

## Preparation and X-Ray Crystal and Molecular Structure† of 6-Bromopyrrolizin-3-one

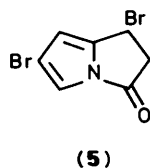
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The X-ray crystal structure of 6-bromopyrrolizin-3-one (**2**) shows that the lactam unit has a long C–N bond and a short C=O bond, although the molecule as a whole is planar. By comparison with data for model compounds it appears that the two rings behave independently, save for a reduced amount of amide-like interaction typical of *N*-acylazoles. There is no evidence for cyclic delocalisation of the resulting 8 $\pi$ -electron system.

In recent papers, we have described synthetic routes to pyrrolizin-3-one (**1**)<sup>1</sup> and certain of its aza analogues.<sup>2</sup> An unusual feature of the electron delocalisation in these molecules is that normal amide-type resonance [canonical forms (**1B** and **C**)] generates an 8 $\pi$ -electron system, and hence might be expected to be disfavoured. There is some spectroscopic evidence that such cyclic delocalisation is disfavoured,<sup>3,4</sup> but the problem is clearly best resolved by a structural investigation. We have therefore prepared a crystalline derivative, and report here the details of its X-ray structure.

The crystalline 6-bromopyrrolizin-3-one (**2**) was obtained by an extension of the original route<sup>1</sup> (Scheme). 4-Bromopyrrole-2-carbaldehyde (**3**) was obtained satisfactorily by the three-step literature procedure,<sup>5</sup> though a considerably longer reaction time was necessary, in our hands, for the actual bromination step. Knoevenagel condensation of (**3**) with Meldrum's acid in acetonitrile solution was effected in 66% yield in the absence of a catalyst. Small-scale flash vacuum pyrolysis of (**4**) at 600 °C and 10<sup>-3</sup> Torr gave the pyrrolizinone (**2**) in 88% yield as the sole product, though on a larger scale it was contaminated with a second product tentatively identified as the dibromo compound (**5**) on the basis of its spectra and elemental analysis. Its



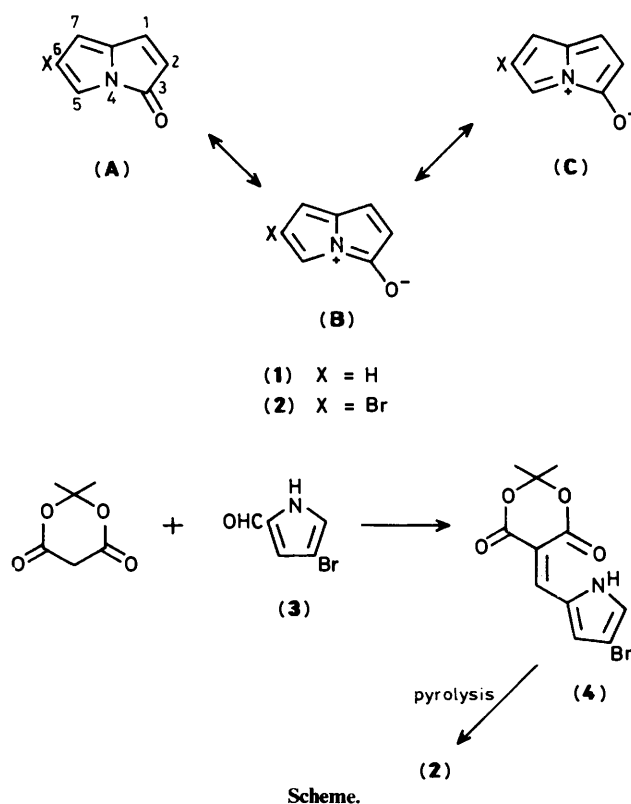
formation may be due to decomposition of (**4**) in the solid state, with evolution of HBr, at the higher inlet temperatures required to give a reasonable throughput rate.

