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Reappraising the formation of Jaffé's base: studies of the treatment of imidazolidine-2-thione with mild oxidising agents

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Throughout reports detailing the preparation of Jaffé's Base, which date as far back as 1894, its identity and the nature of an intermediate prior to its formation have been constant points of conjecture. This report presents firm evidence that the oxidation of imidazolidine-2-thione, $SCN(H)C_2H_4N(H)$, with potassium triiodide yields the 'thiol' condensation product 2,2′-bis(4,5-dihydro-1*H*-imidazolidine)disulfide $\{NC_2H_4N(H)CS\}_2$ (**1**), which under mild conditions undergoes partial self condensation to yield 1-(4,5-dihydro-1*H*-imidazolidin-2-yl)imidazolidine-2-thione, Jaffé's Base – $SCN(CNC_2H_4N(H))C_2H_4NH$, (**2**). Crystallisation of **1** from acetone results in the unexpected formation of heterobicyclic 3-methyl-5,6-dihydroimidazolidin[2,1-*b*]thiazole, **3**. The conversion of **1** to **3** has been studied by ^{1}H NMR spectroscopy, which suggests the concurrent formation of **2** as an unreactive by-product. The solid state structures of **2**, its HBr salt (**2**·HBr) and **3**·($HI·I_2$), the latter being the isolated form of **3** under the conditions employed, have been determined using XRD methods.

Introduction

A frequent by-product in syntheses that use imidazolidine-2-thione in the presence of mild oxidising agents, *e.g.* $C(S)Cl_2$,[1] $Cu(NO_3)_2$,[2] HgO,[3] $CSCl_2/CaCO_3$[4] or I_2,[3,5–7] is a heterocyclic compound of composition $C_6H_{10}N_4S$, otherwise known as Jaffé's Base. From several syntheses that unintentionally used conditions conducive to the generation of this base,[1–4,6,8] two viable structures have emerged (see Fig. 1, **A** and **B**). The symmetrical 2,2′-bis(4,5-dihydro-1*H*-imidazolidine)sulfide (**A**) has precedent in recent mechanistic discussions concerning the ureidation of picoline *N*-oxides with 2-chloro-4,5-dihydro-1*H*-imidazolidine,[8] but, as early as 1953 and more remarkably, in the absence of routine NMR spectroscopy and X-ray crystallography, Lecher and Gubernator[7] (correctly) proposed the unsymmetrical 1-[4,5-dihydro-1*H*-imidazolidin-2-yl]imidazolidine-2-thione, **B** (Fig. 1), on the basis of detailed experiments concerning the mercuric oxide oxidation of *N,N,N′,N′*-tetramethylthiourea. This assignment found favour with the group of Poos who subsequently used HgO,[3] rather than the KI_3[5] and cumbersome thiophosgene[1] paths previously reported by Johnson and Edens[5] and Jaffé and Kühn,[1] to form Jaffé's Base. However, it was not until 1984 that a compound containing Jaffé's Base had been reported,[6] the uncertainty as to the true connectivity, be it **A** or **B**, remaining. To complicate matters further, the unexpected formation of this compound as a by-product often led to its isolation as an acid salt or a co-ordination complex.[3–6] Throughout this period (1942–1984) there was significant discussion as to the path of formation of Jaffé's Base,[3–6] in particular the identity of intermediates.

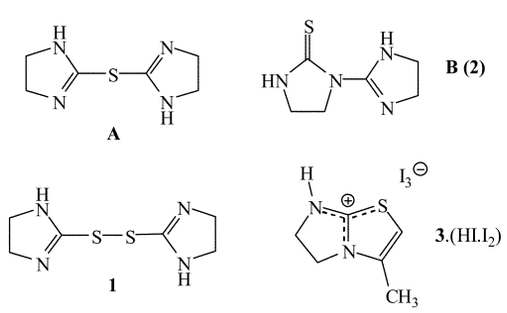

Fig. 1 The two probable structures for Jaffé's Base (**A** and **B**), the suggested 'KI_3' path disulfide intermediate, **1**, and the thiazolium salt formed upon treatment of **1**.($HI·2I_2$) with acetone, **3**·($HI·I_2$).

A common theme in reports[3,5] that describe the preparation of Jaffé's Base utilising the most common synthetic methodology, *i.e.* that of Johnson and Edens[5] employing *in situ* generated I_3^-, is the prior generation of a 'sulfur-rich' compound; 2,2′-bis(4,5-dihydro-1*H*-imidazolidine)disulfide – $\{NC_2H_4N(H)CS\}_2$ (**1**) (see Fig. 1). It is generally accepted that this species undergoes rearrangement followed by partial self-condensation to yield Jaffé's Base.[3,5,6] However, while Jaffé's Base had purportedly been structurally authenticated in 1984 in the form of a fortuitously isolated co-crystallate of diiodine adducted imidazolidine-2-thione (structure that of **B**, from now on termed '**2**'),[6] **1** had not been characterised in the solid state. Correspondingly it was suggested that, in the absence of spectroscopic or structural data to the contrary, **1** was not an intermediate in the formation of **2** and that its inferred presence during the treatment of imidazolidine-2-thione with KI_3[3,5] was an artefact of an elemental analysis that coincidentally possessed the composition **1**·($HI·2I_2$).[3]

In view of this ongoing doubt, which has now continued for more than a century, we thought it prudent to study the formation of **2** utilising both the mercuric oxide path of Poos *et al.*[3] and the aforementioned KI/I_2 (KI_3) path.[1,3,5,6] As detailed herein, this has entailed the full structural characterisation of **2** and its hydrobromide salt (**2**·HBr), thereby eliminating any doubt as to the connectivity, geometry and hydrogen atom disposition of Jaffé's Base, and permitted full spectroscopic (^{1}H, ^{13}C NMR and FTIR) and spectrometric (ES-MS) characterisation of the intensely coloured charge-transfer hydroperiodide intermediate **1**·($HI·2I_2$), which according to both Poos *et al.*[3] and Johnson and Edens,[5] yields colourless **2**·(HI) after prolonged digestion in refluxing H_2O. In addition, and perhaps most surprisingly, the recrystallisation of **1**·($HI·2I_2$) from acetone, as recommended by Johnson and Edens,[5] does not yield pure **1**·($HI·2I_2$) but instead is found to yield the 3-methyl-5,6-dihydroimidazolidin[2,1-*b*]thiazole salt, 3-methyl-5,6-dihydro-

