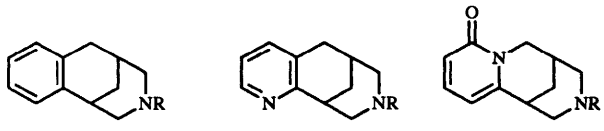
Synthesis of some analogues of cytisine: unusual reduction pathways for tertiary nitro groups in sterically constrained molecules

Kristina J. Blackall,[a] David Hendry,[b] Robert J. Pryce*[,b] and Stanley M. Roberts[a]
[a] *Department of Chemistry, Exeter University, Exeter EX4 4QD, UK*
[b] *Sittingbourne Research Centre, Sittingbourne, Kent ME9 8AG, UK*

The naphthalene derivative **4** was converted into the dinitro compound **5** by a 'double Mannich' reaction. Reduction of the compound **5** with tributylstannane gave the hydroxylamines **6** and **7** in low yield. Treatment of **5** with methanethiolate in DMSO gave the sulfides **8**, **9** and/or **10** in varying ratios, depending on the reaction conditions. Raney nickel reduction of **10** gave the cytisine analogue **1**. Similarly the dinitroquinoline **13** was converted into the dinitro compound **14**. Treatment of **14** with sodium methanethiolate gave a mixture of the sulfides **15**–**17**. Reduction of the compounds **16** and **17** with Raney nickel gave the pyridoazocine **2**. The mechanisms of formation of the hydroxylamines **6** and **7** and the sulfides **8**–**10**, **15**–**17** are discussed.

In connection with our interest in the preparation of novel compounds of potential importance to the agrochemical industry[1] we report an investigation into the synthesis of benzoazocine **1** and pyridoazocine **2** as analogues of cytisine **3** (R = H).



1 **2** **3**

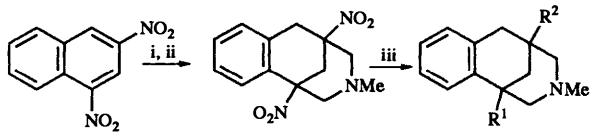
Cytisine is a powerful insecticide, acting as a potent agonist on acetylcholine receptors.[2] The compound also exhibits cholinergic activity in the mammalian nervous system and hence analogues have been sought which have differential activities on the mammalian and the insect receptors. Compounds of type **1** and **2** are designed to explore the importance of 2-pyridone moiety of cytisine *vis-à-vis* its biological activity.

Results and discussion

The preparation of the target structure **1** was approached by a 'double Mannich' reaction.[3] Thus, treatment of 1,3-dinitronaphthalene **4** with sodium boranuide followed by formaldehyde, methylamine and acid furnished the benzoazocinone **5** in an excellent (71%) and reproducible yield (Scheme 1). We believe that this is the first time that a 'double Mannich' reaction on a bicyclic aromatic compound has been reported.

Attempted hydrodenitration of compound **5** using tributylstannane[4] gave two compounds in 9 and 21% yields (based on recovered starting material). The compounds were identified as the hydroxylamines **6** and **7**, unexpected products from a reaction of this type. A speculative mechanism involving initial formation of a nitroxide radical[5] is shown in Scheme 2.

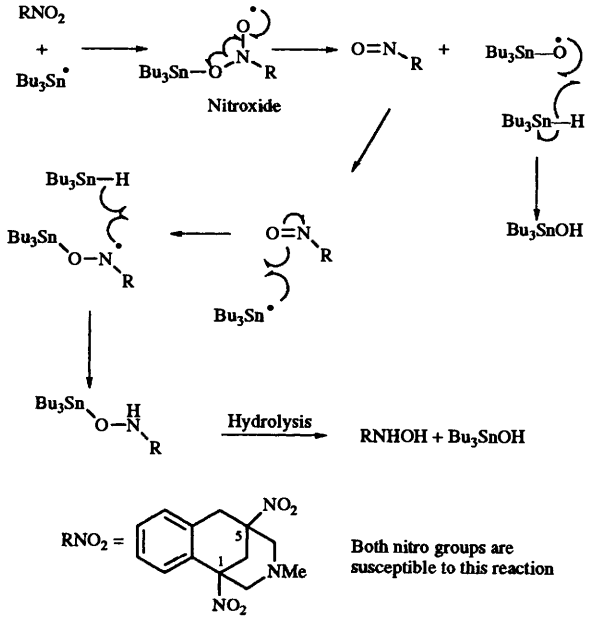
An attempt was made to denitrate the tricyclic compound **5** using sodium methanethiolate: treatment of **5** with the thiolate (6 equiv.) in DMSO over 18 h gave the mononitro compounds **8** and **9** in 68 and 6% yield respectively (Scheme 3). On allowing the reaction to proceed for 72 h, the sulfides **8** (36%) and **9** (9%) were isolated together with the reduced compound **10** (7%). Raising the temperature of the reaction to 50 and 80 °C gave only **8** and **10** in ratios of 1 : 1 (78% yield) and 1 : 10 (56% yield) respectively. Precedents for these results are provided by Carlson *et al.*:[6] reaction of α-nitrocumenes [$ArC(NO_2)Me_2$] with methanethiolate in DMSO gave the sulfide $ArC(SMe)Me_2$ in a rapid reaction (15 min); a prolonged reaction (48 h) under



