Rearrangement of *cis*- and *trans*-1-methyl-2-(2-thienyl)pyrrolidinium 1-methylides in a non-basic medium

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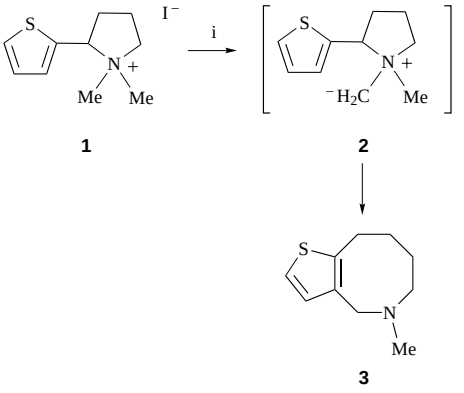
***cis*-1-Methyl-2-(2-thienyl)pyrrolidinium 1-methylide *cis*-2 generated in a non-basic medium isomerize to a mixture of (*E*)- and (*Z*)-5-methyl-3a,4,5,6,7,8-hexahydrothieno[3,2-*c*]azocine, (*E*)-6 and (*Z*)-6. The latter (*Z*)-6 has been cyclized to the *cis-cisoid-cis*-5-methyl-3a,6,7,8,8a,8b-hexahydro-4*H*-thieno[2′,3′-*c*]-pyrrolo[1,2-*a*]pyrrolium salt 8 in water; *trans*-2 gives a mixture of 1-methyl-3-(2-thienyl)piperidine 7 and (*E*)-6 *via* a radical–cleavage and –recombination pathway.**

Introduction

Sommelet–Hauser rearrangement of α-aryl-cyclic ammonium *N*-alkylides is useful for the ring enlargement of cyclic amines by three carbons.[1] For example, the reaction of 1,1-dimethyl-2-phenylpiperidinium halides with sodium amide in liquid ammonia gave 2-methyl-2,3,4,5,6,7-hexahydro-1*H*-2-benzazonines *via* a piperidinium 1-methylide intermediate.[2] However, when the same ylide intermediate was generated in non-basic media by fluoride ion-induced desilylation of 1-methyl-2-phenyl-1-[(trimethylsilyl)methyl]piperidinium iodides, isomerization of the ylides stopped at a [2,3] sigmatropic rearrangement to give 2-methyl-1,3,4,5,6,11a-hexahydro-2*H*-2-benzazonines (isotoluene derivatives).[3] Hasiak and co-workers[4] prepared 2-methyl-1,2,3,4,5,6-hexahydro-2-methylthieno[3,2-*c*]-azocine **3** by the base-induced ylide formation of 1,1-dimethyl-2-(2-thienyl)pyrrolidinium iodide **1** (Scheme 1). This paper

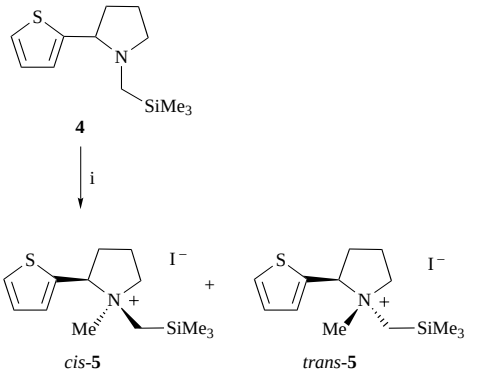


Scheme 1 *Reagents and conditions:* i, $NaNH_2$, liquid NH_3

reports the isomerization products of 1-methyl-2-(2-thienyl)pyrrolidinium 1-methylide **2** in a non-basic medium.

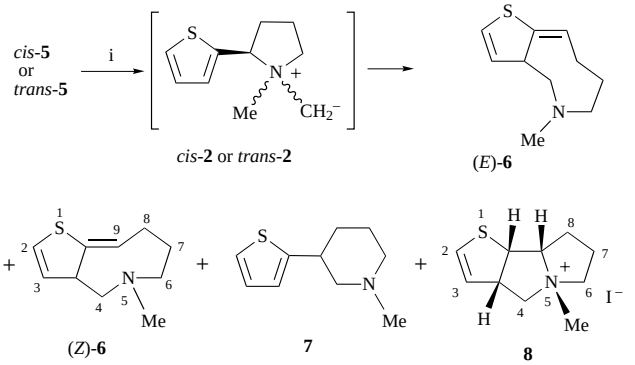
Results and discussion

Quaternization of 1-[(trimethylsilyl)methyl]-2-(2-thienyl)pyrrolidine **4** with iodomethane gave a mixture of *cis*- and *trans*-1-methyl-1-[(trimethylsilyl)methyl]-2-(2-thienyl)pyrrolidinium iodide (*cis*-**5** and *trans*-**5**) in a ratio of 26:74 (Scheme 2). The isomers were separated by repeated recrystallization. The stereochemistry of the major isomer, which had a higher melting point, was considered to be *trans* based on the measurement of an NOE.



