Imidazoline-4-thiones from Cyanothioformamides and Aldehyde Imines: Formation, Aromatization, and Acetylation

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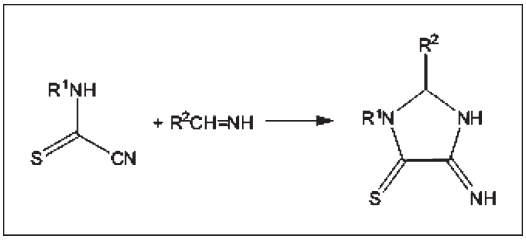

The reaction of *N*-methyl- (**3a**) or *N*-phenylcyanothioformamide (**3b**) with acetaldimine (**5a**, as 1-amino-1-ethanol) gives 5-(amino)imidazolidine-4-thiones **6B**. Product **6a** reacts with a second equivalent of **3a** to give **8** which in turn is oxidized to disulfide **9**. Using araldimines **5b**,**c**, only 1:2 intermediates **10** derived from **3a**, **b** and two moles of the imine **5** are formed, but proved to be easily oxidized to disulfides **11**. Acetylation of **6** occurs chemoselectively on the exocyclic nitrogen and finally also on the thione sulfur to give **14** *via* **13**.

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INTRODUCTION

There is continuing interest in the design and evolution of novel antioxidants as a means to alleviate oxidative stress in biochemical processes [1–3]. For the heterocyclic chemist, an attractive lead structure appears to be the unusual amino acid family of ovothiols **1a–c** [4–7]. So, imidazole-4-thiols **2** have become attractive targets for synthesis (Scheme 1).

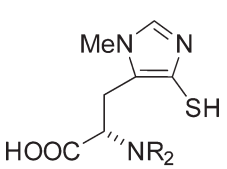
N-Acylaminoacid thioamides are possible precursors of ovothiols **1** [4], but their cyclization is not always reproducible [5]. Similarly, the *Asinger* group has reported the formation of imidazolethiols **2** from α-oxothioamides and aldimines [8]. Recently, we have reported the synthesis of oxazolidines **4** from cyanothioformamides **3** and aldehydes or ketones [9] as part of our study on heterocyclic ring-closure reactions [10–16] and now envisaged that cyanothioformamides **3** and *N*-unsubstituted aldimines should give products of type **2**, though with a 5-amino group as additional feature which may assist in free-radical trapping. However, the position of the tautomeric equilibrium in the probable cyclization products **6** between iminothiones **6A**, aminothiones **6B**, and aminothiols **6C** is a priori open (Scheme 2). On the other hand, heterocycles **6** are also of special interest as precursors of the elusive bicyclic heteroaromatic products of type **12** (Scheme 5).

RESULTS AND DISCUSSION

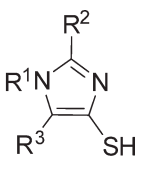
We selected *N*-methyl- (**3a**) and *N*-phenylcyanothioformamide (**3b**) as nucleophiles, and acetaldimine **5a** (as 1-amino-1-ethanol [17]) or benzaldimines **5b**,**c** as electrophiles. Triethylamine was used as a catalyst.

Thioamide **3a** and acetaldimine **5a** give a smooth reaction to furnish 1:1 product **6a** as the only defined

Scheme 1. Imidazole-4-thiols.