4 **5** **6**

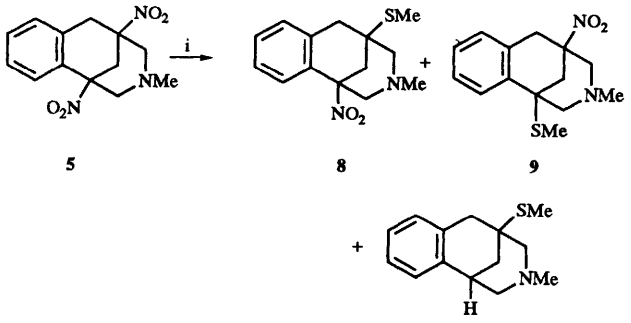
6 R^1 = NHOH; R^2 = NO_2
7 R^1 = NO_2; R^2 = NHOH

Scheme 1 *Reagents and conditions:* i, $NaBH_4$, 0–20 °C; ii, H_2CO, H^+, $MeNH_2$, 0–15 °C; iii, Bu_3SnH, AIBN, toluene, heat

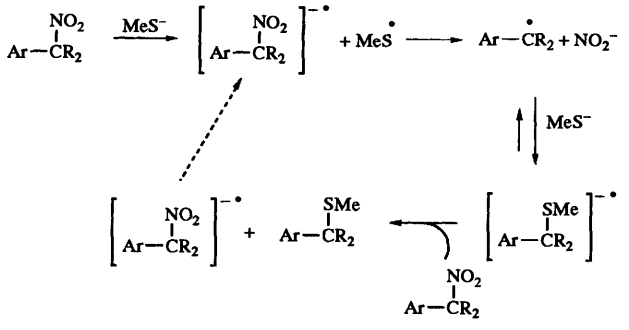


Scheme 2

* *Present address:* Professor R. J. Pryce, University of Coventry, Priory Street, Coventry CV1 5FB.



Scheme 3 *Reagents and conditions:* i, NaSMe, DMSO, room temperature or 50 °C or 80 °C



Scheme 4

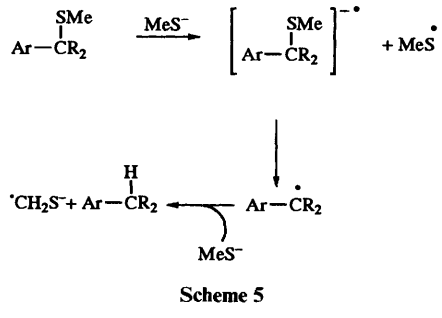
the same conditions gave the cumene $ArCHMe_2$. *tert*-Nitro groups at non-benzylic positions tended to react slower, while both types of nitro group suffer replacement at elevated temperatures.

The proposed mechanism[6] for the production of sulfides from nitroalkenes involves the initial formation of a radical anion, loss of nitrite ion and attack by the tertiary radical on the methanethiolate ion. The involvement of a second molecule of nitro compound continues the chain process (Scheme 4). Alternatively, the direct combination of $ArR_2C^{\bullet}$ and $MeS^{\bullet}$ leads to the observed product.

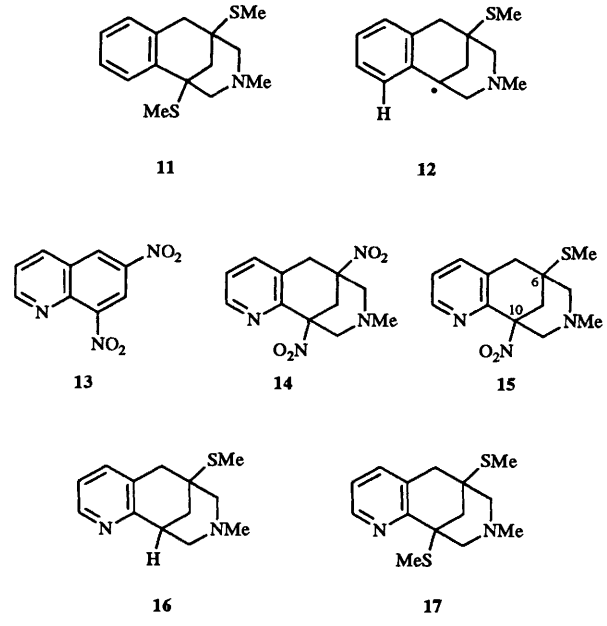
The replacement of the methylsulfanyl moiety by a hydrogen atom is believed[6] to take place by attack of a methanethiolate ion on the sulfide as indicated in Scheme 5.

There are several interesting features regarding the reaction of the dinitro compound **5** with methanethiolate. Firstly the nitro-group β to the aromatic ring is replaced more readily by a methylsulfanyl unit at ambient temperature (*NB* reaction of **5** with NaSMe at room temperature gives only **8** and **9** in a ratio *ca.* 11:1). This probably reflects the inability of the aromatic ring to stabilize the intermediate radical (anion) formed at C-1. The methylsulfanyl unit at C-1 but not at C-5 is slowly replaced by a hydrogen atom. Thus, both sulfides **8** and **9** gave only the hydrodenitrated compound **10** on treatment with sodium methanethiolate in DMSO at 40 °C overnight. Repeating the latter reactions in $[^2H_6]$-DMSO gave **10** from **8** and 6-[^{2}H]-**10** from **9** showing (*a*) the hydrogen atom at C-1 in compound **10** is derived from methanethiolate and not the solvent and (*b*) the presence of the nitro group at C-5 renders the benzylic protons at C-6 susceptible to abstraction by the methanethiolate ion (pK_a 10–11).