The <sup>1</sup>H and <sup>13</sup>C n.m.r. spectra of the 6-bromopyrrolizin-3-one (**2**) are consistent with those of the parent compound<sup>4</sup> (Figure 1). The bromine atom has little effect on the <sup>1</sup>H n.m.r. parameters; the C-6 resonance is shielded by *ca.* 12 p.p.m., relative to the parent compound, a rather greater effect than that found for corresponding benzene derivatives.<sup>6</sup> The <sup>1</sup>H-coupled <sup>13</sup>C n.m.r. spectrum showed considerable second-order effects at 50 MHz, and so only approximate one-bond coupling constants are quoted. The carbonyl absorption in the i.r. spectrum is at 1760 cm<sup>-1</sup>, a typical value for pyrrolizinones,<sup>3</sup> while the mass spectrum shows the expected<sup>2</sup> cleavage of the carbonyl group, followed by loss of the bromine atom.

A sample of (**2**) recrystallised from hexane gave suitable

Table 1. Bond lengths (Å) with standard deviations

C(1)–C(2)	1.340(11)	N(4)–C(8)	1.375(9)
C(1)–C(8)	1.456(10)	C(5)–C(6)	1.353(10)
C(2)–C(3)	1.475(11)	C(6)–Br(6)	1.874(7)
C(3)–O(3)	1.198(9)	C(6)–C(7)	1.446(10)
C(3)–N(4)	1.419(9)	C(7)–C(8)	1.367(10)
N(4)–C(5)	1.370(9)		



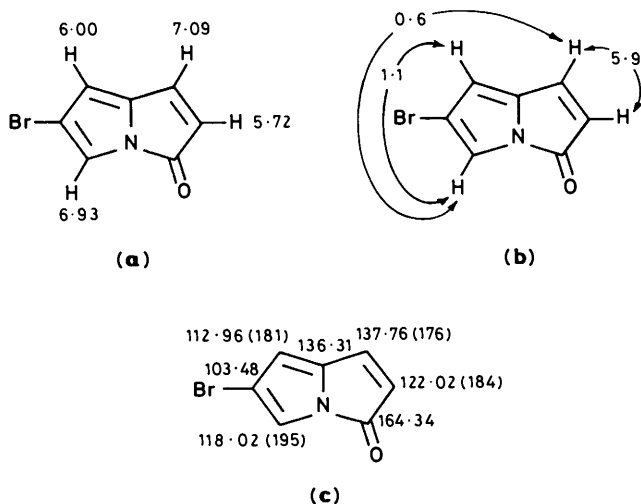
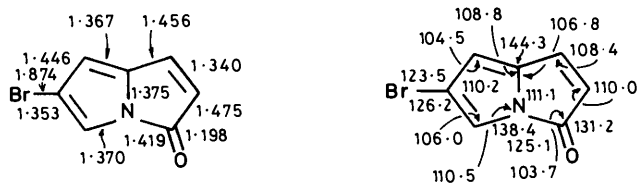
crystals for X-ray analysis; the structural parameters are given in Tables 1–3, and the bond lengths and angles are shown in Figure 2. Figure 3 is an ORTEP plot of a single molecule, showing the atom numbering scheme.

The chief chemical interest in the structure is to delineate the extent (if any) of 'normal' amide resonance which generates the 8 $\pi$ -canonical forms (**1B** and **C**). The key parameters are therefore: (i) the overall planarity of the molecule; (ii) bond alternation in each individual five-membered ring, which should

† Supplementary data (see section 5.6.3 of Instructions for Authors, in the January issue). H-Atom co-ordinates and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

**Table 2.** Angles (degrees) with standard deviations

C(2)–C(1)–C(8)	108.4(7)	N(4)–C(5)–C(6)	106.0(6)
C(1)–C(2)–C(3)	110.0(7)	C(5)–C(6)–Br(6)	126.2(5)
C(2)–C(3)–O(3)	131.2(7)	C(5)–C(6)–C(7)	110.2(6)
C(2)–C(3)–N(4)	103.7(6)	Br(6)–C(6)–C(7)	123.5(5)
O(3)–C(3)–N(4)	125.1(7)	C(6)–C(7)–C(8)	104.5(6)
C(3)–N(4)–C(5)	138.4(6)	C(1)–C(8)–N(4)	106.8(6)
C(3)–N(4)–C(8)	111.1(6)	C(1)–C(8)–C(7)	144.3(7)
C(5)–N(4)–C(8)	110.5(6)	N(4)–C(8)–C(7)	108.8(6)