1a: R = H
1b: NR_2 = NHMe
1c: R = Me



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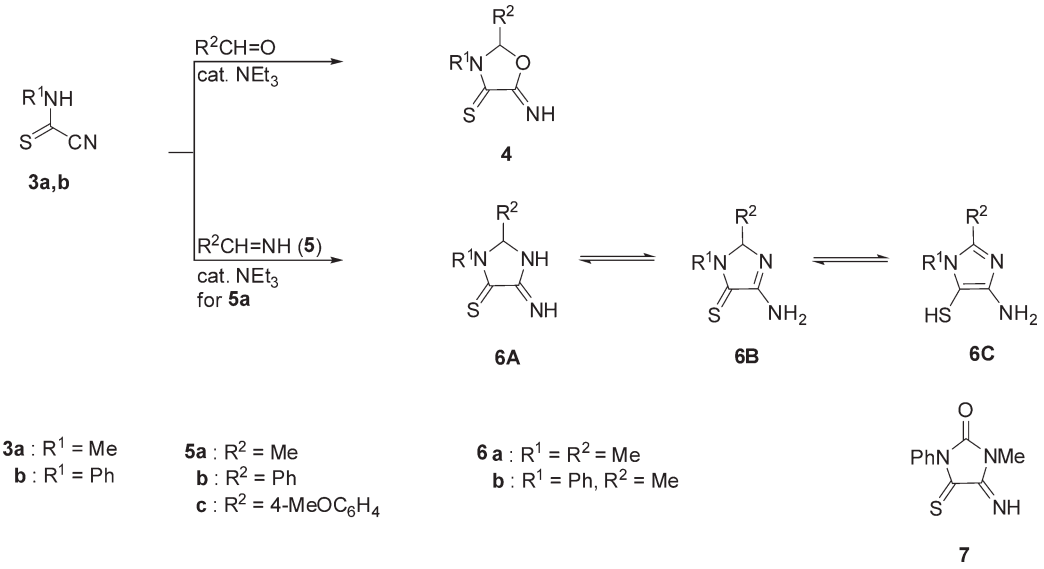
Scheme 2. Reactions of cyanothioformamides with aldehydes or acetaldimine.



product. An analogous product **6b** is formed from thioamide **3b** und **5a** (Scheme 2). As to the position of the tautomeric equilibrium, appearance of the 2-methyl signal of **6a** as a doublet in the ^{1}H NMR spectrum and a low-field ^{13}C NMR signal (ca. 182 ppm) pointing toward the presence of a thiocarbonyl carbon as in **6A** and **6B** allow to rule out tautomer **6C**. Another low-field ^{13}C NMR peak at δ about 159 ppm occurs at definitely lower field than for the exocyclic imino group in model compound **7** (δ 154.2 ppm) [10,11,18], and in the ^{1}H NMR spectrum, the two NH protons are magnetically equivalent as expected for **6B**. Moreover, the IR spectra lack a strong vibration in the 1650–1670 cm^{-1} range which is observed for **7** (1659 cm^{-1}) and in other authentic 5-imino-imidazolidine-4-thiones [13,18]. So obviously, tautomer **6B** is preferred indicating that the greatest degree of stabilization is achieved by conjugation within the transoid S═C─C═N unit of tautomer **6B** when compared with the corresponding cisoid system in **6A** or the aromaticity of **6C**.

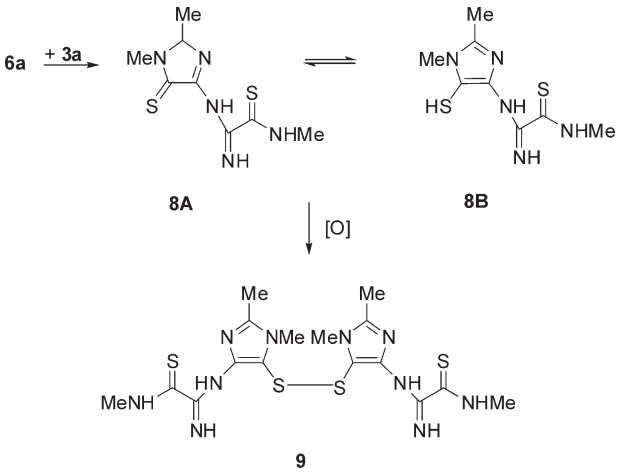
Prolonged reaction times in the addition of **3a** to **5a** showed that the thioamide **3a** adds faster to cyclization product **6a** than to **5a** giving rise to a 2:1 adduct **8** as well as aromatic disulfide **9** as oxidation product (Scheme 3).

An X-ray crystallographic study revealed the structure of **9** and so implicitly also of precursor **8**. As the spectroscopic data for **8** are similar to those of **6**, we assume that the imidazole unit in **8** has structure **B** as in the preferred tautomer **B** of **6**. In the formation of **8**, the second mole of **3a** has been incorporated *via* its nitrile function by addition to the exocyclic imino group of **6a** and this is obviously followed by aromatization and oxidation to the disulfide **9** (Fig. 1).

Reactions of thioamides **3** with aromatic aldimines **5b**,**c** take a different course (Scheme 4). Here, invariably dehydrogenated 2:1 products **11a–c** are formed obviously *via* intermediate **6**, followed by Schiff base formation with a second equivalent of the imine **5** to give azomethines **10** with loss of ammonia, and finally oxidative aromatization. Even when the reactions were run under nitrogen, conventional work-up led to oxidation to give the aromatic disulfides **11**. So, there is a striking difference in the sensitivity to oxidation between the 2-methyl (R^2 = Me) products **6a**,**b** and their 2-aryl congeners **10**.

