SHORT PAPER

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Coordination chemistry of a pyrazoline derived from 2,4-pentanedione bis(4-methylthiosemicarbazone). Crystal structure of the pyrazoline and evidence for metal-mediated ring opening[†]

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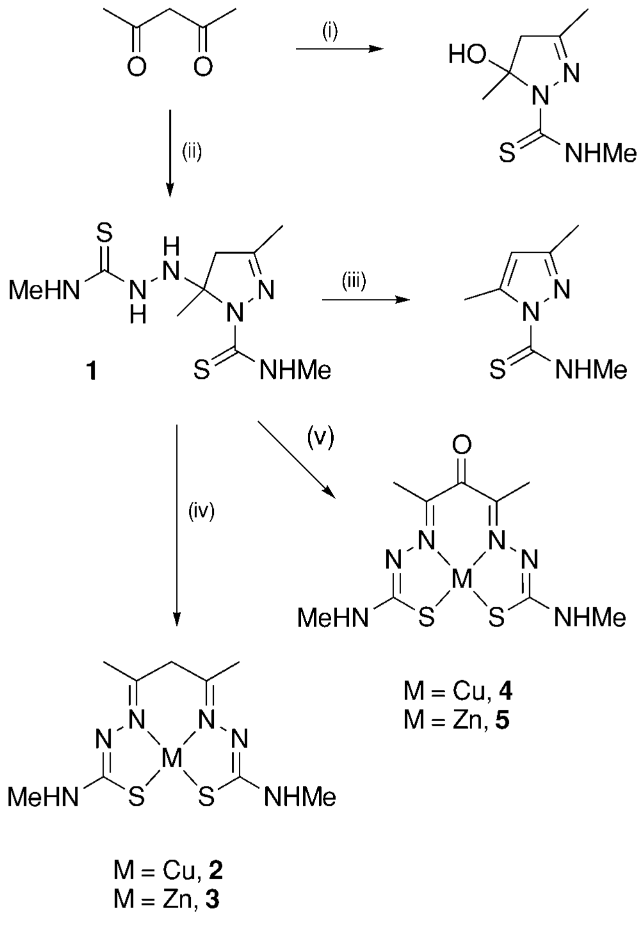
The heterocyclic structure of the pyrazoline obtained from reaction of 2,4-pentanedione with 4-methyl-3-thiosemicarbazide has been confirmed by X-ray crystallography. Reactions of the pyrazoline with Cu^{II} and Zn^{II} have been probed by EPR and NMR spectroscopies respectively. The results suggest that the pyrazoline undergoes ring-opening back to the bis-thiosemicarbazone upon coordination to the transition metal, accompanied by oxidation of the central methylene group when the reactions are carried out under air.

Keywords: pyrazoline, 2,4-pentanedione bis(4-methylthiosemicarbazone)

The importance of thiosemicarbazones and their copper complexes in a variety of biological contexts is well established.[1,2] In particular, copper(II) complexes of 1,2-bisthiosemicarbazones have found applications as ^{62}Cu perfusion tracers in positron emission tomographic studies of cerebral and myocardial blood flow.[3,4] The synthesis of 1,3-bisthiosemicarbazones is complicated by the fact that 1,3-diketones such as 2,4-pentanedione undergo competing cyclisation reactions with one or two equivalents of thiosemicarbazide such that the isolated product is usually the isomeric pyrazoline,[5] which can itself undergo further reaction in the presence of acid to give the corresponding 1-substituted pyrazole (Scheme 1).[6] To avoid this problem, O'Callaghan and Twomey described an indirect synthesis of 2,4-pentanedione bis(4-methylthiosemicarbazone) via 2,3-dihydro-5,7-dimethyl-6*H*-1,4-diazepine.[7] Recently, the identity of the product of this synthesis has also been questioned.[8] However, it occurred to us that the pyrazoline itself might undergo ring-opening back to the bisthiosemicarbazone in the presence of a transition metal. In this paper, we report the reactions of 1-methylaminothiocarbonyl-3,5-dimethyl-5-(1′-{4′-methylthiosemicarbazido})pyrazoline (Scheme 1, **1**) with copper(II) acetate and zinc(II) tetrafluoroborate to give the ring-opened complexes **2**–**5**.