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7*H*-imidazolidin[2,1-*b*]thiazolium triiodide, **3**·(HI·I_2) (see Fig. 1). This compound has been characterised in full and its preparation from **1**·(HI·2I_2) and acetone studied by ^{1}H NMR in d_4-methanol. The potential preparation of 3-alkyl/aryl substituted 5,6-dihydroimidazolidin[2,1-*b*]thiazoles from the reaction of a methyl substituted ketone with **1**·(HI·2I_2) may represent a facile and hitherto unprecedented path to the study of such compounds and their unusually low basicity.[9]

Results and discussion

Preparation and structure of Jaffé's Base and its hydrobromide salt

In order to allay any confusion regarding the true connectivity of 'Jaffé's Base' the synthetic methodology first proposed by Lecher and Gubernator[7] and subsequently utilised by Poos *et al.*,[3] wherein imidazolidine-2-thione is refluxed in xylene with an equimolar amount of mercuric oxide, was employed for its preparation. Subsequent to recrystallisation from ethanol, this gave a significantly improved yield of **2** over that reported (25% tan needles, reference 3; 9%). Further to this, a portion of pure **2** was recrystallised from aqueous hydrobromic acid to render colourless prisms of the monohydrobromide salt; **2**·HBr. Accordingly, both compounds were characterised by single crystal X-ray structure determination (Figs. 2 and 3). This permitted firm structural assignment of **2** as the 1-[4,5-dihydro-1*H*-imidazolidin-2-yl]imidazolidine-2-thione (Fig. 1, **B**) first proposed by Lecher and Gubernator.[7] A summary of X-ray diffraction data for all structurally characterised complexes is given in the experimental section, whilst relevant bond lengths and angles for **2** and **2**·HBr are presented comparatively in Table 1.

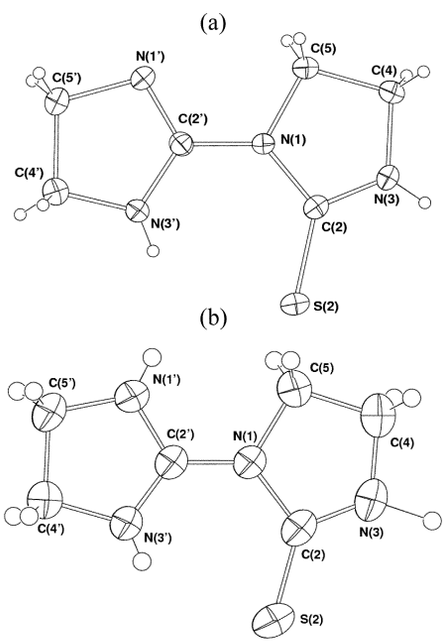

Fig. 2 Projections of **2** (a) and the **2**H$^+$ cation of **2**·HBr (b) normal to their non-hydrogen atom planes.

The results of the single crystal X-ray studies of Jaffé's Base and its hydrobromide (**2** and **2**·HBr respectively) are consistent with the expected stoichiometry and connectivity, both species are either *quasi*- or exactly planar. One formula unit of the former and half a formula unit of the latter (all non-hydrogen components contained in the crystallographic mirror planes of the space group *Pnma*), inclusive of anion, comprise the asymmetric units of the structures (Figs. 2 and 3). With respect to the parent base, **2** (Fig. 2(a)), refinement behaviour indicates that the non-protonated nitrogen atom is N(1′). This is supported

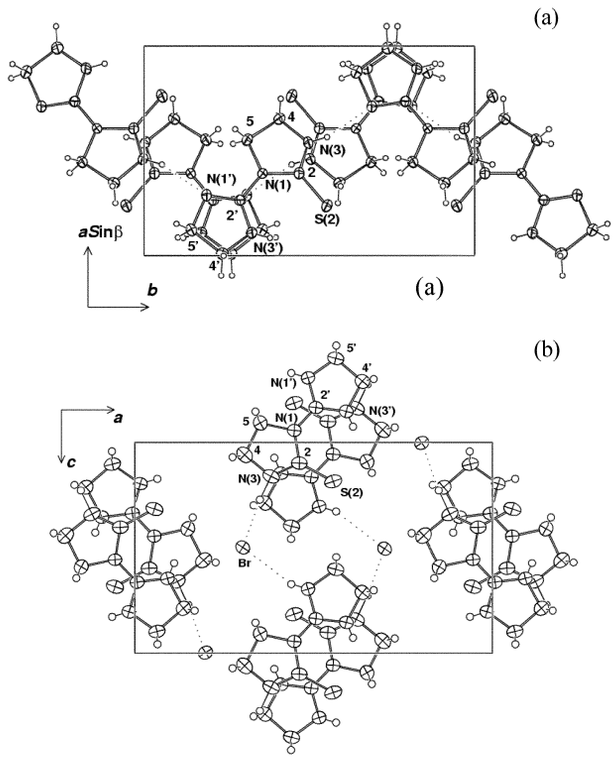

Fig. 3 Projections of the unit cell contents of **2** (a) and **2**·HBr (b) down the *c*- (7.7913 Å) and *b*- axes (6.895(7) Å) respectively.

by the observation of maximum double bond character for N(1′)–C(2′) (1.282(6) Å) which constitutes a component of the conjugated system that extends into the other coplanar ring. The hydrogen H(3′) (bonded to N(3′)), see Fig. 2(a), may be considered to interact intramolecularly with the sulfur atom S(2) (H(3′) ··· S(2) 2.538(4) Å), while H(3) (bonded to N(3), see Fig. 2(a)) hydrogen-bonds intermolecularly to the unprotonated nitrogen in an adjacent asymmetric unit (N,H(3) ··· N(1′) ($1 - x$, ½ + y, ½ − z) 2.857(5) Å and 2.14(4) Å respectively). The unit cell projection of **2** (Fig. 3(a)) is suggestive of parallel charge-transfer type stacking between adjacent molecules, but there are no unusually close contacts in this respect, the interplanar spacing approximating the *c*-axis (= 7.7913(7) Å/2). Lastly, the molecular C_6N_4S non-hydrogen skeleton of **2** is effectively planar, the maximum deviation from planarity being that of N(3′) (0.069(6) Å, $\chi^2 = 2481$).