Attempts to cyclize **6a**,**b** using acetic anhydride gave no indication for the formation of the bicyclic hetarene **12**, but simple monoacetylation is observed (Scheme 5). The spectroscopic data allow no unambiguous

Scheme 3. Oxidation of imidazolinethione **6a**.



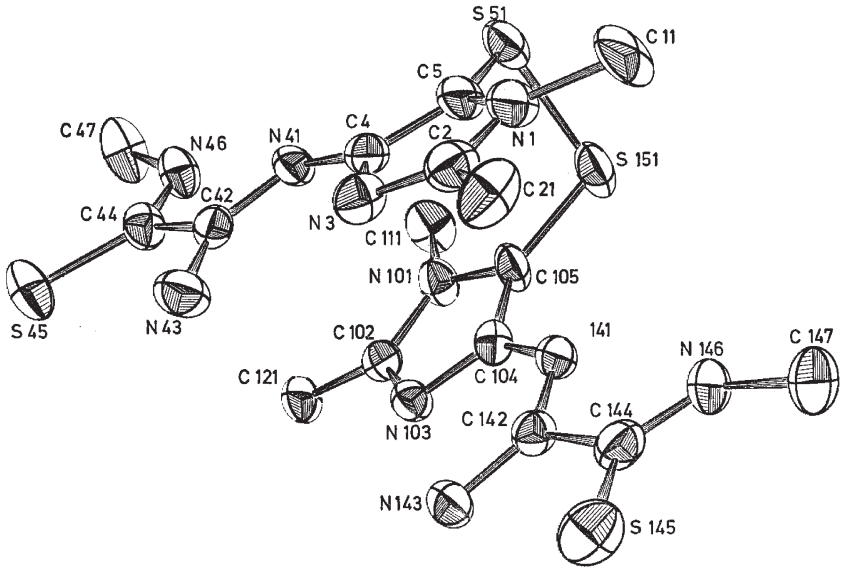


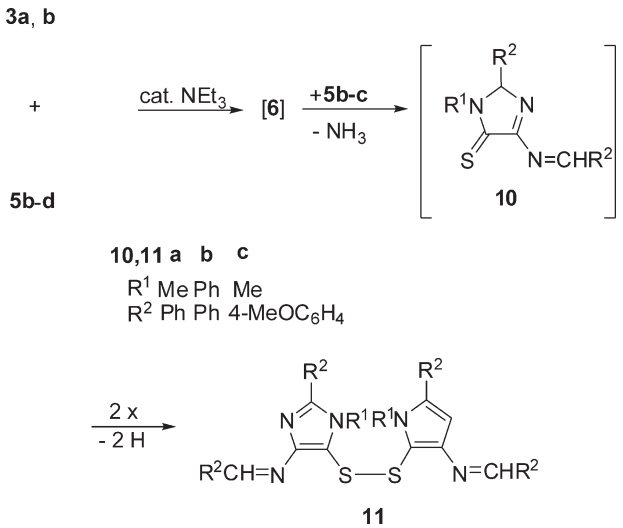
Figure 1. ORTEP drawing of disulfide **9** with salient bond lengths [Å]: S51-C5 1.840(9), S51-S151 2.176(4), N1-C2 1.367(11), N3-C2 1.323(10), N3-C4 1.402(10), C4-C5 1.395(10), N41-C42 1.298(9), N43-C42 1.385(10), S45-C-44 1.676(8), N46-C44 1.295(9), S151-C105 1.712(7), N101-C105 1.405(9), N101-C102 1.356(9), N103-C102 1.320(9), N103-C104 1.365(8), C104-C105 1.401(10), N141-C142 1.270(8), N143-C142 1.331(9), S145-C144 1.751(8), N146-C144 1.303(10).

distinction between acetylation of the endocyclic or the exocyclic nitrogen, but further acetylation of the product derived from **6b** yields a triacetylated product for which structure **14** is suggested based on the magnetic equivalence of two acetyl residues. Mutatis mutandis this leads to structure **13** for the *N*-monoacetylated products. Similarly, monoacetylation in the exocyclic position is observed when the hydrolysis product **15** of imine **6a** is acetylated to give apparently an ester derivative **16**. This is evident particularly from the high-wavenumber carbonyl absorptions (1762, 1731 cm^{-1}) of the product.