Results and discussion

The ^{1}H NMR spectrum of **1** in $CDCl_3$ has been reported previously[5] and is consistent with the compound being a pyrazoline rather than a bisthiosemicarbazone. The protons of the methylene group are diastereotopic, and appear as an AB type multiplet in CD_3OD solution (see Experimental). In DMSO-d_6, the corresponding signals appear as a singlet at 2.79 ppm at room temperature. However, on warming to 65°C, an AB type multiplet centred at 2.82 ppm (J = *ca* 8 Hz) is resolved. The ^{13}C NMR spectrum (see Experimental) is also consistent with the pyrazoline structure. Definitive proof is provided by the X-ray crystal structure of **1**, shown in Fig. 1. The crystal structure of **1** has recently been independently reported by Hunter *et al.*;[8] although the two structures show minor differences, the overall geometries are similar.



Scheme 1
(i), $H_2NNHC(S)NHMe$ (ref. 5); (ii), $2H_2NNHC(S)NHMe$, reflux 24 h.; (iii), H_3O^+ (ref. 6); (iv), $Cu(OAc)_2$, N_2 atmosphere, reflux 2 h or $Zn(BF_4)_2$, N_2 atmosphere, room temp., 3 h followed by Na_2CO_3; (v) as for (iv), under air.

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[†] This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M)*.

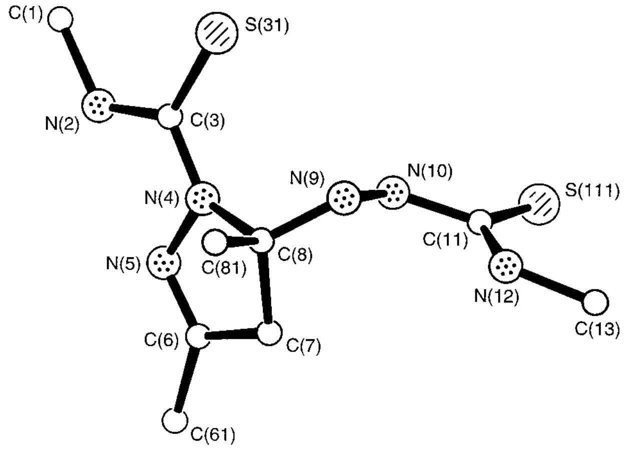

Fig. 1 View of a molecule of **1**, showing the atom numbering scheme.

Reaction of **1** with copper(II) acetate in boiling ethanol under air gave a dark red solid. This was subsequently characterised as the ligand-oxidised complex **4** (Scheme 1). Oxidation of the ligand is suggested by the microanalytical data (see Experimental), and confirmed by the electron impact mass spectrum. This showed the molecular ion at *m/z* = 349 and 351 for the ^{63}Cu and ^{65}Cu species respectively, in the correct isotopic ratio. There is a precedent for this type of behaviour, in the case of the nickel(II) complex of 2,4-pentanedione bis(thiosemicarbazone), which was also found to undergo oxidation readily in air.[9] The observation that a single oxygen is added, and two hydrogens lost, suggests that it is the central methylene group which is oxidised, since this is the only unique site. When the reaction was carried out under rigorous exclusion of oxygen, a brown powder analysing as the non-oxidised complex **2** was isolated.

The room temperature EPR spectrum of **4** in methyltetrahydrofuran solution consists of four resolved copper lines (Fig. 2). The magnetic interaction of the unpaired electron with two nitrogens further splits the two high-field copper hyperfine lines. The five superhyperfine components of each of the high-field copper lines have equal separations of 14 G and intensity ratios 1:4:6:4:1. The EPR parameters obtained are $\langle g \rangle$ = 2.067, $\langle a \rangle$ = 89.3. The corresponding spectrum at liquid helium temperature is shown in Fig. 3; it exhibits a typical copper hyperfine pattern with approximately axial symmetry ($g_{xx} = g_{yy}$). In addition to copper hyperfine splittings, the low-field copper lines $m_I = -3/2$ and $m_I = -1/2$ are clearly resolved and each is split into five lines arising from two equivalent nitrogen nuclei with separations approximately 11 G. The relative intensities of the five superhyperfine lines along the parallel components are very close to those predicted for two nitrogens, which suggests that these two nitrogen atoms are equivalent. This observation is consistent with ring opening of **1** to give a complex with C_{2v} symmetry, since all six nitrogens in **1** are distinct. The following EPR spin Hamiltonian parameters were estimated from the spectrum; a_{iso} = 0.0042 cm^{-1}, g_{ave} = 2.067, $g_{\parallel}$ = 2.134, $g_{\perp}$ = 2.034, $A_{\parallel}^{Cu}$ = 0.0185 cm^{-1}, $A_{\perp}^{Cu}$ = 0.0038 cm^{-1}, $A_{\parallel}^{N}$ = 0.0012 cm^{-1}, $A_{\perp}^{N}$ = 0.0013 cm^{-1}. These parameters are characteristic of a d^9 ion with an unpaired electron in the $d_{x^2-y^2}$ orbital ($g_{\parallel} > g_{\perp} > g_e$).