The determination of **2**.HBr, including refinement of all hydrogen atom parameters, exhibits a hydrogen atom distribution for which each of the peripheral nitrogen atoms has one associated hydrogen (Fig. 2(b)). In this structure, like that of **2**, there is no evidence that H(3′) (bonded to N(3′)) exhibits intermolecular hydrogen bonding, presumably due to its intramolecular proximity to S(2) (2.48(7) Å). In the present array, H(3) and H(1′) (bonded to N(3) and N(1′) respectively) exhibit close hydrogen-bonding to coplanar bromide ions, Br ··· H(1′) (x, y, 1 + z); 2.61(5) Å; Br ··· H(3) 2.14(9) Å, linking the ionic components of **2**.HBr into an infinite hydrogen bonded string along axis *c*, wherein the cation skeleton (apart from the methylene hydrogen atoms) is disposed in the $y = 0.25$ crystallographic mirror plane, as is the bromide, with successive cations, related by the unit *c*-translation, tethered by hydrogen-bonded bromide ions (Fig. 3(b)). This planar array of cations and anions is separated from adjacent layers along the *b*-axis by a spacing of *b*/2 (6.895(7) Å/2). This is less than the analogous distance for **2** in spite of the repulsion that two proximal 'like-charged' entities, in this case the cationic heterocycles (see Fig. 3(b)), would presumably evince. However, unlike **2**, the 'non-eclipsed' overlaying of these hydrogen bonded strings is not explicitly suggestive of π-stacking within the structure.

Table 1 Non-hydrogen geometries for Jaffé's Base (**2**) and its protonated (**2**·HBr) and *N*,*S*-chelated forms (**2**(Cu)). The three values in each entry are for **2**, $\mathbf{2H}^+$ and **2**(Cu) (reference 2) respectively

Atoms	Parameter	Atoms	Parameter
Distances/Å			
C(2)–S	1.663(5), 1.650(4), 1.688(3)	C(2′)–N(1)	1.373(5), 1.353(5), 1.374(4)
N(1)–C(2)	1.386(5), 1.415(5), 1.366(5)	N(1′)–C(2′)	1.282(6), 1.323(5), 1.340(5)
N(1)–C(5)	1.462(6), 1.478(6), 1.486(3)	N(1′)–C(5′)	1.481(6), 1.454(6), 1.451(4)
C(2)–N(3)	1.310(6), 1.332(6), 1.319(3)	C(2′)–N(3′)	1.342(6), 1.305(6), 1.305(3)
N(3)–C(4)	1.439(7), 1.455(6), 1.455(5)	N(3′)–C(4′)	1.422(7), 1.459(6), 1.485(5)
C(4)–C(5)	1.513(7), 1.516(7), 1.520(5)	C(4′)–C(5′)	1.516(8), 1.507(7), 1.526(5)
Angles (degrees)			
S–C(2)–N(1)	127.8(3), 127.4(3), 128.3(3)	C(2′)–N(1)–C(5)	119.3(3), 121.6(3), 120.6(3)
S–C(2)–N(3)	124.7(3), 126.7(3), 123.0(3)	N(1)–C(2′)–N(3′)	123.1(4), 126.8(4), 125.2(3)
C(2)–N(1)–C(5)	110.9(3), 111.5(3), 110.9(3)	C(2′)–N(1′)–C(5′)	105.0(4), 110.2(4), 108.8(3)
N(1)–C(2)–N(3)	107.6(4), 105.9(3), 108.7(3)	N(1′)–C(2′)–N(3′)	116.6(4), 112.2(4), 115.7(3)
C(2)–N(3)–C(4)	115.1(4), 115.9(4), 113.9(3)	C(2′)–N(3′)–C(4′)	109.5(4), 110.9(4), 106.2(3)
N(3)–C(4)–C(5)	102.7(4), 102.9(4), 102.9(3)	N(3′)–C(4′)–C(5′)	101.6(5), 103.1(4), 105.1(3)
C(4)–C(5)–N(1)	103.7(4), 103.8(4), 102.7(3)	C(4′)–C(5′)–N(1′)	106.5(4), 103.7(4), 101.7(3)
C(2′)–N(1)–C(2)	129.7(4), 127.0(3), 128.3(3)		

Jaffé's Base has previously been structurally characterised within the compound $[Cu(\mathbf{2})(NO_3)(bipy)][NO_3]\cdot H_2O$ (bipy = 2,2′-bipyridyl),[2] wherein it behaves as a quasi-planar *N*,*S* chelate ligand. This entails placement of the imidazole ring amino proton *anti* to the sulfur of the thione. In comparison to **2** and **2**·HBr (see Figs. 2 and 3), this represents a progression in relative amino hydrogen placement, *i.e.* for **2** the proton of the imidazole ring is placed *syn* to the thione while 2.HBr possesses a protonated imidazole ring. Thus, reorientation of the imidazole ring occurs upon complexation to copper. This incurs a gradual change in bond orders to either side of C(2′) (see Fig. 2 and Table 1), with contrary trends beyond in the outer C–N bonds. Surprisingly, this has little effect on the angles contained in the chelate ring – presumably as the *N*,*S* chelate mode does little to perturb the non-hydrogen geometry of **2**. This is confirmed by the comparable N(3′) ··· S distances in **2** (3.065(5) Å) and the copper complex (3.130(4) Å).[2]

The generation of 2,2′-bis(4,5-dihydro-1*H*-imidazolidine)-disulfide: an intermediate in the formation of Jaffé's Base