Most noteworthy is the fact that the bis sulfide **11** was never isolated from the above reactions. It seems that the presence of the methylsulfanyl unit at C-5 stabilizes the radical at C-1 such that formation of the radical **12** (*e.g.* from the sulfide **11**) is readily reversible until the irreversible formation of **10** by



Scheme 5



abstraction of a hydrogen atom from the methanethiolate takes place.

From a synthetic viewpoint quantities of the sulfide **10** became available. Reduction of this compound with Raney nickel in acetone containing some ethanol at 60 °C gave the target compound **1** in 49% yield (80% based on recovered starting material).

The second target molecule **2** was approached in a similar manner. 6,8-Dinitroquinoline **13** was prepared from 2,4-dinitroaniline by a modified Skraup[7] procedure. Treatment of the quinoline **13** with sodium boranuide followed by methylamine, formaldehyde and acid gave the dinitro compound **14** (39%). Reaction of **14** with sodium methanethiolate in DMSO for 4 days at 40 °C gave the mononitro compound **15** (36%), the reduced compound **16** (10%) and, surprisingly, the bis sulfide **17** (23%). Thus, the relative instability of the disulfanyl compound **11** relative to the radical **12** must be due, in part, to steric crowding of the methylsulfanyl group at C-1 by the adjacent proton attached to the aromatic ring.

Reduction of the monosulfide **16** or the bis sulfide **17** with hydrogen in the presence of Raney nickel gave the pyrido[2,3-*d*]azocine **2** in 67% yield (78% based on recovered starting material).

In summary, the tricyclic amines **1** and **2** have been synthesised from simple starting materials in three-step procedures. The biological activity of these two compounds will be reported elsewhere.

Experimental

Melting points were determined on an electrothermal device and are uncorrected. IR spectra were recorded on a Perkin-Elmer 881 grating Infra-red Spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AM-250 (250 MHz) or Bruker AM-300 (300 MHz). ^{13}C NMR were also recorded on a Bruker AM-250 (62.9 MHz) or Bruker Am-300 (75.5 MHz). *J* Values are given in Hz. Mass spectra were recorded under EI conditions on a Kratos Profile Instrument. All solvents were purified before use. Dichloromethane and ethyl acetate were distilled from calcium hydride and ethanol from magnesium and iodine. Tetrahydrofuran (THF) and diethyl ether were distilled using the sodium–benzophenone ketyl method. Petroleum refers to light petroleum bp 60–80 °C, which was also distilled before use.

3-Methyl-1,5-dinitro-1,2,3,4,5,6-hexahydro-1,5-methano-3-benzoazocine 5

Sodium boranuide ($NaBH_4$; 3.85 g, 100 mmol) was slowly added over a period of 20 min to a solution of 1,3-dinitronaphthalene **4** (4 g, 18 mmol) in THF (15 cm^3), ethanol (31 cm^3) and formamide (12 cm^3). The temperature was kept below 20 °C using an ice bath. After 30 min the mixture was diluted with ice-cold water (77 cm^3), and quenched with a solution of methylamine 30%, 25 cm^3), formaldehyde (40%, 25 cm^3) and water (25 cm^3). Finally glacial acetic acid (25 cm^3) was added to give a brown precipitate. The precipitate was isolated by vacuum filtration and recrystallized from THF to yield the title benzoazocine **5** (3.61 g, 71%) as a cream crystalline solid, mp 151.5–152.0 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 2806 (CH, NCH_3), 1547, 1381, 1369 and 1347 (NO_2); δ_H(300 MHz; C_6D_6) 6.92 (1 H, dd, *J* 7.5 and 1.5, 10-H), 6.84 (1 H, ddd, *J* 7.5, 7.5 and 1.5, 8-H), 6.77 (1 H, ddd, *J* 7.5, 7.5 and 1.5, 9-H), 6.56 (1 H, dd, *J* 7.5 and 1.5, 7-H), 2.99 (1 H, ddd, *J* 11, 1.5 and 1.5, 1′-H_A), 2.97–2.92 (2 H, m, 4-H_B, 6-H_B), 2.84 (1 H, d, *J* 17.5, 6-H_A), 2.77 (1 H, ddd, *J* 10.5, 1.5 and 1.5, 2-H_B), 1.98 (1 H, dd, *J* 11 and 1.5, 1′-H_B), 1.93 (1 H, d, *J* 10.5, 4-H_A), 1.77 (1 H, dd, *J* 10.5 and 1.5, 2-H_A) and 1.60 (3 H, s, CH_3); δ_C(75.5 MHz; C_6D_6) 134.93 (C), 134.23 (C), 128.76 (CH), 128.07 (CH), 127.09 (CH), 122.54 (CH), 89.20 (C-NO_2), 84.23 (C-NO_2), 63.63 (CH_2), 62.25 (CH_2), 44.87 (CH_3), 39.13 (CH_2) and 37.66 (CH_2) (Found: M$^+$, 277.1051. $C_{13}H_{15}N_3O_4$ requires *M*, 277.1063) *m*/*z* 277 (5.3%, M$^+$), 217 (20.1, M$^+$ − NO − NO) and 184 (26.7, M$^+$ − NO_2 − NO_2 − H).