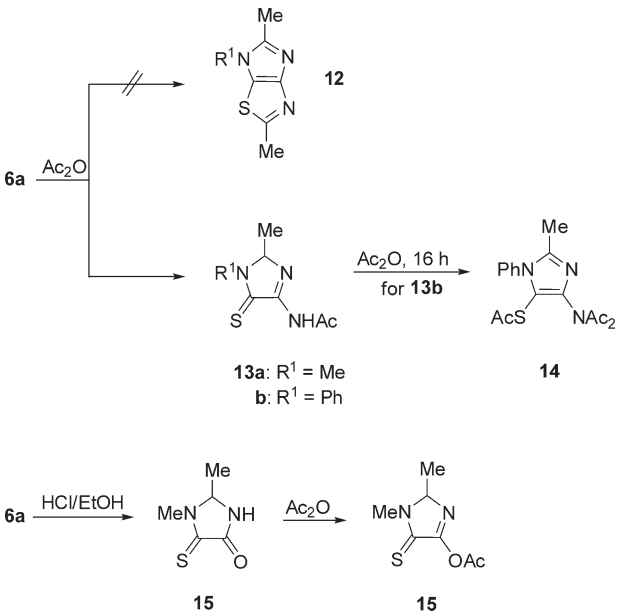
CONCLUSIONS

The reaction of cyanothioformamides **3** with aldimines **5** takes the expected initial course when the

Scheme 4. Cyanothioformamides and araldimines.



Scheme 5. Acylation of imidazolinethiones **6**.



nitrogen in the thioamide moiety in **3** attacks the electrophilic imine carbon of **5**, whereas the nitrile function provides the opportunity for subsequent cyclization to give imidazolidines **6**. However, among the possible tautomers **6B** is apparently preferred and can be isolated for R^2 = methyl whereas compounds with R^2 = aryl tend to add a second equivalent of imine **5** and easily undergo oxidative dimerization. The ready oxidation of imidazole-4-thiols had been seen before in similar examples [5,8]. Unfortunately, the disulfide form of L-ovothiol A (**1a**) is biologically inactive [6] and this may also be anticipated for the disulfides of this work.

EXPERIMENTAL

General. NMR: Bruker WP 80–FT, AMX 400, or Varian FT–80A; $CDCl_3$ as solvent unless stated otherwise, with TMS as internal standard; coupling constants *J* are given in Hz. IR: Perkin–Elmer FTIR 1720 X or Pye-Unicam SP3-200 spectrometers. Elemental analyses: Institut für Pharmazeutische Chemie, TU Braunschweig.

N-Methylcyanothioformamide (**3a**) [9] and cyanothioformanilide (**3b**) [19] were prepared as previously described, though in the preparation of **3b** we found use of THF as solvent advantageous. For the synthesis of imine **5a** see ref. [17], for benzaldimine (**5b**) see ref. [20]; imine **5c** [21] was prepared analogously.

5-Amino-2,3-dimethyl-5-imidazoline-4-thione (6a). An ethereal (20 mL) solution of **3a** (2.38 g, 20 mmol), **5a** (3.66 g, 20 mmol), and triethylamine (three drops) was stirred for 30 min at 20°C to give **6a** as reddish–brown crystals (745 mg, 26%); m.p. 137°C (dec.). IR (KBr): $\tilde{\nu}$ = 3370, 3180, 2950, 1470, 1140 cm^{-1}. ^1H NMR: δ = 1.44 (d, *J* = 6.4, 3 H, CCH_3), 3.36 (s, 3 H, CH_3N), 5.13 (q, *J* = 6.4, 1 H, CH), 5.58 (broad, 2 H, NH). ^{13}C NMR: δ = 181.96 (C═S), 159.37 (N═C), 84.64 (C─Me), 32.28 (N─Me), 18.80 (Me). MS: m/z (%) = 143 (100) [M], 128 (23) [M─CH_3], 74 (28), 69 (31). HRMS for ($C_5H_9N_3S$ + H): calcd 144.0595, found 144.0601.