**Figure 1.** (a) <sup>1</sup>H N.m.r. chemical shifts (p.p.m.) and (b) coupling constants (Hz) of 6-bromopyrrolizin-3-one in [<sup>2</sup>H]chloroform; (c) <sup>13</sup>C n.m.r. chemical shifts (p.p.m.) and (in parentheses) one-bond coupling constants of 6-bromopyrrolizin-3-one in [<sup>2</sup>H]chloroform**Figure 2.** Bond lengths (Å) and angles of 6-bromopyrrolizin-3-one

be substantial if cyclic delocalisation is disfavoured; and (iii) the geometry of the amide function itself, where a particularly long C–N bond and short C=O bond might be predicted for similar reasons.

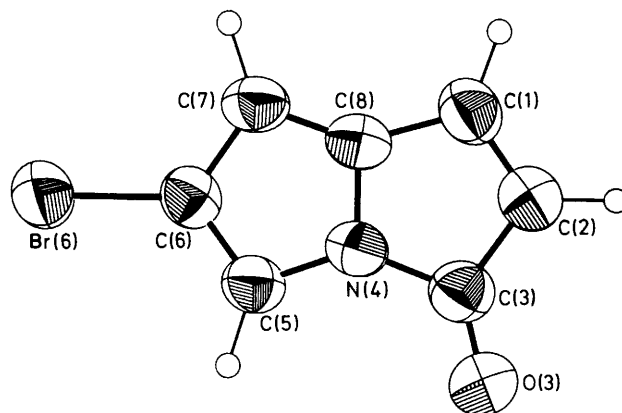
First, the molecule is indeed planar. All the skeletal torsion angles (Table 3) are within three standard deviations of 0 or 180°, and the sum of the bond angles at both ring junctions and at the 3-position is similarly 360°: the planarity at the nitrogen atom is particularly noteworthy. Secondly, the molecule shows substantial bond alternation. Bond lengths in the pyrrole-type ring are, if anything, consistent with more localisation than in pyrrole (6) itself,<sup>7</sup> while the contrast with the analogous, but 10π-electron, [3.2.2]cycloazine (7) is remarkable (Figure 4). Similarly, the bond lengths of the enone fragment correspond closely to those in acyclic environments, such as in the benzenoid derivative (8).<sup>9</sup> The geometry of the pyridone (9)<sup>10</sup> is also of interest, since substantial delocalisation of an enone fragment would be expected in this case. Indeed, the formal single bonds shown (Figure 4) are all much shorter than in the

**Table 3.** Torsion angles (degrees) with standard deviations

C(8)–C(1)–C(2)–C(3)	–0.3(9)	C(3)–N(4)–C(8)–C(1)	–0.7(8)
C(2)–C(1)–C(8)–N(4)	0.6(8)	C(3)–N(4)–C(8)–C(7)	178.3(6)
C(2)–C(1)–C(8)–C(7)	–177.6(10)	C(5)–N(4)–C(8)–C(1)	–179.9(6)
C(1)–C(2)–C(3)–O(3)	–179.0(8)	C(5)–N(4)–C(8)–C(7)	–1.1(8)
C(1)–C(2)–C(3)–N(4)	–0.1(8)	N(4)–C(5)–C(6)–Br(6)	176.1(5)
C(2)–C(3)–N(4)–C(5)	179.5(8)	N(4)–C(5)–C(6)–C(7)	–0.5(8)
C(2)–C(3)–N(4)–C(8)	0.4(8)	C(5)–C(6)–C(7)–C(8)	–0.1(8)
O(3)–C(3)–N(4)–C(5)	–1.5(14)	Br(6)–C(6)–C(7)–C(8)	–176.8(5)
O(3)–C(3)–N(4)–C(8)	179.5(7)	C(6)–C(7)–C(8)–C(1)	178.9(10)
C(3)–N(4)–C(5)–C(6)	–178.1(8)	C(6)–C(7)–C(8)–N(4)	0.7(8)
C(8)–N(4)–C(5)–C(6)	1.0(8)		