1-Hydroxyamino-3-methyl-5-nitro-1,2,3,4,5,6-hexahydro-1,5-methano-3-benzoazocine 6 and 5-hydroxyamino-3-methyl-1-nitro-1,2,3,4,5,6-hexahydro-1,5-methano-3-benzoazocine 7

Under argon, tributylstannane (2.10 g, 7.2 mmol) was added to a solution of the benzoazocine (**5**) (0.20 g, 0.7 mmol) in benzene or toluene (10 cm^3) at reflux, followed by AIBN (10 mg, cat.). The mixture was refluxed for 12 h. The solvent was evaporated from the mixture under reduced pressure and the residue purified by flash chromatography on silica gel eluting with petroleum–ethyl acetate (90:10–50:50) and finally 100% ethyl acetate. Starting material **5** (86 mg, 43%) was eluted first, followed by the hydroxylamine **6** [9 mg, 5%, R_f 0.57 (ethyl acetate)] as a white solid, mp 135.1–137.5 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3587 (OH), 3353 (NH), 2793 (C-H, NCH_3), 1538, 1380 and 1346 (NO_2); δ_H[300 MHz; $(CD_3)_2SO$] 7.55 (1 H, m, 10-H), 7.24 (1 H, s, NH), 7.15–7.08 (3 H, m, 7-H, 8-H and 9-H), 6.25 (1 H, br s, OH), 3.44 (1 H, d, *J* 17, 6-H_A), 3.36 (1 H, d, *J* 17, 6-H_B), 3.30 (1 H, d, *J* 10, 4-H_B), 2.55 (1 H, ddd, *J* 11.5, 2 and 2, 1′-H_A), 2.40 (1 H, d, *J* 10, 4-H_A), 2.33 (1 H, d, *J* 10, 2-H_B), 2.25 (1 H, dd, *J* 11.5 and 1, 1′-H_B), 2.10 (3 H, s, NCH_3) and 2.08 (1 H, d, *J* 10, 2-H_A); δ_C(62.9 MHz; $CDCl_3$) 138.43 (C), 135.59 (C), 127.73 (CH), 127.48 (CH), 126.41 (CH), 122.97 (CH), 85.42 (C-NO_2), 64.92 (CH_2), 63.26 (CH_2), 62.08 (C-NHOH), 45.78 (NCH_3), 39.76 (CH_2) and 37.49 (CH_2) [Found: (M + H)$^+$, 264.1354. $C_{13}H_{17}N_3O_3$ requires (*M* + H), 264.1348] *m*/*z* 264 [5.6%, (M$^+$ + H)], 263 (0.1, M$^+$) and 247 [32.1, (M$^+$ + H) −OH].

Hydroxylamine **7** [20 mg, 12%, R_f 0.32 (ethyl acetate)] was eluted last and isolated as a white solid, mp 138.3–140.7 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3584 (OH), 3286 (NH), 2798 (C-H, NCH_3), 1541, 1380 and 1351 (NO_2); δ_H(250 MHz; $CDCl_3$) 7.26 (1 H, s, NH), 7.24 (1 H, dd, *J* 6.5 and 1, 10-H), 7.19–7.11 (2 H, m, 9-H and 8-H), 6.98 (1 H, dd, *J* 8 and 1.5, 7-H), 4.65 (1 H, br s, OH), 3.32 (1 H, ddd, *J* 10.5, 1.5 and 1.5, 4-H_B), 3.15 (1 H, d, *J* 17, 6-H_A), 3.00 (1 H, d, *J* 17, 6-H_B), 2.89 (1 H, ddd, *J* 10.5, 1.5 and 1.5, 2-H_B), 2.80 (1 H, ddd, *J* 11, 2 and 2, 1′-H_A), 2.53 (1 H, d, *J* 10.5, 4-H_A), 2.25 (3 H, s, NCH_3), 2.19 (1 H, dd, *J* 10.5 and 1.5, 2-H_A) and 2.01 (1 H, dd, *J* 11.5 and 1.5, 1′-H_B); δ_C(62.9 MHz; $CDCl_3$) 136.49 (C), 134.95 (C), 128.46 (CH), 128.17 (CH), 126.24 (CH), 122.44 (CH), 89.59 (C-NO_2), 64.39 (CH_2), 63.23 (CH_2), 57.61 (C-NHOH), 45.94 (NCH_3), 38.52 (CH_2) and 38.45 (CH_2) [Found: (M + H)$^+$, 264.1336. $C_{13}H_{17}N_3O_3$ requires (*M* + H), 264.1348] *m*/*z* 264 [4.4%, (M$^+$ + H)], 263 (0.2, M$^+$) and 247 [22.8, (M$^+$ + H) −OH].

Reactions involving sodium methanethiolate 3-methyl-5-methylsulfanyl-1-nitro-1,2,3,4,5,6-hexahydro-1,5-methano-3-benzoazocine 8, 3-methyl-1-methylsulfanyl-5-nitro-1,2,3,4,5,6-hexahydro-1,5-methano-3-benzoazocine 9 and 3-methyl-5-methylsulfanyl-1,2,3,4,5,6-hexahydro-1,5-methano-3-benzoazocine 10

Method 1. The benzoazocine **5** (0.50 g, 1.8 mmol) and sodium methanethiolate (0.76 g, 10.8 mmol) were stirred in DMSO (20 cm^3) at room temperature for 24 h. The reaction was quenched with water (25 cm^3) and extracted with diethyl ether (3 × 15 cm^3). The combined organic extracts were washed with brine (25 cm^3), dried (anhydrous $MgSO_4$), filtered and the solvent was removed from the filtrate under reduced pressure to give a mixture of two crude products as a brown oil. Purification by silica gel flash chromatography using petroleum–ethyl acetate (80:20) as eluent gave first the sulfide **9** (32 mg, 6%, R_f 0.41) as a cream crystalline solid, followed by the sulfide **8** (340 mg, 68%, R_f 0.30) also as a cream crystalline solid.