5-Amino-2-methyl-3-phenyl-5-imidazoline-4-thione (6b). An ethereal (25 mL) solution of **3b** (1.62 g, 10 mmol), **5a** (1.83 g, 10 mmol), and triethylamine (three drops) was stirred for 15 min and then diluted with hexane. The gummy residue was extracted several times with hexane. These extracts were combined with the ether-hexane solution. Removal of the solvents under reduced pressure gave **6b** as reddish brown crystals (308 mg, 15%); m.p. 125–127°C. IR (KBr): $\tilde{\nu}$ = 3350, 3270, 2950, 1470, 1130 cm^{-1}. ^1H NMR: δ = 1.33 (d, *J* = 6.4 Hz, 3 H, CH_3), 5.78–5.60 (q, *J* = 6.4, 1 H, CH and broad, 2 H, NH_2, exchangeable with D_2O), 7.48 (m, 5 H, ArH). ^{13}C NMR: δ = 181.80 (C═S), 159.03 (N═C), 129.49, 128.44, 125.01 (Ph), 85.47 (*C*─Me), 19.63 (Me). MS: *m/z* (%) = 205 (68) [M], 204 (8), 190 (7), 135 (12), 70 (100). $C_{10}H_{11}N_3S$ (205.3); calcd C 58.51, H 5.40, N 20.47, S. 15.62; found C 58.31, H 5.52, N 20.10, S 15.23.

5-Imino-1-methyl-3-phenyl-4-thioxoimidazolidin-2-one (7). The compound had been prepared before [10,16]. IR (KBr): 1766 (C═O), 1659 (C═N) cm^{-1}. ^{13}C NMR (CH_3): δ =181.9 (C═S), 154.8 (C═O), 154.2. (C═NH), 132.5 (Ar), 129.4, 129.3, 126.9 (ArH), 26.8 (NCH_3).

2-(1,2-Dimethyl-5-mercaptoimidazol-4-yl)amino-2-imino-N-methyl-thioacetamide (8B) and bis[4-(imino-(N-methylthiocarbamoyl)methyl)amino-1,2-dimethylimidazol-5-yl] disulfide (9). An ethereal (20 mL) solution of **3a** (3.24 g, 20 mmol), **6a** (3.66 g, 20 mmol), and triethylamine (three drops) was stirred at 20°C for 30 min and then allowed to stand for 16 h. The solid product was extracted several times with cold ethanol. The remaining solid was recrystallized from boiling ethanol to give **8** as yellow crystals (9.73 g, 20%); m.p. 173–175°C. IR (KBr): $\tilde{\nu}$ = 3150–3300, 2930–2970, 1450, 1130 cm^{-1}. ^1H NMR: δ = 2.50 (s, 3 H, CCH_3), 2.90 (d, *J* = 6 Hz, 3 H, NHC*H*$_3$, collapses to s with D_2O), 3.56 (s, 3 H, CH_3N), 7.63, 9.33, 10.40 (each s, 3H, broad NH, exchanges with D_2O). Concentration of the ethanolic extract from earlier gave **9** as reddish crystals (145 mg, 30%); m.p. 195–197°C. IR (KBr): $\tilde{\nu}$ = 3350–3230 (broad, NH), 2910–2980, 1470, 1150 cm^{-1}. ^1H NMR: δ = 2.29 (s, 6 H, CH_3C), 3.21 (s, 6 H, C*H*$_3$NH), 3.3 (s, 6 H, CH_3N), 7.47, 8.99, 9.88 (each broad, NH; exchanges with D_2O). $C_{16}H_{24}N_{10}S_4$. (484.7): calcd. C 39.65, H 4.99, N 28.90, S 26.46; found C 39.60, H 5.00, N 29.00, S 26.50.

Bis(4-benzylidenamino-1-methyl-2-phenyl-imidazole)-5,5′-diyl disulfide (11a). An ethereal solution (20 mL) of **3a** (1.0 g, 10 mmol), **5b** (1.05 g, 10 mmol), and triethylamine was stirred at 20°C for 0.5–2 h to provide yellow crystals (750 mg, 51%), m.p. 187–190°C. IR (KBr): $\tilde{\nu}$ = 1605, 1573. ^1H NMR: δ = 3.85 (s, 3 H, CH_3), 7.2–7.78 (m, 10 H, Ph, CH), 8.99 (s, 1 H, PhCH═N). ^{13}C NMR: δ = 158.6 (N═CH), 155.7 (C-2), 149.8 (C-4), 136.3, 130.9, 128.9, 128.7, 128.6, 128.4, 128.2 (Ar), 116.4 (C-5), 32.5 (NCH_3). MS: m/z (%) = 585 (48) [M + H], 481 (58), 437 (59), 393 (92), 349 (100). $C_{34}H_{28}N_6S_2$ (584.8): calcd. for C 69.83, H 4.83, N 14.37, S 10.97; found C 69.13, H 4.96, N 14.51, S. 10.65.