As discussed, since the original preparation of **2**[1] there has been some confusion as to the connectivity of Jaffé's Base.[3,5–7] This has been perpetuated by conflicting reports initiated in 1942 with the assertion of Johnson and Edens[5] that, contrary to the original synthesis of Jaffé and Kühn,[1] **2** does not form directly upon mild oxidation of imidazolidine-2-thione. Instead, on the basis of a microanalysis that supported a species of composition '$C_6H_{11}N_4S_2I_5$', they argued that, in the presence of molecular diiodine, imidazolidine-2-thione first underwent the oxidation of a 'true' thiol (see Fig. 4) to yield a disulfide (subsequent to elimination of hydrogen iodide), which then co-crystallised with incorporated I_2 yielding the analytically observed hydroperiodide composition. In essence, this report served to highlight a step in the formation of **2** that had been overlooked in earlier work.[1] More recently (1984), the preparation of Johnson and Edens was revisited with the aid of several X-ray structure determinations.[6] These suggested that, although the preparation of **2** was indeed a two step process,[3,5] the material analysing as '$C_6H_{11}N_4S_2I_5$' **1**·(HI·2I_2) was in fact a composite material containing an unknown number of diiodine adducted imidazolidine-2-thione species and a co-crystallate of diiodine adducted imidazolidine-2-thione with an equimolar proportion of the hydrotriiodide salt of what was presumed to be **2** (see Fig. 1B). The connectivity of this alleged **2**-derived salt provided the first structural endorsement of the Jaffé's Base proposed by Lecher and Gubernator.[7] Frustratingly, however, this report[6] failed to detail any microanalyses of this composite material, speculating that rearrangement under the mild conditions of recrystallisation could not account for such a considerable difference in structure from the disulfide.[5] In the light of such convincing structural data, this report effectively dismissed the disulfide intermediate postulated. Further to this, the authors also confirmed that heating of the composite material led to **2**·HI,[6] which had (in 1959) been duly evidenced by microanalyses upon the same material prepared by Poos *et al.*[3] Additionally, the earlier report of Poos *et al.*, which also made use of 'Johnson and Edens' preparation,[5] listed a deep purple/red material that emanated from the 'KI_3' treatment of imidazolidine-2-thione. Poos *et al.* studied this compound by UV spectroscopy, the λ_{max} values obtained being at variance with Herbstein and Schwotzer's later suggestion of a composite material[6] by intimating that the compound characterising as **1**·(HI·2I_2) was a single product.

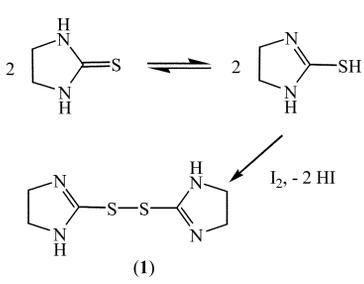

Fig. 4 The proposed thiol condensation path to intermediate **1** according to Johnson and Edens.[5]

In reappraising the synthesis of Jaffé's Base our intention was not only to eliminate any confusion surrounding the connectivity of **2** but also to address the nature of any intermediates suggested by previous authors.[3,5,6] In doing this, the original 'KI_3' synthesis was repeated with particular attention focused on the highly coloured intermediate precipitate described[5] by earlier authors. From our findings, this material closely resembles that described by Johnson and Edens[5] and Poos *et al.*[3] in that the microcrystalline material is indeed deep magenta/purple in appearance. Isolation by filtration and washing with cold hexane gave a clean material that, by ^{1}H and ^{13}C NMR spectroscopy (see experimental section), possesses a symmetry consistent with the original disulfide suggested by Johnson and Edens[5] (^{1}H NMR; two singlets situated at 3.90 and 8.90 ppm, 4 : 1 ratio, ^{13}C NMR; two singlets situated at 47.1 and 174.6 ppm). Whether this results from equilibration in solution is open to question, however, electrospray mass spectrometry suggests the presence of a cation that exhibits a mass/charge ratio consistent with protonated **1** (*m*/*z* = 203.2). This, combined with satisfactory microanalyses from prior reports,[5] leaves little doubt regarding the formation of **1**·(HI·2I_2) as the

proposed disulfide. Attempts to recrystallise this material from ethanol or methanol, two solvents suggested by Johnson and Edens,[5] returned compounds that lacked the colour or spectroscopic properties of the original material (mixture of products by ^{1}H NMR, d_4-methanol); this is discussed below. Also, the recrystallisation of **1**·(HI·2I$_2$) implied in the report of Herbstein and Schwotzer[6] may explain their failure to structurally authenticate **1**·(HI·2I$_2$). Further attempts to recrystallise **1**·(HI·2I$_2$) from diethyl ether and ethyl acetate (also recommended by Johnson and Edens)[5] failed to recover crystalline material of suitable quality for X-ray structure analysis.

Beyond ethanol, methanol, diethyl ether and ethyl acetate, Johnson and Edens also suggested **1**·(HI·2I$_2$) could be purified *via* recrystallisation from acetone.[5] Given the failure of the aforementioned solvents to satisfactorily provide crystalline **1**·(HI·2I$_2$) a "^{1}H NMR" pure sample of **1**·(HI·2I$_2$) was dissolved in acetone and the solvent allowed to partially evaporate overnight yielding dark plates suitable for X-ray structure determination. As can be seen from an X-ray structure determination of the recrystallisation product (see Fig. 5), this yielded the unusual bicyclic imidazolidin[2,1-*b*]thiazole salt **3**·(HI·I$_2$), which differs markedly from **1** and **2** and bears a three carbon "allylic" chain that tethers the original 2- and 3-positions of imidazolidine-2-thione at carbons 1 and 2 of the C$_3$ moiety. In order to countenance the inclusion of the three carbon fragment, we propose that **1** undergoes a nucleophilic substitution upon exposure to acetone (Fig. 6), followed by ring closure and condensation to render **3** and one equivalent of imidazolidine-2-thione.