Method 2. The benzoazocine **5** (0.40 g, 1.4 mmol), sodium methanethiolate (0.60 g, 8.6 mmol) and DMSO (10 cm^3) were stirred under argon at room temperature for 72 h. The reaction was quenched and worked up as above to yield a mixture of three crude products. Flash chromatography of the crude oil on silica gel, eluting with petroleum–ethyl acetate (90:10 rising to 70:30), first yielded the sulfide **9** [34 mg, 9%, R_f 0.53 (petroleum–ethyl acetate, 75:25)] as a cream crystalline solid, mp 86.5–87.0 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 2793 (C-H, NCH_3), 1536, 1379, 1358, 1342 and 1315 (NO_2); δ_H(300 MHz; $CDCl_3$) 7.80 (1 H, dd, *J* 7 and 2, 10-H), 7.27–7.18 (2 H, m, 9-H and 8-H), 7.11 (1 H, dd, *J* 7 and 2, 7-H), 3.48 (2 H, br s, 6-H_A, 6-H_B), 3.39 (1 H, d, *J* 10.5, 4-H_B), 2.77 (1 H, ddd, *J* 12, 2 and 2, 1′-H_A), 2.63 (1 H, dd, *J* 11 and 1, 2-H_B), 2.54 (1 H, d, *J* 10.5, 4-H_A), 2.40 (1 H, d, *J* 12, 1′-H_B), 2.22 (1 H, d, *J* 11, 2-H_A), 2.18 (3 H, s, NCH_3) and 1.99 (3 H, s, SCH_3); δ_C(75.5 MHz; $CDCl_3$) 137.54 (C), 136.08 (C), 127.61 (C-7), 127.25 (C-9), 126.63 (C-8), 126.29 (C-10), 84.85 (C-5), 65.93 (C-2), 64.58 (C-4), 50.09 (C-1), 45.59 (NCH_3), 40.12 (C-1′), 39.82 (C-6) and 10.48 (SCH_3) (Found: M$^+$, 278.1091. $C_{14}H_{18}N_2O_2S$ requires *M*, 278.1089) *m*/*z* 278 (1.8%, M$^+$), 231 (4.0, M$^+$ − NO_2 − H) and 141 [50, M$^+$ − NO_2 − SCH_3 − $N(CH_3)CH_2$].

Sulfide **8** [145 mg, 36%, R_F 0.40 (petroleum–ethyl acetate, 75:25] was eluted secondly and isolated as a cream crystalline solid, mp 97.0–98.5 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 2791 (C-H, NCH_3), 1538, 1379, 1359 and 1346 (NO_2); δ_H(300 MHz; $CDCl_3$) 7.26 (1 H, ddd, *J* 7.5, 7.5 and 1.5, 9-H), 7.17 (2 H, m, 8-H and 7-H), 6.07 (1 H, dd, *J* 7.5 and 1, 10-H), 3.31 (2 H, m, 6-H_B and 2-H_B), 3.09 (1 H, d, *J* 17, 6-H_A), 2.91 (2 H, m, 1′-H_A and 4-H_B), 2.54 (1 H, d,

J 10.5, 2-H_A), 2.27 (1 H, dd, J 11 and 1, 4-H_A), 2.24 (3 H, s, NCH_3), 2.17 (3 H, s, SCH_3) and 2.10 (1 H, dd, J 12 and 1.5, 1'-H_B); δ_C(75.5 MHz; $CDCl_3$) 137.08 (C), 134.72 (C), 128.44 (C-9), 127.64 (C-7), 126.26 (C-8), 122.49 (C-10), 89.03 (C-1), 66.63 (C-4), 63.00 (C-2), 45.74 (NCH_3), 42.57 (C-5), 40.87 (C-6), 40.75 (C-1') and 10.20 (SCH_3) (Found: M^+, 278.1097. $C_{14}H_{18}N_2O_2S$ requires M, 278.1089) m/z 278 (40.6%, M^+), 232 (41.3, $M^+ - NO_2$) and 185 (17.3, $M^+ - NO_2 - SCH_3$).