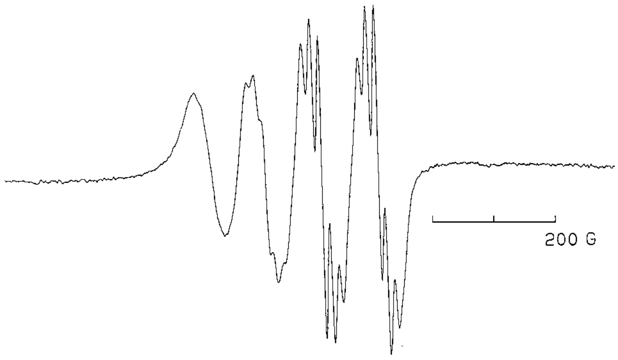

Fig. 2 EPR spectrum of **4** in methyltetrahydrofuran recorded at room temperature. Spectrometer conditions: modulation amplitude, 4.63 G; modulation frequency, 100 kHz; microwave power, 1 mW; microwave frequency, 9.178 GHz; gain, 1.25 × 10^4.

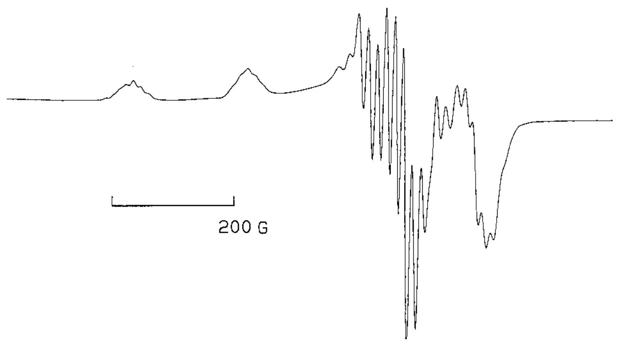

Fig. 3 EPR spectrum of **4** in methyltetrahydrofuran recorded at 10 K. Spectrometer conditions: modulation amplitude, 4.72 G; modulation frequency, 100 kHz; microwave power, 2 mW; microwave frequency, 9.52 GHz; gain, 3.2 × 10^4.

In order to obtain further evidence for metal-mediated ring opening of **1**, we examined its reaction with zinc(II) by NMR spectroscopy. The ^{1}H NMR spectrum of **1** in methanol-d$_4$ is relatively simple, due to deuterium exchange of the NH protons (see Experimental). In particular, the two pairs of methyl resonances (arising from 3- and 5-CH$_3$ and the two NCH$_3$ groups) are readily distinguished. The spectrum is unchanged after several days, indicating that pure **1** is stable in solution. Addition of Me$_3$SiCl to the CD$_3$OD solution to generate DCl *in situ* resulted in loss of the CH$_2$ signal, presumably by acid-catalysed exchange, and deshielding of the four methyl resonances by 0–0.55 ppm. However, there was no sign of decomposition of the compound, even after 24 hours. By way of contrast, addition of HCl to a solution of **1** in DMSO-d$_6$ led to complete decomposition after 2 hours; the final spectrum showed a set of resonances which could be assigned to the corresponding pyrazole, as shown in Scheme 1.

Addition of zinc(II) tetrafluoroborate to a solution of **1** in CD$_3$OD in air initiated a sequence of changes in the spectrum. After 90 minutes the original four methyl resonances had been replaced by two signals, at 2.29 and 3.15 ppm. Neutralisation of the solution with potassium carbonate caused slight shifts, to 2.27 and 2.94 ppm respectively. The possibility that these peaks could be due to degradation of **1** to the starting materials, 2,4-pentanedione and 4-methylthiosemicarbazide, was excluded by recording the spectra of these compounds in CD$_3$OD in the presence of zinc tetrafluoroborate. Rather, the peaks can be assigned to the CCH$_3$ and NCH$_3$ resonances respectively in the complex of the symmetrical oxidised bis(thiosemicarbazone) obtained by ring-opening (Scheme 1, **5**), similar to the copper system described above. The ^{13}C{^{1}H} NMR spectrum similarly showed only two methyl resonances, at 21.5 and 32.0 ppm, plus two singlets at 161.9 and 179.8 ppm which we assign to the two pairs of imino carbons. The NMR experiment also showed other, minor peaks which grew slowly with time, indicating that the reaction was not entirely clean and that the product has limited stability in solution.