The results of the third single crystal study are consistent with a formulation as the triiodide salt of the novel 3-methyl-5,6-dihydro-7*H*-imidazolidin[2,1-*b*]thiazolium cation, [C$_6$H$_9$N$_2$S][I$_3$], with one ion pair, devoid of crystallographic symmetry, comprising the asymmetric unit of the structure. The triiodide is a near-linear symmetrical triatomic species, the I–I distances (Table 2) being comparable to values found in multitudinous other examples. The cation (Fig. 5(a), Table 2) has not been structurally characterised previously, although a study of the related 3-methyl-6-*para*-tolyl-7-phenylimidazo[2,1-*b*]thiazolium species has been described as its bromide monohydrate salt.[10] Bond lengths and angles are given comparatively for the two species in Table 2, showing them to generally be very similar, except in the peripheral region of the system – saturated in the present, unsaturated in the bromide. The present adduct also packs with parallel cation planes lying in sheets *quasi* normal to *c* and spaced by *c* (= 14.439(1) Å)/4 (Fig. 5(b)), the triiodide ions being *quasi*-coplanar and hydrogen bonded (Fig. 5(c)).

To corroborate the mechanism of formation proposed for **3**·(HI·I$_2$) (Fig. 6), approximately three equivalents of acetone (15 μL, 0.20 mmol) were added to an unstirred solution of 2,2′-bis(4,5-dihydro-1*H*-imidazolidine)disulfide hydroperiodide, **1**·(HI·2I$_2$), (0.05 g, 0.06 mmol) in d_4-methanol (1 cm^3) and the resulting conversion to **3** monitored by ^{1}H NMR. (This took *ca*. five days to complete due to high dilution with respect to the previous recrystallisation step in which the formation of **3**·(HI·I$_2$) took place almost immediately, as indicated by a rapid colour change from deep red-purple to deep orange). After four hours both the N–H (7.60 ppm) and C$_2$H$_4$ (3.67 ppm) resonances of imidazolidine-2-thione could be observed in a proportion equimolar to the known resonances of compound **3**·(HI·I$_2$) (2.30, 4.44 and 6.47 ppm, 3 : 4 : 1 ratio) and **1**·(HI·2I$_2$) (3.90 and 8.90, 4 : 1 ratio). A further three hours later (7 hours in total) these signals had subsided, giving way to a third, more complex, product (**4**) that remained in solution with **3**·(HI·I$_2$) (no further reaction). Although compound **4** was not studied further, the signals obtained from this experiment (3.72 (s), 3.98 (s), ≈ 4.5 (multiplet obscured by C$_2$H$_4$ signals of **3**), 9.21 (br s), 9.52 (br s) and 9.64 (br s) ppm, 2 : 2 : 4 : 1 : 1 : 1 ratio) bear a close resemblance to those in the ^{1}H NMR spectroscopy data

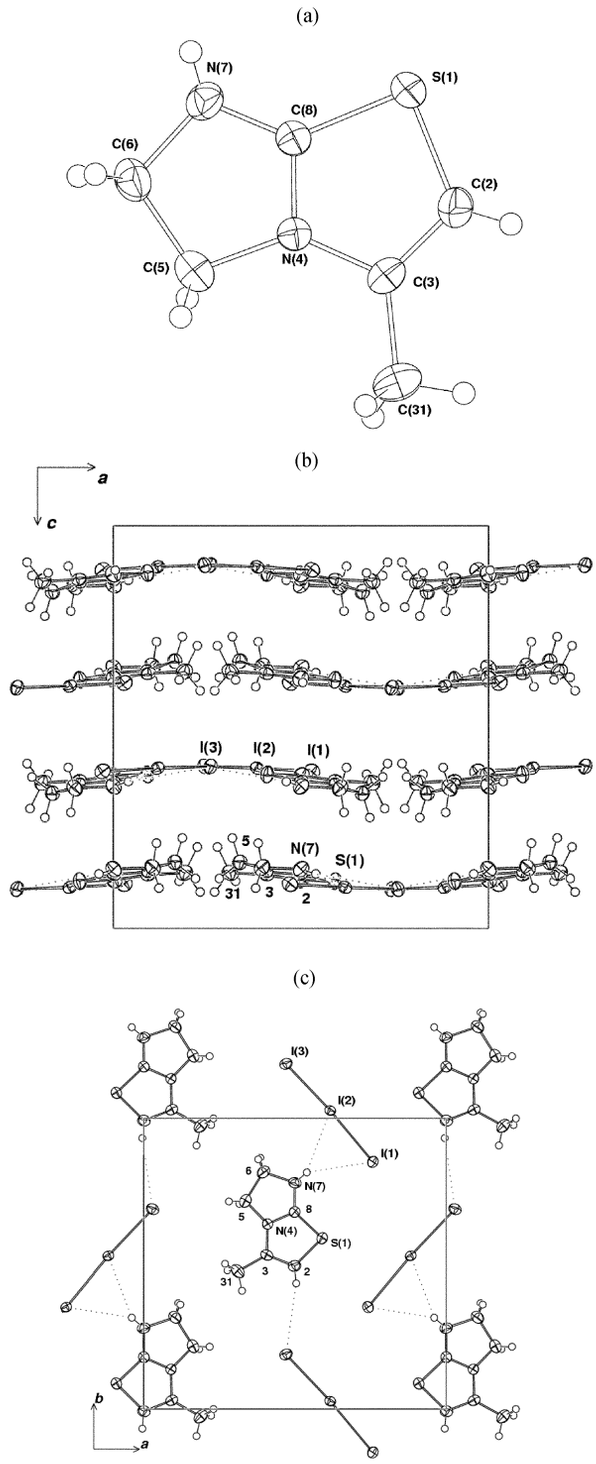

Fig. 5 (a) Projection of the **3**H$^+$ cation normal to the heterocyclic plane, (b) Unit cell contents, projected down the *b*-axis and (c) Depiction of I$_3^-$ hydrogen-bonding to **3**H$^+$ cations, projected down the *c*-axis.