Finally sulfide **10** [20 mg, 7%, R_f 0.19 (petroleum–ethyl acetate, 75:25)] was eluted as a waxy brown oil; ν_{max}($CHCl_3$)/cm^{-1} 2788 (C-H, NCH_3) and 739 (S–C); δ_H(300 MHz; $CDCl_3$) 7.20–7.10 (4 H, m, 4 × Ar–H), 3.24 (1 H, d, J 17, 6-H_B), 3.16 (1 H, d, J 17, 6-H_A), 3.08 (1 H, dddd, J 3, 3, 3 and 3, 1-H), 2.98 (1 H, ddd, J 11, 2 and 2, 4-H_B), 2.77 (1 H, dddd, J 11, 3, 2 and 2, 2-H_B), 2.28 (1 H, dd, J 11 and 1, 4-H_A), 2.21 (1 H, dd, J 11 and 3, 2-H_A), 2.17 (3 H, s, SCH_3), 2.15 (3 H, s, NCH_3), 2.03 (1 H, dddd, J 12, 2, 2 and 3, 1'-H_A) and 1.85 (1 H, ddd, J 12, 3 and 1, 1'-H_B); δ_C(62.9 MHz; $CDCl_3$), 140.07 (C), 137.74 (C), 127.38 (CH), 127.20 (CH), 126.23 (CH), 125.30 (CH), 68.44 (CH_2), 62.09 (CH_2), 46.43 (NCH_3), 42.42 (C), 41.38 (CH_2), 37.69 (CH), 35.57 (CH_2) and 9.88 (SCH_3) (Found: M^+, 233.1236. $C_{14}H_{19}NS$ requires M, 233.1238) m/z 233 (39.6%, M^+) and 186 (3.1, $M^+ - SCH_3$).

Method 3. The benzoazocine **5** (0.88 g, 3.2 mmol), sodium methanethiolate (1.34 g, 19.1 mmol) and DMSO (40 cm^3) were stirred under argon at 50 °C for 36 h. TLC showed incomplete conversion and further sodium methanethiolate (3 equiv., 0.67 g, 9.55 mmol) was added. After a total of 48 h the reaction was quenched and worked up to give a mixture of products as a crude brown oil. Purification by silica gel flash chromatography, yielded first a mixture of **8** with a trace of **9** (0.34 g, 39%), followed by **10** [0.29 g, 39%, R_f 0.29 (petroleum–ethyl acetate, 70:30].

Method 4. The benzoazocine **5** (0.40 g, 1.4 mmol), sodium methanethiolate (0.60 g, 8.6 mmol) and DMSO (25 cm^3) were stirred under argon at room temperature for 24 h. Further sodium methanethiolate 3 equiv., 0.30 g, 4.3 mmol) was added at this stage. The reaction mixture was then heated at 80 °C overnight before being quenched and worked up as before. Flash chromatography of the crude oil on silica gel, eluting with petroleum–ethyl acetate (90:10 rising to 70:30) gave only the sulfides **8** (20 mg, 5%) and **10** (170 mg, 50.5%).

3-Methyl-1,2,3,4,5,6-hexahydro-1,5-methano-3-benzoazocine 1 (R = Me)

An excess of Raney nickel was added under argon to the sulfide **10** (0.23 g, 0.97 mmol) in acetone–ethanol (9:1; 20 cm^3) and the reaction mixture was stirred vigorously at 60 °C overnight. TLC analysis at this point showed some remaining starting material and a further quantity of Raney nickel was added. After a total of 48 h the solution was decanted and the amalgam rinsed with ethanol (2 × 10 cm^3). The combined organic phases were evaporated under reduced pressure to yield a colourless oil which was purified by flash chromatography on silica gel, eluting with petroleum–ethyl acetate (50:50). A mixture of the starting sulfide **10** and product **1** (86 mg) was recovered first, followed by the pure amine **1** (88 mg, 49%, R_f 0.38); ν_{max}($CHCl_3$)/cm^{-1} 2779 (C-H, NCH_3); δ_H(250 MHz; $CDCl_3$) 7.15–7.05 (4 H, m, 10-H, 9-H, 8-H and 7-H), 3.13 (1 H, dd, J 17 and 7.5, 6-H_B), 2.94–2.83 (3 H, m, 6-H_A, 4-H_B and 1-H), 2.80 (1 H, dd, J 10.5 and 2, 2-H_B), 2.35–2.18 (3 H, m, 2-H_A, 4-H_A and 5-H), 2.06 (3 H, s, NCH_3) and 1.80 (2 H, m, 1'-H_A and 1'-H_B); δ_C(62.9 MHz; $CDCl_3$) 141.44 (C), 138.28 (C), 127.93 (CH), 127.53 (CH), 125.94 (CH), 124.91 (CH), 63.89 (CH_2), 62.81 (CH_2), 46.98 (NCH_3), 35.78 (CH), 34.90 (CH_2), 29.50 (CH_2) and 28.60 (CH) (Found: M^+, 187.1342. $C_{13}H_{17}N$ requires M, 187.1361); m/z 187 (5.7%, M^+) and 127 (19.8, $C_{10}H_7^+$).

8-Methyl-6,10-dinitro-5,6,7,8,9,10-hexahydro-6,10-methanopyrido[2,3-*d*]azocine, 14