Nevertheless, we were able to isolate an orange complex which analyzed as the oxidised complex **5** in Scheme 1. The mass spectrum likewise clearly showed the appropriate molecular ion, with the correct isotopic pattern for zinc. When the reaction was carried out under a nitrogen atmosphere, the only isolated product was a red tar. The spectroscopic properties of this material suggested that a complicated decomposition, probably involving the solvent, had occurred. We conclude that **3** itself is very prone to oxidation. Dioxygen reacts with **3** to give **5** in a reasonably controlled fashion, but in the absence of air complicated side-reactions ensue. Once precipitated, **5** is difficult to redissolve; a solution of the compound in DMSO-d_6 plus a trace of acid initially gave the same peaks in the ^{1}H NMR, however, other peaks were also present and the spectrum changed markedly over the course of a few hours.

Whereas **1** itself shows two distinct sets of ν(NH) bands in the infrared, at 3125–3275 and 3300–3375 cm^{-1}, all three isolated complexes show only one set, at *ca* 3275–3425 cm^{-1}. This is consistent with a reduction in the number of non-equivalent NH groups from four in **1** to one in the complexes. Below 1650 cm^{-1} the spectra are complicated and contain little diagnostic information. However we note the absence of a strong carbonyl absorption for **4** and **5**. Rather, there is a medium intensity band at 1580 and 1572 cm^{-1} respectively, absent from the spectrum of **2**. It may be that the carbonyl group is essentially in the enolate form in the oxidised complexes.

The electronic spectra of the complexes in neutral and acid solution are summarised in Table 1. Both **2** and **4** show a weak d–d transition at 779 nm, which disappears completely upon acidification. Apart from this band, the spectra of the oxidized copper and zinc complexes **4** and **5** in neutral solution are very similar, both show several medium- to high-intensity bands in the 250–500 nm region which can be assigned to ligand to metal charge transfer and intraligand transitions. On addition of a trace of acid, all of these bands are shifted to higher energies, consistent with protonation at the ligand. Addition of base restores the original spectra. Oxidation of solutions of **2** occurs rapidly on exposure to air, shown by the transformation of the electronic spectrum to that of **4**.

The site of protonation in all three complexes is probably the enolate oxygen (see above) or the iminethiolato nitrogens. The X-ray crystal structure of a closely related nickel(II) complex, $[Ni(CH\{C(Me)NNHC(S)NH_2\}_2)]NCS$, clearly showed the bis(thiosemicarbazone) ligand to be monoanionic, having undergone deprotonation at the central CH_2 group, and coordinating via an N_2S_2 donor set with both sulfurs in the thione form.[10]

Conclusions

The ready formation of pyrazolines from thiosemicarbazones derived from 1,3-diketones, together with the acidic nature of the protons in the CH_2 group of 1,3-bisthiosemicarbazones, are important factors distinguishing the chemistry of these compounds from 1,2-bisthiosemicarbazones. Nevertheless, the results of this study indicate that the pyrazolines themselves may be used to prepare bisthiosemicarbazone complexes via metal-mediated ring opening. Indeed, it is quite possible that a number of previous studies of 1,3-bisthiosemicarbazone complexes have actually involved pyrazolines as proligands, since the two tautomers are only distinguished by detailed NMR or X-ray crystal structure analysis. In this regard, we note the study of Arano *et al.* on technetium-99m complexes of 2,4-pentanedione bis(4-methylthiosemicarbazone).[11] These authors used a modified version of the synthesis reported by O'Callaghan and Twomey[7] to obtain a product identified as the free 1,3-bisthiosemicarbazone, however the ^{1}H NMR data they reported for this material in DMSO-d_6 solution are essentially identical to those we obtained for the crystallographically established pyrazoline tautomer (see above). Finally, we note the high susceptibility of these complexes, particularly the zinc species, towards oxidation at the methylene carbon. In both cases, exposure to dioxygen gives a reasonably well-controlled oxidation, but under anaerobic conditions, the zinc complex undergoes uncontrolled decomposition, presumably involving the solvent.