(d_6-DMSO) reported by Herbstein and Schwotzer[6] for their co-crystallised salt of Jaffé's Base that derives from the proposed diiodine mediated partial self-condensation of imidazolidine-2-thione (3.53 (s), 3.69 (s), 3.6–4.1 (m), 8.92 (br s), 9.53 (br s) and 10.40 (br s) ppm, ratio not explicitly stated). On this basis, and with stoichiometry permitting, it could be that **4** is Jaffé's Base, **2**, or a related salt. Accordingly, it may be that Herbstein and Schwotzer's product[6] was: (a) formed from digestion of **1**·(HI·2I$_2$) with boiling H$_2$O–EtOH during crystallisation, (b) the serendipitous by-product of exposure of preformed **1** to residual acetone, unlikely given that **3**·(HI·I$_2$) was not observed during their meticulously reported synthesis, or (c) isolated due

Table 2 Selected bond lengths and angles for **3**·(HI·I_2)[a] and the cation of 3-methyl-6-*para*-tolyl-7-phenylimidazo[2,1-*b*]thiazolium bromide monohydrate respectively (reference 10)

Atoms	Parameter	Atoms	Parameter
Distances/Å			
S(1)–C(2)	1.741(5), 1.744(5)	N(4)–C(5)	1.461(7), 1.379(7)
S(1)–C(8)	1.708(5), 1.715(6)	C(5)–C(6)	1.529(8), 1.361(7)
C(2)–C(3)	1.335(7), 1.337(8)	C(6)–N(7)	1.475(7), 1.410(7)
C(3)–N(4)	1.385(6), 1.407(7)	N(7)–C(8)	1.319(6), 1.324(7)
N(4)–C(8)	1.321(6), 1.341(6)		
Angles (degrees)			
C(2)–S(1)–C(8)	88.7(2), 88.4(3)	C(3)–N(4)–C(5)	134.7(4), 137.0(4)
S(1)–C(2)–C(3)	113.3(4), 114.6(4)	C(5)–N(4)–C(8)	110.0(4), 108.9(4)
C(31)–C(3)–C(2)	129.2(5), 130.9(5)	S(1)–C(8)–N(7)	114.0(4), 137.7(4)
C(31)–C(3)–N(4)	120.2(4), 119.1(5)	N(4)–C(8)–N(7)	113.4(4), 109.3(5)
C(2)–C(3)–N(4)	110.6(4), 110.0(4)	N(4)–C(5)–C(6)	102.5(4), 107.0(4)
C(3)–N(4)–C(8)	115.0(4), 114.0(4)	C(6)–N(7)–C(8)	108.6(4), 107.9(4)
S(1)–C(8)–N(4)	112.4(3), 113.0(4)	C(5)–C(6)–N(7)	103.0(4), 106.9(4)

[a] In the I_3^- anion, I(2)–I(1,3) are 2.8627(5), 2.9657(5) Å, I(1)–I(2)–I(3) 176.15(2)°. I(1) ··· H(2) (1−*x*, ½ + *y*, 1½ + *z*) is 3.2; I(2,3) ··· H(7) (1−*x*, *y*−½, 1½−*z*) 3.0 Å (× 2) (all estimated).

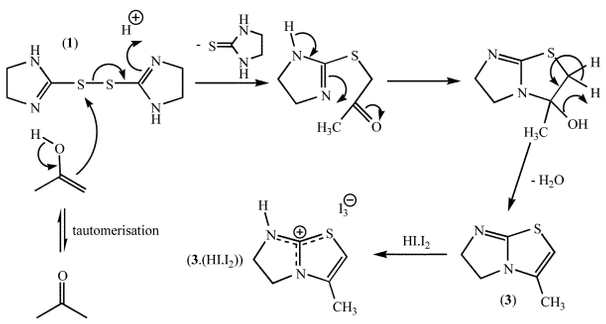

Fig. 6 The generation of **3**·(HI·I_2) *via* the putative nucleophilic attack of enol-tautomerised acetone on **1**.

to a deficiency of potassium iodide which permitted diiodine to mediate the partial self-condensation of imidazolidine-2-thione in the absence of *in situ* generated KI_3. However, as found by Herbstein and Schwotzer,[6] crystallographic analyses of methanol and ethanol derived "^{1}H NMR" pure **1**·(HI·2I_2) crystallisation products repeatedly indicated the presence of only Herbstein and Schwotzer's co-crystallate and the bis(diiodine) adduct of imidazolidine-2-thione.[11] This implies that solvent induced rearrangement during recrystallisation was responsible for the formation of Herbstein and Schwotzer's product from **1**·(HI·2I_2), as was refuted,[6] but does not necessarily contradict their supposition that an intermediate polyiodide is responsible for the generation of their co-crystallate. This could still represent an intermediate in the crystallisation process alluded to above, and, hence, it could be that **1**·(HI·2I_2) equilibrates in alcohol solution with trace amounts (therefore not observed by ^{1}H NMR) of **2**, diiodine adducted imidazolidine-2-thione and dissolved H_2S, thereby allowing the greater insolubility of the co-crystallate and the diiodine adduct to selectively drive crystallisation of both from solution. This, as encountered here, would make **1**·(HI·2I_2) non-isolable from alcohol solvents.

Conclusion

The spectroscopic and mass spectrometric studies presented herein suggest that **1**·(HI·2I_2) is an intermediate in the formation of **2** when prepared using the 'KI_3' methodology of Johnson and Edens [3,5] even though it has not been structurally authenticated. This was not suggested on the basis of the crystalline products of Herbstein and Schwotzer, the microanalyses of which would be sulfur deficient relative to **1**·(HI·2I_2) due to the required elimination of H_2S from imidazolidine-2-thione to yield their **2**-containing co-crystallate. In addition, this infers that Jaffé's Base may be formed from the elimination of hydrogen sulfide from imidazolidine-2-thione in the presence of diiodine and absence of KI when conducted in alcohol solvents. Furthermore, these studies suggest **1**, or a salt thereof, may exist in equilibrium (in alcohol solution) with trace amounts of Herbstein and Schwotzer's co-crystallate,[6] imidazolidine-2-thione adducted to diiodine and dissolved hydrogen sulfide as the former two can only be isolated when crystallisation is attempted from ethanol and methanol, and only **1** is observed in d_4-methanol solution (^{1}H NMR). The isolation of **3**·(HI·I_2) from acetone recrystallisation of **1**·(HI·2I_2) strongly suggests that carbonyl containing solvents capable of keto–enol tautomerisation are not good solvents for this compound due to its predisposition toward nucleophilic attack. This explains the low yield of **2** reported by Poos *et al.* when using acetone extraction.[3] Finally, the route to species **3** described herein (see Fig. 6), which in principle represents a facile path to 3-alkyl/aryl substituted 5,6-dihydroimidazolidin[2,1-*b*]-thiazoles *via* the synthetically trivial addition of **1**·(HI·2I_2) to methyl substituted ketones, is entirely new and presents a probable means to the formation of sulfur substituted bicyclic heterocycles that have found potential pharmaceutical utility as anti-inflammatory drugs [12] and hyperglycaemic agents.[13]