Sodium boranuide (3 g, 0.079 mol) was slowly added to a solution of 6,8-dinitroquinoline **13** (3 g, 0.014 mol) in THF (12 cm^3), ethanol (24 cm^3) and formamide (9 cm^3) over a period of 20 min. The temperature was kept at all times below 20 °C using an ice bath. After a further 30 min the mixture was diluted with ice-cold water (30 cm^3) before the reaction was quenched with a solution of methylamine (30%, 15 cm^3), formaldehyde (40%, 15 cm^3) and water (15 cm^3). Finally glacial acetic acid (15 cm^3) was added at which point a brown precipitate formed. The precipitate was isolated by vacuum filtration and recrystallized from THF to yield the title compound **14** (1.48 g, 39%) as a brown crystalline solid, mp 183–186 °C; ν_{max}($CHCl_3$)/cm^{-1} 2809 (C-H, NCH_3), 1551, 1380, 1371, 1347 and 1321 (NO_2); δ_H(250 MHz; $CDCl_3$) 8.43 (1 H, dd, J 5 and 1, 2-H), 7.50 (1 H, dd, J 7.5 and 1, 4-H), 7.25 (1 H, dd, J 7.5 and 5, 3-H), 3.60 (1 H, d, J 17, 5-H_B), 3.50 (1 H, d, J 17, 5-H_A), 3.46–3.34 (3 H, m, 1'-H_A, 9-H_B and 7-H_B), 2.74–2.68 (3 H, m, 1'-H_B, 9-H_A and 7-H_A) and 2.30 (3 H, s, NCH_3); δ_C(62.9 MHz; $CDCl_3$) 157.23 (C), 147.80 (CH), 135.45 (CH), 129.93 (C), 123.77 (CH), 88.49 (C-NO_2), 83.77 (C-NO_2), 64.15 (CH_2), 60.62 (CH_2), 45.30 (NCH_3) and 38.18 (2 × CH_2) (Found: M^+, 278.1012. $C_{12}H_{14}N_4O_4$ requires M, 278.1015) m/z 278 (4.6%, M^+), 232 (49.6, $M^+ - NO_2$) and 185 (100).

8-Methyl-6-methylsulfanyl-10-nitro-5,6,7,8,9,10-hexahydro-6,10-methanopyrido[2,3-*d*]azocine 15, 8-methyl-6-methylsulfanyl-5,6,7,8,9,10-hexahydro-6,10-methanopyrido[2,3-*d*]azocine 16 and 8-methyl-6,10-di(methylsulfanyl)-5,6,7,8,9,10-hexahydro-6,10-methanopyrido[2,3-*d*]azocine 17

Method 1. Under an atmosphere of argon the pyridoazocine **14** (0.30 g, 1.1 mmol), sodium methanethiolate (0.45 g, 6.5 mmol) and DMSO (20 cm^3) were stirred at room temperature for 7 days. The reaction was quenched with water (15 cm^3) and the mixture extracted with diethyl ether (3 × 10 cm^3). The combined organic extracts were washed with brine (15 cm^3), dried (anhydrous $MgSO_4$) and filtered and the solvent was evaporated from the filtrate under reduced pressure to give a brown crude oil. Purification by flash chromatography on silica gel, eluting with petroleum–ethyl acetate (50:50–100% ethyl acetate) and finally dichloromethane–ethanol–ammonia (100:10:1) gave three major products. Sulfide **15** [109 mg, 36%, R_f 0.1 (petroleum–ethyl acetate, 70:30)] was eluted first and isolated as a white crystalline solid, mp 143.5–146.4 °C; ν_{max}($CHCl_3$)/cm^{-1} 2801 (C-H, NCH_3), 1552, 1372, 1350 and 1317 (NO_2); δ_H(250 MHz; $CDCl_3$) 8.31 (1 H, dd, J 5 and 1, 2-H), 7.39 (1 H, dd, J 8 and 1, 4-H), 7.14 (1 H, dd, J 7.5 and 5, 3-H), 3.38 (1 H, ddd, J 10.5, 2 and 2, 9-H_B), 3.25 (1 H, d, J 17, 5-H_B), 3.05 (1 H, d, J 17, 5-H_A), 2.95 (1 H, ddd, J 11.5, 2 and 2, 1'-H_A), 2.87 (1 H, ddd, J 11, 2 and 2, 7-H_B), 2.55 (1 H, d, J 10.5, 9-H_A), 2.30 (1 H, dd, J 11 and 1, 7-H_A), 2.20 (3 H, s, NCH_3), 2.16 (1 H, dd, J 11.5 and 2, 1'-H_B) and 2.15 (3 H, s, SCH_3); δ_C(62.9 MHz; $CDCl_3$) 152.95 (C), 148.93 (CH), 135.18 (CH), 132.45 (C), 123.35 (CH), 88.58 (C-NO_2), 66.61 (CH_2), 61.15 (CH_2), 45.55 (NCH_3), 42.27 (*C*-SCH_3), 40.88 (CH_2), 39.98 (CH_2), and 10.32 (SCH_3) (Found: M^+, 279.1045. $C_{13}H_{17}N_3O_2S$ requires M, 279.1042) m/z 279 (0.5%, M^+), 233 (13.8, $M^+ - NO_2$) and 202 (100, $M^+ - SCH_3 - NO$).

Bissulfide **17** [69 mg, 23%, R_f 0.06 (petroleum–ethyl acetate, 50:50)] was eluted secondly and isolated as a white crystalline solid, mp 117–119 °C; ν_{max}($CHCl_3$)/cm^{-1} 2788 (C-H, NCH_3); δ_H(300 MHz; $CDCl_3$) 8.43 (1 H, dd, J 5 and 1, 2-H), 7.31 (1 H, dd, J 8.5 and 1, 4-H), 7.04 (1 H, dd, J 8.5 and 5, 3-H), 3.17 (1 H, d, J 17, 5-H_B), 3.00 (1 H, d, J 17, 5-H_A), 2.88 (1 H, ddd, J 10.5, 2 and 2, 7-H_B), 2.83 (1 H, ddd, J 10.5, 2 and 2, 9-H_B), 2.27 (1 H, ddd, J 12, 2 and 2, 1'-H_A), 2.25 (1 H, dd, J 10.5 and 1, 7-H_A), 2.18 (1 H, d, J 10.5, 9-H_A), 2.14 (3 H, s, 10-SCH_3), 2.08 (3 H, s,