Experimental

General: All chemicals were reagent grade and were purchased from Aldrich. EPR spectra were recorded on a Bruker SRC-200 D spectrometer operating at X-band equipped with an Oxford Instruments ESR 900 cryostat for low-temperature measurements. NMR spectra were recorded on a JEOL GSX 270 spectrometer and referenced to tetramethylsilane. IR and electronic spectra were recorded on Shimadzu FTIR-8300 and UV-2101PC spectrophotometers respectively. Elemental analyses were obtained from the Microanalytical Service at the University of East Anglia, UK. Electron impact mass spectra were obtained from the Institute of Food Research, UK.

1-methylaminothiocarbonyl-3,5-dimethyl-5-[1′-(4′-methylthiosemicarbazido)]-pyrazoline (**1**): The pyrazoline was prepared by boiling a 2:1 molar ratio of 4-methyl-3-thiosemicarbazide and 2,4-pentanedione in ethanol under reflux for 24 h. Upon reducing the volume, **1** was precipitated as a white crystalline solid, yield 36%, and recrystallised from hot ethanol. M.p. 180°C (lit.[8] 174–176°C). (Found: C, 39.4; H, 6.6; N, 30.8. Calcd. for $C_9H_{18}N_6S_2$: C, 39.4; H, 6.6; N, 30.7%). ^{1}H NMR (DMSO-d_6): 1.73 (s, 3H, 5-CH_3), 1.96 (s, 3H, 3-CH_3), 2.79 (s, 2H, CH_2), 2.88 (d, J = 4.6 Hz, CH_3N), 2.89 (d, J = 4.6 Hz, CH_3N), 6.40 (s, 1H, 5-NH), 7.78 (s, 1H, NHN*H*), 8.19 (m, 2H, N*H*CH_3). ^{1}H NMR (CD_3OD): 1.81 (s, 3H, 5-CH_3), 2.00 (s, 3H, 3-CH_3), 2.76 (d, 1H, J = 18 Hz, CH_2), 2.89 (d, 1H, J = 18 Hz, CH_2), 3.03 (s, 3H, CH_3N), 3.05 (s, 3H, CH_3N). ^{13}C NMR (DMSO-d_6): 15.86 (q, J = 128.4 Hz, 3-CH_3), 23.46 (q, J = 129.5 Hz, 5-CH_3), 30.42 (q, J = 138.4 Hz, $NHCH_3$), 30.63 (q, J = 138.7 Hz, $NHCH_3$), 46.87 (t, J = 134.5 Hz, CH_2), 84.44 (s, C5), 154.26 (s, C3), 174.69 (s, C=S), 182.71 (s, C=S). *m/z* (%) 274 (M^+,1.8), 170 ($[M - CH_3NHC(S)NHNH]^+$, 73), 105 ($[CH_3NHC(S)NHNH_2]^+$, 58), 97 ($[C_5H_9N_2]^+$, 100), 74 ($[CH_3NHCS]^+$, 71). UV-VIS: λ, nm (ε, dm^3/mol/cm): 243 (25,400), 270 (19,400), both C=S $\pi \rightarrow \pi^*$.

Reaction of **1** *with copper(II) acetate*: A mixture of **1** (1.42 g, 5.2 mmol) and $Cu(OAc)_2.H_2O$ (1.00 g, 5.0 mmol) in ethanol (150 cm^3) was boiled under reflux in air for 2 h, then allowed to cool to room temperature. Filtration gave a dark red solid, which was washed with ethanol and dried *in vacuo* as **4**. Yield 1.36 g (78%), m.p. 188°C (dec.). (Found: C, 30.7; H, 4.2; N, 24.0. Calcd. for $C_9H_{14}CuN_6OS_2$: C, 30.9; H, 4.0; N, 24.0%). IR ν_{max}/cm^{-1} (Nujol) 3312, 1630, 1580, 1526, 1275, 1169, 1043, 812, 713. *m/z* (%) 349 (M^+, 100), 248 (21), 224 (17), 192 (43), 119 (83), 74 (CH_3NHCS^+, 29). Λ_M (methanol): 1 S cm^2/mol.

When the reaction was repeated under a nitrogen atmosphere, a dark brown microcrystalline powder characterized as **2** was obtained in 64% yield, m.p. 180°C (dec.). (Found: C, 31.5; H, 4.5; N, 25.2. Calcd. for $C_9H_{16}CuN_6S_2$: C, 32.2; H, 4.8; N, 25.0%). IR ν_{max}/cm^{-1}

Table 1 Electronic spectra of the complexes[a]

Complex	λ_{max}, nm (ε, dm^3/mol/cm)
2 (neutral)	272 (19700), 353 (5980), 413 (5860), 553 (557), 779 (639)
2 (acid)[b]	296 (24100), 399 (9290), 415 (10200), 469sh (1330)
4 (neutral)	288 (20800), 314 (14400), 363 (11700), 483 (2610), 779 (924)
4 (acid)[b]	288 (21600), 380sh (4980), 455 (3120)
5 (neutral)	281 (13200), 362 (8210), 463 (3560)
5 (acid)[b]	273 (13900), 321 (4490)

[a]In methanol solution; [b]acidified with HCl.