Scheme 2 *Reagents and conditions:* i, MeI, MeCN, RT, 24 h

When *cis*-**5** was allowed to react with cesium fluoride in dimethylformamide (DMF) at room temperature for 2 h and the reaction was quenched with water, the product was not **3**, but rather a non-distillable oil. Although this oil was believed to be a stereoisomer of 2-methyl-1,2,3,4,5,9a-hexahydrothieno-[3,2-*c*]azocine **6** based on a ^1H NMR spectrometric analysis, confirmation of the stereochemistry was difficult. A similar treatment of *trans*-**5** gave 1-methyl-3-(2-thienyl)piperidine **7** (Stevens rearrangement product) as the main product, and the yield of **6** was very low (Table 1, entries 1,3). However, the total amine yields in both reactions were unexpectedly low, whereas the ammonium salt **8** was isolated from the respective aqueous layers after ether extraction. The structure of **8** was determined to be *cis-cisoid-cis*-5-methyl-3a,6,7,8,8a,8b-hexahydro-4*H*-thieno[2′,3′-*c*]pyrrolo[1,2-*a*]pyrrolium iodide based on an X-ray crystallographic analysis (see Experimental section).



Scheme 3 *Reagents and conditions:* i, CsF, DMF, RT

Table 1 Reaction of 1-methyl-2-(2-thienyl)pyrrolidinium iodides (*cis*-**5**, *trans*-**5**) with CsF in DMF at RT for 2 h

Entry	Salt	Work up[a]	Total amine yield (%)	Product ratio (*E*)-**6**	(*Z*)-**6**	**7**	Yield of **8** (%)
1	*cis*-**5**	A	28	100	0	0	60[b]
2	*cis*-**5**	B	91	31	69	0	0
3	*trans*-**5**	A	64	13	0	87	20[b]
4	*trans*-**5**	B	79	11	26	63	0

[a] Work up conditions A: the reaction mixture was poured into water and then extracted with Et_2O; B: the reaction mixture was mixed with ether and washed with water. [b] Crude yield.

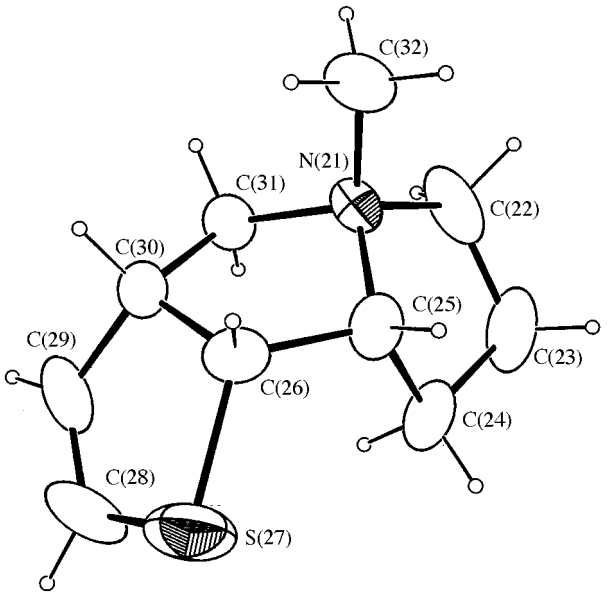
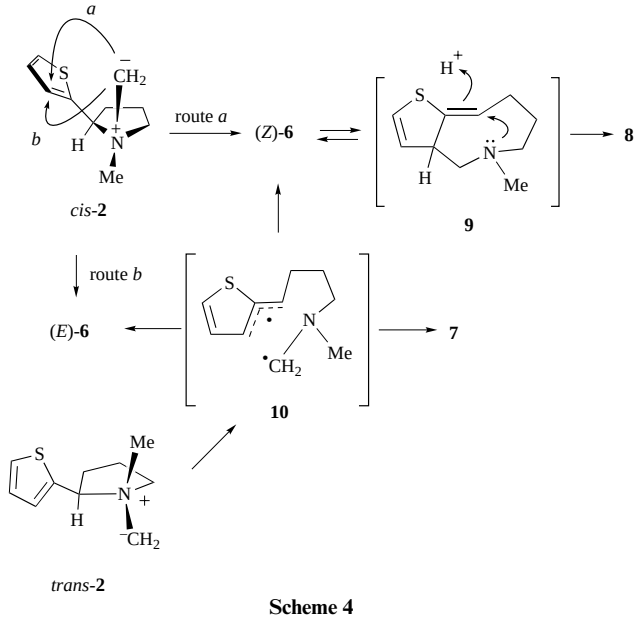


Fig. 1 ORTEP view of **8** showing 30% thermal ellipsoids with crystallographic numbering scheme

We noticed that the ethereal extracts occasionally contained another stereoisomer of **6**; *i.e.*, **6′**. When the reaction mixture was diluted with a large volume of ether and then washed with water, instead of the ordinary quenching by the addition of water followed by ether extraction, the product was changed to mixtures of **6** and **6′**, the salt **8** not being detected in the aqueous washings (compare entry 1 to 2, and 3 to 4). This result suggests that **6′** was changed to **8** when the reaction mixture was quenched by the addition of water.

