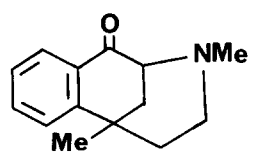

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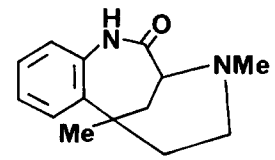
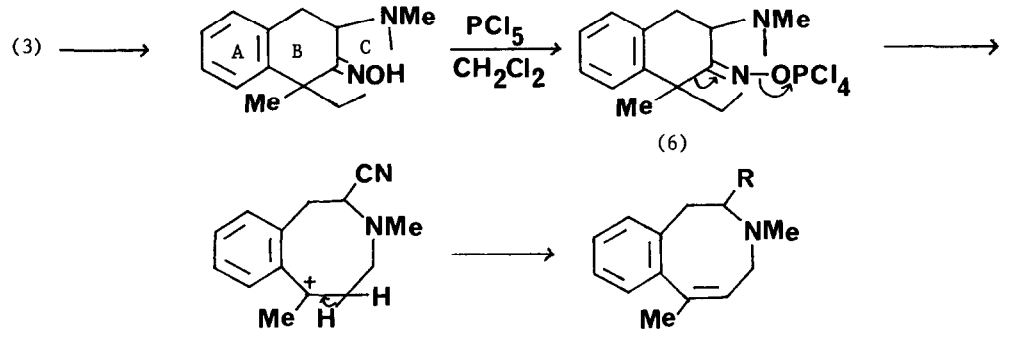


(5)

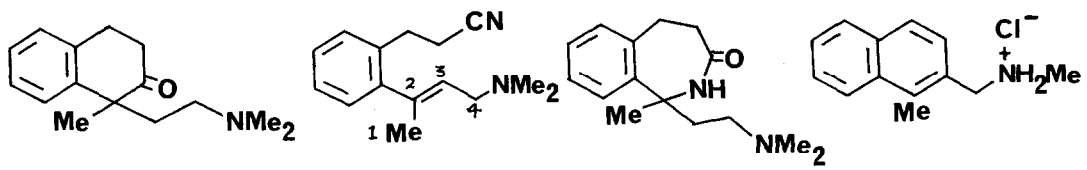
A solution of the oxime[8] of (3) (4.4 mmol) in anhydrous dichloromethane (40 ml) was added to a stirred suspension of phosphorus pentachloride (8.6 mmol) in the same solvent (40 ml) at ambient temperature. The mixture was stirred for a further 5 min, 10% aqueous ammonium hydroxide (50 ml) added and, after separation of the organic layer, evaporation of

the solvent, and chromatography on silica [eluant: ethyl acetate-chloroform], we obtained the novel 3-benzazocine (8) (59%), m.p. 75-77°C [from ethyl acetate-chloroform]; $\nu_{max.}$ ($CHBr_3$) 2220wk (CN); δ ($CDCl_3$) 2.06 (s, 3H, Me), 2.30-3.30 (m, 2H, 4-CH_2), 2.52 (s, 3H, NMe), 3.02 (d, 2H, 1-CH_2), 4.05 (t, 1H, H-2), 5.85 (m, 1H, H-5), and 7.20-7.50 (m, 4H, aromatic): hydrochloride, m.p. 159-161°C [from chloroform-light petroleum (b.p. 40-60°C)].