Experimental

General

Imidazolidine-2-thione, mercuric oxide, potassium iodide and diiodine were acquired from Sigma-Aldrich and used as received. The solvents H_2O, ethanol, methanol, acetone, xylene and chloroform were freshly distilled prior to use. Compounds **1**·(HI·2I_2) and **2** were formed using reported synthetic procedures.[3,5] Infrared spectra were recorded as Nujol mulls using sodium chloride plates on a Nicolet Nexus FTIR spectrometer. ^{1}H NMR spectra were recorded at 300.13 MHz and ^{13}C NMR spectra were recorded at 75.46 MHz using a Bruker DPX 300 spectrometer with chemical shifts referenced to the residual ^{1}H or ^{13}C resonances of the *deutero*-methanol solvent employed. Melting points were determined in glass capillaries. Mass spectrometric analyses were conducted using a VG Fisons Platform II instrument under ES conditions. The microanalyses of **3**·(HI·I_2) were conducted at the University of Otago, P.O. Box 56, Dunedin, New Zealand.

2,2′-Bis(4,5-dihydro-1*H*-imidazolidine)disulfide hydroperiodide, [1·(HI·2I_2)]

This was prepared using the synthetic procedure of Johnson and Edens.[5]

Mp 75–76 °C (no decomposition). ^{1}H NMR (CD_3OD, 298 K): δ 3.90 (s, 8H, C_2H_4), 8.90 (br s, 2H, NH). ^{13}C NMR (CD_3OD, 298 K): δ 47.1 (s, C_2H_4), 174.6 (s, SCN_2). MS ES: *m*/*z* (%) 203.2 ([M − I_5]$^+$, 11), 171.3 ([M − (S + I_5)]$^+$, 10), 102.1 ([imidazolidine-2-thione]$^+$, 100). IR (Nujol) ν/cm^{-1}: 3343s br, 1629w br, 1511s sh, 1378w sh, 1310m sh, 1275m sh, 1191m sh, 1038w, 909m sh.

1-[4,5-dihydro-1*H*-imidazolidin-2-yl]imidazolidine-2-thione, [2], and its hydrobromide salt, [2·HBr]

Following the procedure of Poos *et al.* utilising mercuric oxide,[3,7] a suspension of imidazolidine-2-thione (4.0 g, 39.2 mmol) and mercuric oxide (8.00 g, 36.9 mmol) was heated in xylene (40 cm^3) under reflux (4 h) and filtered while hot. The resultant dark insolubles were further extracted with chloroform and combined with the xylene residues. Removal of the solvent *in vacuo* yielded a yellow solid (*ca.* 0.75 g, 25% yield by imidazolidine-2-thione), which was recrystallised from ethanol as rather fine tan needles. Recrystallisation of these needles from an equimolar amount of aqueous hydrobromic acid yielded colourless prisms of the monohydrobromide salt, **2**·HBr.

3-Methyl-5,6-dihydro-7*H*-imidazolidin[2,1-*b*]thiazolium triiodide, [3·(HI·I_2)]

Deep magenta 2,2′-bis(4,5-dihydro-1*H*-imidazolidine)disulfide hydroperiodide, **1**·(HI·2I_2), (0.3 g, 0.36 mmol) was dissolved in acetone (*ca.* 10 cm^3) rendering a deep orange solution that yielded dark plate-like crystals upon standing at room temperature. These were collected by filtration and washed with cold hexane (3 × 5 cm^3) (0.09 g, 48%). Mp 70–72 °C. ^{1}H NMR (CD_3OD, 298 K): δ 2.30 (d, 3H, 3-CH_3, $^4J_{HH}$ 1.34 Hz), 4.44 (m, 4H, C_2H_4), 6.47 (d, 1H, SCH=C, $^4J_{HH}$ 1.35 Hz). ^{13}C NMR (CD_3OD, 298 K): δ 13.0 (s, 3-CH_3), 44.9 (s, CH_2), 49.9 (s, CH_2), 103.8 (s, S*C*=C), 133.7 (s, 3-C), 172.3 (s, $^+CN_2S$). MS APCI: *m*/*z* (%) 141.7 ([M − I_3]$^+$, 100). IR (Nujol) ν/cm^{-1}: 3493w br, 3400m sh, 1591w sh, 1558s sh, 1294m, 1200w sh, 1166w sh. Calc. for $C_6H_9N_2S_1I_3$: C; 13.81, H; 1.74, N; 5.37, S; 6.14. Found (best): C; 14.10, H; 1.84, N; 6.61, S; 7.47%. [Microanalyses for **3**·(HI·I_2) were routinely high in both N and S content, thereby suggesting that recrystallised samples were consistently contaminated by imidazolidine-2-thione.2I_2 even after repeated recrystallisation from acetone. This tentatively provides further evidence for the reaction mechanism proposed in Fig. 6, which eliminates imidazolidine-2-thione].