(Nujol) 3342, 1630, 1524, 1277, 1169, 1040, 812, 723. Λ_M (methanol): 1 S cm^2/mol.

Reaction of **1** *with zinc(II) tetrafluoroborate*: Solid Zn(BF4)$_2$.H$_2$O (1.00 g, 4.2 mmol) was added to a solution of **1** (1.15 g, 4.2 mmol) in methanol (200 cm^3). The yellow solution was stirred under air at 20°C for 3 h, then excess Na_2CO_3 was added. The mixture was stirred for 15 min, then filtered. The filtrate was concentrated *in vacuo* to *ca* 50 cm^3, then kept at –20°C overnight. The orange precipitate was filtered off, washed with ether, and dried *in vacuo* as **5**. Yield 0.52 g (35%), decomposes gradually without melting. (Found: C, 30.8; H, 4.2; N, 23.8. Calcd. for $C_9H_{14}N_6OS_2Zn$: C, 30.7; H, 4.0; N, 23.9%). IR ν_{max}/cm^{-1}, Nujol 3342, 1609, 1572, 1556, 1499, 1173, 1043, 831, 787; *m/z* (%) 350 (M$^+$, 20), 225 (9), 129 (88), 96 (100), 73 (CH_3NCS^+, 88). Λ_M (methanol): 10 S cm^2/mol.

When the reaction was repeated under a nitrogen atmosphere, a spectroscopically intractable red tar was the only isolable product.

Crystal structure analysis of **1**: $C_9H_{18}N_6S_2$, M = 274.4. Monoclinic, space group F2/d (equiv. to no. 15), a = 28.988(5), b = 13.411(2), c = 14.233(3) Å, β = 97.15(2)°, V = 5490(2) Å^3. Z = 16, Dc = 1.328 g cm^{-3}, F(000) = 2336, μ(Mo-Kα) = 3.8 cm^{-1}, T = 293 K, λ(Mo–Kα) = 0.71069 Å. Crystals are colourless, square prisms with pyramid-capped ends. One was cut to *ca.* 0.14 × 0.14 × 0.02 mm, mounted on a glass fibre and, after preliminary photographic examination, transferred to an Enraf-Nonius CAD4 diffractometer (with monochromated radiation) for determination of accurate cell parameters (from the settings of 25 reflections, θ = 9–10°, each centred in four orientations) and for measurement of diffraction intensities (1671 unique reflections to θ_{max} = 22°; 520 were 'observed' with $I > 2\sigma_I$).

During processing, corrections were applied for Lorentz-polarisation effects, slight deterioration (7.3% overall), absorption (by semi-empirical ψ-scan methods) and to eliminate negative net intensities (by Bayesian statistical methods). The structure (Fig. 1) was determined by direct methods in the SHELXS program[12] and refined (on F^2's) by full-matrix least-squares methods in SHELXL.[13] H atoms were included in idealised positions: the methyl groups were allowed to refine by rotation about the C–C or C–N bond; the amino H's were input in idealised tetrahedral positions and for N(2), N(10) and N(12), one was preferred and this hydrogen atom refined with only an N–H distance constraint; on N(9), the two tetrahedral sites were maintained, each half-occupied. The non-H atoms were refined with anisotropic thermal parameters and the H-atom U_{iso} values were set to ride on the U_{eq}'s of the parent C-atoms, or, for the N-hydrogens, allowed to refine freely. At the conclusion of the refinement, R_1 = 0.127 and wR_2 = 0.152 for the 989 reflections[13] with $I > \sigma I$ and weighted $w = \{\sigma^2(Fo^2) + (0.0303P)^2\}^{-1}$ where $P = (Fo^2 + 2Fc^2)/3$; for the 520 'observed' data, R_1 = 0.067. In the final difference map, the highest peak (*ca* 0.3 eÅ^{-3}) was close to the ring atom C(7). Scattering factors for neutral atoms were taken from ref. 14. Computer programs used in this analysis have been noted above or in Table 4 of ref. 15, and were run on a DEC-AlphaStation 200 4/100 in the Department of Biological Chemistry, John Innes Centre.

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