**Table 4.** Fractional co-ordinates of atoms, with standard deviations

	x	y	z
C(1)	0.345 7(12)	0.330 4(12)	0.120 9(4)
C(2)	0.425 3(12)	0.213 6(12)	0.070 2(4)
C(3)	0.640 3(12)	0.302 5(12)	0.049 1(4)
O(3)	0.762 9(9)	0.248 0(9)	0.005 6(3)
N(4)	0.675 2(10)	0.481 1(8)	0.092 4(3)
C(5)	0.832 2(10)	0.637 9(12)	0.103 8(4)
C(6)	0.759 4(11)	0.755 7(11)	0.156 2(4)
Br(6)	0.912 69(14)	0.985 52(12)	0.199 35(5)
C(7)	0.548 7(11)	0.672 6(12)	0.178 5(4)
C(8)	0.503 6(11)	0.502 3(10)	0.136 4(4)

**Figure 3.** ORTEP plot of the pyrrolizinone (2), showing crystallographic numbering scheme

acyclic example (8) or in the pyrrolizinone (2), though the lengths of the formal double bonds (Figure 4) are surprisingly little affected.

The structure of the amide function has been the subject of a detailed study by Chakrabarti and Dunitz.<sup>11</sup> Standard dimensions for a cyclic tertiary amide are C–N, 1.335(9) Å and C=O, 1.234(11) Å, and data for the pyridone (9)<sup>10</sup> (Figure 4) are in agreement with these. It is clear that in the pyrrolizinone (2) the C–N bond [1.419(9) Å] is dramatically longer than for a typical amide, and the C–O bond [1.198(9) Å] shows signs of being shorter, despite the expected lengthening effect of the enone conjugation. In a scatter-plot of C–N vs. C=O bond lengths for *N*-arylamides given by Chakrabarti and Dunitz,<sup>11</sup> the values for (2) are consistent with the trend, but fall outside the range of their plot! Certain fused β-lactam derivatives also show long C–N and short C=O bonds,<sup>12</sup> but these cases are characterised by a substantial deviation of the nitrogen atom from the plane of its three bonded atoms, in contrast to the pyrrolizinone case, where overall planarity is well defined.

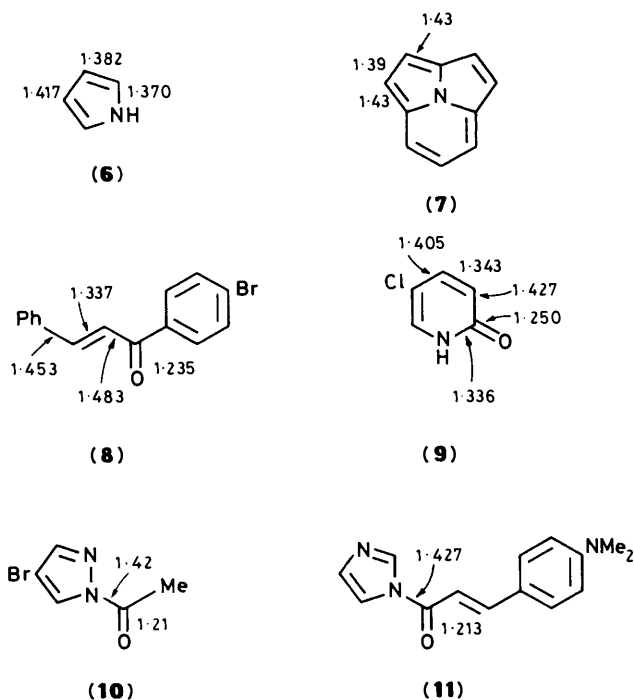
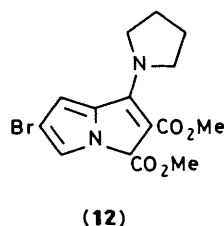


Figure 4. Bond lengths (Å) of selected compounds related to pyrrolizin-3-ones

These results demonstrate that the amide geometry within the pyrrolizinone system shows the effect of reduced delocalisation, but do not establish that this is due to the resultant formation of an  $8\pi$ -system: reduced lone-pair availability due to 'normal' pyrrole resonance must be taken into account. The amide geometry of the *N*-acyl heterocycles (10)<sup>13</sup> and (11)<sup>14</sup> is relevant here (Figure 4), since, within two standard deviations, the results are the same as for the pyrrolizinone (2). This *X*-ray work therefore corroborates the earlier n.m.r. conclusions,<sup>4</sup> namely that the two rings of pyrrolizin-3-one behave independently, save for a small amount of amide-like interaction typical of *N*-acylazoles: there is no evidence for cyclic delocalisation of the resulting  $8\pi$ -system.