Structure determinations

For **2** and **2**·HBr unique single-counter four-circle diffractometer data sets were measured at *ca* 295 K, yielding *N* unique reflections, N_0 as defined below being considered 'observed' and used in the full matrix least squares refinement, **2**·HBr data being subject to analytical absorption correction. Anisotropic displacement parameter forms were refined for the non-hydrogen atoms, (x, y, z, U_{iso})$_H$ being refined (**3** excepted). For **3**·(HI·I_2), a full sphere of CCD area-detector diffractometer data was measured (Bruker AXS instrument, ω-scans; monochromatic Mo Kα radiation, λ = 0.71073 Å (all structures); *T ca.* 153 K), $N_{t(otal)}$ reflections merging to *N* unique after 'empirical'/multiscan absorption correction (proprietary software). Conventional residuals on |*F*|, *R*, R_w (weights: ($\sigma^2(F)$ + 0.0004 F^2)$^{-1}$) are cited at convergence; neutral atom complex scattering factors were employed within the context of the Xtal 3.7 program system.[14] Pertinent results are given below and in the Tables and Figures, the latter showing 20 (295 K) or 50% (153 K) probability amplitude displacement ellipsoids for the non-hydrogen atoms, hydrogen atoms having arbitrary radii of 0.1 Å.CIF depositions have been made with the Cambridge Crystallographic Data Base.†

Crystal/refinement data

2 = $C_6H_{10}N_4S$, *M* = 170.2. Monoclinic, space group $P2_1/c$ (C_{2h}^5, No. 14), a = 7.9079(8), b = 12.480(2), c = 7.7913(7) Å, β = 92.89(1)°. V = 768.0 Å^3. D_c (Z = 4) = 1.472 g cm^{-3}. μ_{Mo} = 3.6 cm^{-1}; specimen: cuboidal section, *ca.* 0.12 (no absorption correction). $2\theta_{max}$ = 50°, N = 1249, N_0 = 762 ($I > 2\sigma(I)$); R = 0.049, R_w = 0.052.

2·HBr = $C_6H_{11}BrN_4S$, *M* = 251.3. Orthorhombic, space group *Pnma* (D_{2h}^{16}, No. 62), a = 15.295(3), b = 6.895(7), c = 9.063(2) Å, V = 959.7 Å^3. D_c (Z = 4) = 1.745 g cm^{-3}. μ_{Mo} = 45 cm^{-1}; specimen: 0.59 × 0.58 × 0.37 mm; 'T'$_{min,max}$ = 0.16, 0.36. $2\theta_{max}$ = 65°, N_t = 1521, N_0 ($I > 3\sigma(I)$) = 1039; R = 0.033, R_w = 0.049.

3 = ($C_6H_9N_2S$)I_3, *M* = 521.9. Orthorhombic, space group *Pbca* (D_{2h}^{16}, No. 61), a = 13.420(1), b = 12.950(1), c = 14.439(1) Å, V = 2509 Å^3. D_c (Z = 8) = 2.477 g cm^{-3}. μ_{Mo} = 76 cm^{-1}; specimen: 0.18 × 0.15 × 0.13 mm; 'T'$_{min,max}$ = 0.54. $2\theta_{max}$ = 65°, N = 34480, N_0 = 17029 (R_{int} = 0.041), N_0 = 12932; R = 0.037, R_w = 0.044.

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† CCDC reference numbers 187057, 187058 and 211802. See http://www.rsc.org/suppdata/ob/b3/b306647a/ for crystallographic data in .cif or other electronic format.

References

1 M. Jaffé and B. Kühn, *Chem. Ber.*, 1894, **27**, 1663.
2 H. E. Heldal and J. Sletten, *Acta Chem. Scand.*, 1996, **50**, 596.
3 G. I. Poos, J. Kleis and C. K. Cain, *J. Org. Chem.*, 1959, **24**, 645.
4 R. Hull and T. P. Seden, *Synth. Commun.*, 1980, **10**, 489.
5 B. T. Johnson and C. O. Edens, *J. Am. Chem. Soc.*, 1942, **64**, 2706.
6 F. H. Herbstein and W. Schwotzer, *J. Am. Chem. Soc.*, 1984, **106**, 2367.
7 H. Z. Lecher and K. Gubernator, *J. Am. Chem. Soc.*, 1953, **75**, 1087.
8 A. Saczewski, A. Bulakowska and M. Gdaniec, *J. Heterocycl. Chem.*, 2002, **39**, 911.
9 D. C. Kim, K. H. Yoo, K. J. Shin, S. W. Park and D. J. Kim, *J. Heterocycl. Chem.*, 1997, **34**, 57.
10 A. M. Demchenko, V. A. Chumakov, A. N. Krasovsky, E. B. Rusanov, A. N. Chernega, V. V. Pirozhenko and M. O. Lozinsky, *Zh. Obshch. Khim.*, 1997, **67**, 1886.
11 Unit cell data of two products both resulting from EtOH and MeOH recrystallisation of **1**·(HI·2I_2): (all T = 123 K) a; 11.0604(13) Å, b; 11.1829(12) Å, c; 9.5618(12) Å, α; 90°, β; 110.03(1)°, γ; 90° and a; 10.2839(12) Å, b; 9.1691(7) Å, c; 6.7637(7) Å, α; 105.03(1)°, β; 81.09(2)°, γ; 96.42(1)°. Data from reference 4 (T = 298 K) for imidazolidine-2-thione, I_2 co-crystallate of **2**·(HI·I_2), a; 11.102(7) Å, b; 11.193(7) Å, c; 9.551(6) Å, α; 90°, β; 110.00(10)°, γ; 90°. Data from reference 4 (T = 298 K) for bis(diiodine) co-crystallate of imidazolidine-2-thione, a; 10.276(7) Å, b; 9.170(6) Å, c; 6.792(5) Å, α; 105.10(10)°, β; 81.00(10)°, γ; 96.40(10)°.
12 R. C. Moser, L. J. Powers and Z. S. Ariyan, Diamond Shamrock Corp., USA, Cam. Pat. Appl. No. 269, 924, 1982.
13 D. E. Kuhlia, Pfizer Inc., USA, U.S. Pat. Appl. No. 73-399053 19730920, 1975.
14 S. R. Hall, D. J. du Boulay and R. Olthof-Hazekamp (eds.), 'The Xtal 3.7 System', University of Western Australia, 2001.