Bis(4-benzylidenamino-1,2-diphenyl-imidazole)-5,5′-diyl disulfide (11b). An ethereal solution (20 mL) of **3a** (1.62 g, 10 mmol), benzaldimine **5b** (2.10 g, 20 mmol), and triethylamine (three drops) was stirred for 30 min and allowed to stand overnight. The yellow crystals were collected and recrystallized from dichloromethane/methanol; yield 1.60 g (45%). m.p. 195°C (dec.). Repeated crystallization afforded a product with m.p. 207°C (dec.). IR (KBr): $\tilde{\nu}$ = 1605, 1573, 1503, 1316 cm^{-1}. ^1H NMR: δ = 6.96–7.48 (m, 13H), 9.11 (s, 1 H, PhCH═N). ^{13}C NMR: δ = 159.3 (N═CH), 155.7 (C-4), 148.6 (C-2), 136.62, 136.41, 129.52 (Ar), 130.94, 129.07, 128.90, 128.58, 128.48, 128.43, 127.88 (ArH), 119.0 (C-5). MS: *m/z* (%) = 709 (100) [M + H], 337 (18), 289 (9), 161 (19), 105 (8). $C_{44}H_{32}N_6S_2$ (708.9): calcd C 74.55, H 4.55, N 11.86; S 9.05 found C 74.19; H 4.69; N 11.82; S 8.82.

Bis[4-(4-methoxybenzylidenamino)-1-methyl-2-(4-methoxyphenyl)-imidazole]-5,5′-diyl disulfide (11c). Prepared by the procedure described for **11** using **5c** in place of **5b**. Yield 55%, m.p. 155°C. IR (KBr): $\tilde{\nu}$ = 1600, 1470, 1210 cm^{-1}. MS: *m/z* (%) = 352 (25) [M/2], 351 (100), 176 (14), 151 (48). $C_{38}H_{36}N_6O_4S_2$ (704.86) calcd. C 64.75 H 5.15 N 11.92, S 9.10; found C 64.70, H 5.50, N 12.00, S 9.10.

N-*(1,2-Dimethyl-5-thioxo-3-imidazolin-4-yl)acetamide (13a).* A solution of **6a** (100 mg, 0.7 mmol) in acetic anhydride (1.4 mL, 14.8 mmol) was allowed to stand for 16 h. Removal of acetic anhydride under reduced pressure gave a gummy product which was triturated with water to afford dark pink crystals of **13a** (36 mg, 28%); m.p. 107–109°C. IR: $\tilde{\nu}$ = 3191, 1686, 1666, 1537 cm^{-1}. ^1H NMR: δ = 1.63 (d, *J* = 5.6, 3 H, CH_3CN_2), 2.67 (s, 3 H, CH_3CO), 3.39 (s, 3 H, CH_3N), 5.51

(q, J = 5.6, 1 H, CH). ^{13}C NMR: δ = 181.02 (C═S), 170.07 (C═O), 155.77 (C═N), 74.28 (C-2), 84.64 (C─Me), 31.2 (N─Me), 25.72 (Ac-CH_3), 18.68 (2-Me). MS: m/z (%) = 185 (89) [M], 143 (100), 128 (14). HRMS for ($C_7H_{11}N_3OS$ + H): calcd 186.0701, found 186.0696.

N-*(2-Methyl-1-phenyl-5-thioxo-3-imidazolin-4-yl)acetamide (13b).* A solution of **6b** (4.10 g, 20 mmol) in acetic anhydride (10 mL) was allowed to stand at 20°C for 30 min. Removal of the reagent under reduced pressure gave **13b** as yellow crystals (990 mg, 20%); m.p. 115–117°C. IR (KBr): $\tilde{\nu}$ = 3210, 1720, 1450, 1120 cm^{-1}. ^{1}H NMR: δ = 1.5 (d, J = 6.0, 3 H, 2-CH_3), 2.7 (s, 3 H, CH_3CO), 5.5 (q, J = 6.0, 1 H, 2-H), 7.5 (m, 5 H, ArH,), 9.4 (broad s, 1 H, NH, exchanges with D_2O). $C_{12}H_{13}N_3OS$ (247.3): calcd C 58.28, H 5.30, N 16.99, S 12.97; found C 58.19, H 5.16, N 17.11, S 12.89.