Some other structural points, unrelated to the conjugation, require comment. The C-Br bond length in (2) [1.874(7) Å] is identical with that of the pyrazole (10),<sup>13</sup> [1.87(2) Å] and only slightly shorter than that of the benzenoid derivative (8)<sup>9</sup> [1.898(9) Å]. There are no significant non-bonded contacts between molecules. Certain formally trigonal bond angles are surprisingly distorted from 120° (Figure 2), though this appears to be a feature of fused five-membered ring heterocycles with bridgehead nitrogen atoms. For example, the wide angles at the ring junction [C(1)-C(8)-C(7) 144.3(7)°; C(3)-N(4)-C(5) 138.4(6)°] are also found in the cyclazine (7)<sup>8</sup> and in (12), the only other pyrrolizinone for which structural data are available.<sup>15</sup> Finally, we note that the C-C-O angle is some 6° larger than the N-C-O angle of the amide function. Although a similar trend



has been noted in lactones,<sup>16</sup> the present result is substantially in excess both of the standard deviation of the population of  $\gamma$ -lactams which was studied, and of the empirical correlation based on the magnitude of the N-C-C bond angle.<sup>16</sup> Once again, the differences between the pyrrolizinone system and normal lactams are emphasised.

## Experimental

N.m.r. spectra (<sup>1</sup>H and <sup>13</sup>C) were recorded at 200 and 50 MHz (respectively). In the listings of <sup>13</sup>C n.m.r. data, 'q' refers to quaternary carbon atoms.

**5-(4-Bromopyrrol-2-ylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (4).**—A solution of Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) (1.44 g, 10 mmol) in the minimum quantity of acetonitrile (8 ml) was treated with 4-bromopyrrole-2-carbaldehyde<sup>5</sup> (1.46 g, 10 mmol), and the mixture was stirred at room temperature overnight. The yellow precipitate was filtered off and washed with light petroleum (b.p. 40–60 °C) to give the *dione* (1.98 g, 66%) after recrystallisation from ethanol; m.p. 155 °C (decomp.) (Found: C, 43.9; H, 3.3; N, 4.75. C<sub>11</sub>H<sub>10</sub>BrNO<sub>4</sub> requires C, 44.0; H, 3.35; N, 4.65%);  $\delta_{\text{H}}$  ([<sup>2</sup>H<sub>6</sub>]DMSO) 12.54 (1 H, br s), 8.18 (1 H, s), 7.72 (1 H, s), 7.69 (1 H, s), and 1.70 (6 H, s);  $\delta_{\text{C}}$  ([<sup>2</sup>H<sub>6</sub>]DMSO) 163.06 (q), 162.01 (q), 142.05, 131.65 (q), 128.03, 127.89 (q), 103.98, 102.72 (q), 100.05 (q), and 26.71; *m/z* 301 (*M*<sup>+</sup>, 25%), 299 (*M*<sup>+</sup>, 25), 243 (20), 241 (20), 199 (100), 197 (100), 171 (12), 169 (12), 90 (21), and 63 (17).

**6-Bromopyrrolizin-3-one (2).**—Sublimation of (4) (0.051 g, 0.17 mmol) at 140–150 °C and  $2 \times 10^{-3}$  Torr through a silica tube (35 × 2.5 cm) maintained at 600 °C required 35 min. The products were collected in a liquid nitrogen trap, and, after warming to room temperature, consisted solely of acetone and the pyrrolizinone (2) (88%).