NCH_3), 2.06 (3 H, s, 6-SCH_3) and 2.04 (1 H, dd, *J* 12 and 2, 1'-H_B); δ_C(62.9 MHz; $CDCl_3$) 157.92 (C), 146.62 (CH), 134.64 (CH), 133.10 (C), 121.69 (CH), 67.10 (CH_2), 64.90 (CH_2), 50.05 (*C*-SCH_3), 45.66 (NCH_3), 42.43 (*C*-SCH_3), 41.56 (CH_2), 40.78 (CH_2), 11.24 (CH_3) and 10.13 (SCH_3) (Found: M^+, 280.1070. $C_{14}H_{20}N_2S_2$ requires *M*, 280.1068) *m*/*z* 280 (17.8%, M^+) and 190 (32.2).

Using dichloromethane–ethanol–ammonia (100:10:1) the final sulfide **16** (24 mg, 10%, R_f 0.22) was eluted and isolated as a waxy orange oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 2788 (C-H, NCH_3); δ_H(250 MHz; $CDCl_3$) 8.32 (1 H, dd, *J* 5 and 1, 2-H), 7.34 (1 H, dd, *J* 7.5 and 1, 4-H), 7.05 (1 H, dd, *J* 7.5 and 5, 3-H), 3.20 (1 H, m, 10-H), 3.15 (1 H, d, *J* 17.5, 5-H_B), 3.04 (1 H, d, *J* 17.5, 5-H_A), 2.95–2.85 (2 H, m, 7-H_B and 9-H_B), 2.28 (1 H, dd, *J* 11 and 1, 7-H_A), 2.18 (1 H, dd, *J* 11 and 2.5, 9-H_A), 2.12 (3 H, s, SCH_3), 2.10 (3 H, s, NCH_3), 2.04 (1 H, dddd, *J* 12, 3, 2 and 2, 1'-H_A) and 1.90 (1 H, ddd, *J* 12, 3, and 1.5, 1'-H_B); δ_C(62.9 MHz; $CDCl_3$) 159.22 (C), 146.23 (CH), 134.69 (CH), 132.77 (C), 121.36 (CH), 68.17 (CH_2), 60.31 (CH_2), 46.18 (NCH_3), 41.95 (*C*-SCH_3), 40.47 (CH_2), 39.95 (CH), 32.25 (CH_2) and 10.13 (SCH_3) (Found: M^+, 234.1186. $C_{13}H_{18}N_2S$ requires *M*, 234.1191) *m*/*z* 234 (34.3%, M^+) and 219 (32.2, $M^+ - CH_3$).

Method 2. Repeating the above experiment but with a reaction temperature of 40 °C and a reaction time of 4 days gave, after the same work-up and purification procedure, compounds **15** (75 mg, 25%), **17** (93 mg, 31%) and **16** (27 mg, 9%).

8-Methyl-5,6,7,8,9,10-hexahydro-6,10-methanopyrido[2,3-*d*]azocine 2 (R = Me)

An excess of Raney nickel was added under argon to the bissulfide **17** (33 mg, 0.12 mmol) in acetone–ethanol (9:1; 5 cm^3) and the reaction mixture was stirred vigorously at 60 °C overnight. TLC analysis at this point showed some remaining starting material and a further quantity of Raney nickel was added. After a total of 48 h the solution was decanted and the amalgam rinsed with ethanol (2 × 10 cm^3). The combined organic phases were evaporated under reduced pressure to yield a colourless oil which was purified by flash chromatography on silica gel, eluting with dichloromethane–ethanol–ammonia (100:10:1). Monosulfide **16** (4 mg, 14%) and the title compound **2** (15 mg, 67%, R_f 0.10), as a colourless oil, were obtained; $\nu_{max}(CHCl_3)/cm^{-1}$ 2782 (C-H, NCH_3); δ_H(300 MHz; $CDCl_3$) 8.30 (1 H, d, *J* 4.5, 2-H), 7.35 (1 H, d, *J* 7.5, 4-H), 7.03 (1 H, dd, *J* 7.5 and 4.5, 3-H), 3.10–3.00 (2 H, m, 10-H and 5-H_B), 2.93 (1 H, dd, *J* 11 and 2, 7-H_B), 2.85 (1 H, d, *J* 11, 9-H_B), 2.80 (1 H, d, *J* 17, 5-H_A), 2.26–2.16 (3 H, m, 9-H_A, 7-H_A and 6-H), 2.06 (3 H, s, NCH_3) and 1.84 (2 H, br s, 1'-H_A, 1-H_B); δ_C(75.5 MHz; $CDCl_3$) 160.39 (C), 145.84 (C-2), 135.33 (C-4), 133.49 (C), 121.23 (C-3), 63.62 (C-9), 61.09 (C-7), 46.03 (NCH_3), 38.19 (C-10), 33.96 (C-5), 29.18 (C-1') and 28.22 (C-6): (Found: M^+, 188.1307. $C_{12}H_{16}N_2$ requires *M*, 188.1314) *m*/*z* 188 (59.8%, M^+) and 130 (31, $C_9H_8N^+$).

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