N-*(5-Acetylthio-2-methyl-1-phenyl-imidazol-4-yl)diacetamide (14).* The earlier reaction was repeated, but allowed to run for 16 h to give **14** as yellow crystals (1.66 g, 25%); m.p. 110–111°C. IR (KBr): $\tilde{\nu}$ = 2970, 2910, 1690 cm^{-1}. ^{1}H NMR: δ = 2.1, 2.3 (each, s, 3 H, CH_3), 2.4 (s, 6 H, Ac_2N), 7.0–7.6 (m, 5 H, ArH). MS: m/z (%) = 331 (3) [M], 289 (20), 247 (93), 205 (100). $C_{16}H_{17}N_3O_3S$ (331.4): calcd. C 57.99, H 5.17, N 12.68, S 9.68; found C 57.80, H 5.26, N 12.66, S 9.55.

1,2-Dimethyl-5-thioxoimidazolidin-4-one (15) and (1,2-dimethyl-5-thioxo-3-imidazolin-4-yl) acetate (16). A suspension of thione **6a** (50 mg, 0.35 mmol) in EtOH (2.1 mL), and 2*M* HCl (0.35 mL) was refluxed for 30 min. After cooling, water (3.5 mL) was added. Sticky yellow crystals could be removed by filtration and were used as such in the subsequent step. Yield 20 mg (40%). IR (KBr): 3455, 3368, 3211, 1731 cm^{-1}. ^{1}H NMR (MeOD): 1.64 (d, J = 6.2 Hz, 2-CH_3), 3.42 (d, J = 1.2 Hz, 1-CH_3), 5.52 (q + q), J = 1.2; 6.2 Hz, 2-H). ^{13}C NMR (MeOD): δ =177.7 (C═S), 157.5 (C═O), 77.9 (C-2), 32.9 (1-CH_3), 18.2 (2-CH_3). Lactam **15** (17 mg, 0.12 mmol) was added to Ac_2O (0.24 mL, 2.54 mmol) and the mixture allowed to stand at room temperature for 16 h. After concentration *in vacuo*, water was added and the precipitate isolated by filtration. Yield 10 mg (46%), m. p. 125°C. IR: $\tilde{\nu}$ = 1762, 1731, 1533 cm^{-1}. ^{1}H NMR: δ = 1.68 (d, J = 5.8 Hz, 3 H, 2-CH_3), 2.65 (s, 3 H, Ac─CH_3), 3.42 (s, 3 H, CH_3N), 5.44 (q, J = 5.8 Hz, 1 H, 2-H). ^{13}C NMR: δ = 180.6 (C═S), 169.8 (C═O), 156.1 (C═N), 72.3 (C-2), 33.3 (1-CH_3), 25.2 (Ac─CH_3), 18.7 (1-CH_3). MS: m/z (%) = 186 (74) [M], 144 (75), 129 (18), 74 (100).

Crystal structure determinations of disulfide 9. Intensity data were collected with a CAD 4-SDP single-crystal diffractometer (Enraf-Nonius) using graphite-monochromated Cu Kα radiation in the rage θ < 60°. The final refinements were based on 1657 symmetry-independent reflections with $I > 3\sigma$ for I. The structure was solved by the direct-methods program MULTAN. The E map revealed the position of all the heavy atoms. Because of the thinness of the crystal, the positions of the hydrogen atoms were geometrically calculated, but difficult to refine. Convergence was achieved at R = 0.060 (R_w = 0.071). $C_{16}H_{24}N_{10}S_4$, M_r = 484.7, monoclinic, a = 755.2(1), b = 22726(1), c = 1992.8(1) pm, β = 100.32(1)°, V = 2.352 × 10^9 pm^3, T = room temp., space group Cc, Z = 4, $d_{cal.}$ 1.38 g cm^{-1}, $\mu_{Cu\ K\alpha}$ = 38.7 cm^{-1} [22].

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[22] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 733961 The data can be obtained free of charge from the CCDC, via www.ccdc.cam.ac.uk/data_request/cif.