SCHEME

A possible mechanism for this conversion is shown in the Scheme: intermediate (6) fragments and rearranges to give a highly stabilised benzylic carbenium ion (7) (cf. ref. 9). To show that this is the major factor causing cleavage of the C-C σ-bond in (6) and that ring C is not involved we rearranged the oxime {(92% yield), m.p. 106-108°C [from chloroform-light petroleum (b.p. 40-60°C)], hydrochloride, m.p. 207-209°C (from chloroform-ethanol)} of the 2-tetralone (14)[6] under similar conditions to those used for the oxime of tetralone (3). Work-up as described before gave a product which was chromatographed on alumina. Ether eluted: (i) as the major component, the cleaved compound (15) (64%) as a colourless oil; hydrochloride, m.p. 160-162°C [from chloroform-light petroleum (b.p. 40-60°C)]; $\nu_{max.}$ (Nujol) 2200 cm^{-1} (CN); δ (D_2O) 2.15 (s, 3H, Me), 2.70 and 3.00 (2 x t, 4H, 2 x CH_2), 3.00 (s, 6H, NMe_2), 4.00 (d, 2H, 4-CH_2), 5.53 (t, 1H, H-3), and 7.20-7.55 (m, 4H, aromatic): and (ii) a second oily fraction, which was a complex inseparable mixture, possibly containing as the major component the lactam (16), $\nu_{max.}$ (film) 1680 (CO) and 3050 and 3150 cm^{-1} (NH).



(14) (15) (16) (17)

In concentrated hydrochloric acid, even at room temperature, the nitrile (8) gave the acid (9) [isolated as its slightly hygroscopic hydrochloride (65% yield), m.p. 238-240°C

(with decomp.) (from chloroform-ethanol), $\nu_{max.}$ (Nujol) 1740 cm^{-1} (CO)], which gave (in ethanol) its ethyl ester (10), also isolated as its hydrochloride (45%), m.p. 168-170°C [from chloroform-light petroleum (b.p. 40-60°C)], $\nu_{max.}$ (Nujol) 1735 cm^{-1} (CO). Ethereal diazomethane converted the hydrochloride of acid (9) into the methyl ester (11), isolated as its hydrochloride (76%), hygroscopic, m.p. 189-191°C (from ether-chloroform), $\nu_{max.}$ (Nujol) 1730 cm^{-1} (CO). Reduction of the nitrile (8) with lithium aluminium hydride in ether gave the aminomethyl compound (12) (69%) as a colourless oil, isolated as its dihydrobromide salt, m.p. 156°C (with decomp.) [from ethanol-light petroleum (b.p. 40-60°C)], $\nu_{max.}$ (Nujol) 2500-2700br cm^{-1} ($\overset{+}{N}HMe$ and $\overset{+}{N}H_3$). Reaction of the nitrile (8) with anhydrous ethanol saturated with hydrogen chloride (Pinner imidate synthesis[10]) gave a mixture of the hydrochloride of the starting material and the amide (13). With an excess of ethanol, only the amide (13) was obtained, isolated as its hydrochloride (90% yield), m.p. 266-268°C [from ethanol-light petroleum (b.p. 40-60°C)], $\nu_{max.}$ (Nujol) 1700 (CO) and 3100 and 3250 cm^{-1} (NH_2).

An attempt to prepare the ethyl ester (10) by heating under reflux a mixture of the nitrile (8) and 10% aqueous ethanol whilst hydrogen chloride was bubbled through gave instead a product with the properties expected for 1-methyl-2-N-methylaminomethylnaphthalene hydrochloride (17) (55% yield), m.p. 249-251°C [from chloroform-light petroleum (b.p. 40-60°C)]; $\nu_{max.}$ of free base (film) 3300br cm^{-1} (NH); δ(HCl salt in D_2O) 2.70 (s, 3H, Me), 2.92 (s, 3H, NMe), 4.45 (s, 2H, CH_2), 7.50 (d, 1H, H-3), 7.60-7.90 (m, 2H, H-6 and H-7), 7.90 (d, 1H, H-4), 7.90-8.27 (m, 2H, H-5 and H-8). The u.v. spectrum of the hydrochloride salt in ethanol corresponds closely to that of 1,2-dimethylnaphthalene[11] in this solvent. This appears to be the first reported ring contraction reaction of a 3-benzazocine; the mechanism of this reaction will be discussed elsewhere.

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* In the interests of brevity patent references have been omitted; they will be given in the full paper on this work.

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