When the pyrolysis was repeated on a 5 mmol scale, the orange solid obtained (0.66 g) was subjected to bulb-to-bulb distillation at 130 °C (2 Torr), and the distillate was fractionally crystallised from hexane to give, as the less soluble component, 1,6-dibromo-1,2-dihydropyrrolizin-3-one (0.08 g), m.p. 101–103 °C (from hexane) (Found: C, 30.2; H, 1.7; N, 5.15. C<sub>7</sub>H<sub>5</sub>Br<sub>2</sub>NO requires C, 30.3; H, 1.8; N, 5.05%);  $\delta_{\text{H}}$  (C[<sup>2</sup>H]Cl<sub>3</sub>) 7.17 (1 H, d, *J* 1.0 Hz), 6.34 (1 H, d, *J* 1.0 Hz), 5.40 (1 H, m), 3.67 (1 H, dd, *J* 7.3 and 19.4 Hz), and 3.31 (1 H, dd, *J* 2.1 and 19.4 Hz); *m/z* 281 (*M*<sup>+</sup>, 7%), 279 (*M*<sup>+</sup>, 14), 277 (*M*<sup>+</sup>, 7), 200 (98), 198 (100), 172 (32), 170 (33), 91 (34), 90 (29), and 63 (34). The more soluble component, a red solid, was 6-bromopyrrolizin-3-one (2), m.p. 59–60 °C (from hexane) (Found: C, 42.6; H, 2.25; N, 6.9. C<sub>7</sub>H<sub>4</sub>BrNO requires C, 42.65; H, 2.05; N, 7.1%);  $\delta_{\text{H}}$  (C[<sup>2</sup>H]Cl<sub>3</sub>) 7.09 (1 H, dd), 6.93 (1 H, dd), 6.00 (1 H, d), and 5.72 (1 H, d);  $\delta_{\text{C}}$  (C[<sup>2</sup>H]Cl<sub>3</sub>) 164.34 (q), 137.76, 136.31 (q), 122.02, 118.02, 112.96, and 103.48; *m/z* 199 (*M*<sup>+</sup>, 100%), 197 (*M*<sup>+</sup>, 100), 171 (15), 169 (15), 90 (50), and 63 (41).

**Crystallography.**—The crystal was sealed in a Lindemann tube and its quality checked by oscillation and Weissenberg photography.

**Crystal data.** C<sub>7</sub>H<sub>4</sub>BrNO, *M* = 198.01. Monoclinic, *a* = 5.805 1(5), *b* = 6.537 6(9), *c* = 18.613 4(13) Å,  $\beta$  = 97.291(6)°, *V* = 700.69 Å<sup>3</sup> [from 2 $\theta$  values of 35 reflections measured at  $\pm\omega$  (35 < 2 $\theta$  < 40)°,  $\lambda$  = 1.541 83 Å], space group *P*2<sub>1</sub>/*c*, *Z* = 4, *D*<sub>x</sub> = 1.877 g cm<sup>-3</sup>. Red, irregular, columnar crystals. Crystal dimensions 0.50 × 0.25 × 0.30 mm,  $\mu$ (Cu-*K*<sub>α</sub>) = 74.39 cm<sup>-1</sup>.

**Data collection and processing.** Stoe-Siemens AED2 four-circle diffractometer,  $\omega$ -2 $\theta$  scan mode with  $\omega$  scan width 0.80° +  $\alpha$ -doublet separation, graphite-monochromated Cu-*K*<sub>α</sub> radiation; 1 093 unique reflections measured (3 < 2 $\theta$  < 120)°;

$\pm h, k, l$ ), semi-empirical absorption correction derived from  $\psi$  scans of 3 reflections [(1 2 1), (1 3 2), (2 6 4)] giving max., min. transmission factors of 0.192, 0.039, yielding 760 data with  $I > 3\sigma(I)$ .

*Structure analysis and refinement.* Patterson synthesis (Br) followed by iterative rounds of least-squares refinement and  $\Delta F$  synthesis revealed the positions of all non-H atoms. At isotropic convergence, final corrections for absorption were made empirically (DIFABS). Full-matrix least-squares refinement with all non-H atoms anisotropic and H atoms in fixed, calculated positions. The weighting scheme  $w^{-1} = \sigma^2(F) + 0.00043F^2$  gave satisfactory agreement analyses. Final  $R$ ,  $R_w$  values were 0.0495, 0.0702 ( $S = 1.162$ ). Final  $\Delta F$  synthesis showed max., min. residues of 0.54,  $-0.67 \text{ e } \text{\AA}^{-3}$ . Programs used are given in ref. 17.

#### Acknowledgements

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