Route *a* giving (*Z*)-**6** and route *b* giving (*E*)-**6** may be possible in a [2,3] sigmatropic migration of *cis*-**2** (Scheme 4). The nitrogen and C-9 may be close together in (*Z*)-**6** and far apart in (*E*)-**6**. Indeed, the distances calculated by MOPAC AM1[5] are 2.73 Å for (*Z*)-**6** and 3.05 Å for (*E*)-**6**. Furthermore, the atomic charges on C-9a are −0.31 for (*Z*)-**6** and −0.25 for (*E*)-**6**, whereas the charges of other corresponding positions are similar (Table 2). Cyclization from (*Z*)-**6** to **8** occurs in the presence of a protic solvent, while (*E*)-**6** remains in the ethereal extract. Thus, the stereochemistry of **6′** is believed to be *Z* and that of **6** is believed to be *E*.



Scheme 4

Since sigmatropic migration on *trans*-**2** is difficult due to the long distance between the ylide anion and the thienyl ring, C–C bond cleavage occurs to give a diradical intermediate **10**, which subsequently recombines to form (*E*)-**6**, (*Z*)-**6** and **7**. Thus, the isomerization of **2** in a non-basic medium differed strikingly from that in a basic medium.

Experimental

All reactions were carried out in N_2. Dimethylformamide (DMF) was dried by distillation from BaO under reduced pressure. CsF was dried over P_2O_5 at 170 °C under reduced pressure. Distillation of the products was performed using a Büchi Kugelrohr distillation apparatus. All melting points and boiling points (oven temperature) are uncorrected. *J* Values are given in Hz.

1-[(Trimethylsilyl)methyl]-2-(2-thienyl)pyrrolidine 4

A solution of 2-(2-thienyl)pyrrolidine (4.3 g, 28 mmol) and (trimethylsilyl)methyl trifluoromethanesulfonate (8.2 g, 35 mmol) in CH_2Cl_2 (40 cm^3) was stirred at room temperature (RT) for 3 h. The mixture was poured into 5% aqueous NaOH (40 cm^3) and extracted with Et_2O (4 × 100 cm^3). The combined extracts were washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was distilled under reduced pressure to give the *title amine* **4** (4.9 g, 73%), bp 133 °C/15 mmHg (Found: C, 59.8; H, 8.8; N, 5.6. $C_{12}H_{21}NSSi$ requires C, 60.2; H, 8.8; N, 5.85%); ν_{max}(film)/cm^{-1} 2955, 1458, 1418, 1248, 853 and 696; δ_H(400 MHz; $CDCl_3$; −60 °C; Me_4Si)† 0.01 (9 H, s), 1.41 (1 H, d, *J* 14.0), 1.75–1.85 (2 H, m), 1.90–2.02 (1 H, m), 2.12–2.16 (2 H, m), 2.26 (1 H, d, *J* 14.0), 3.29 (1 H, m), 3.37 (1 H, m), 6.93–6.97 (2 H, m) and 7.26 (1 H, br s).

cis- and *trans*-1-Methyl-1-[(trimethylsilyl)methyl]-2-(2-thienyl)-pyrrolidinium iodides *cis*-5, *trans*-5

A solution of **4** (4.75 g, 20 mmol) and iodomethane (14.2 g, 100 mmol) in MeCN (45 cm^3) was stirred at RT for 24 h and then evaporated to give a mixture of *cis*- and *trans*-isomers of the title salts in a ratio of 26:74 (7.5 g, 99%). Both isomers were isolated by repeated recrystallization from acetone–Et_2O.

Compound cis-**5**: yield 0.75 g (10%); mp 140–141 °C (Found: C, 40.8; H, 6.2; N, 3.2. $C_{13}H_{24}INSSi$ requires C, 40.9; H, 6.3; N, 3.7%); ν_{max}(KBr)/cm^{-1} 3046, 2951, 1464, 1254 and 858; δ_H(270 MHz; $CDCl_3$) 0.28 (9 H, s), 2.17–2.23 (1 H, m), 2.28 (1 H, dd, *J* 14.8, 2.0), 2.39–2.50 (1 H, m), 2.52–2.56 (1 H, m), 2.67 (1 H, dd, *J* 1.0, 14.8), 2.72–2.80 (1 H, m), 3.44 (3 H, s), 3.63–3.71 (1 H,

† The signals of the ^1H NMR spectrum of this compound broadened at RT.

Table 2 Calculated atomic charges of (*E*)-**6** and (*Z*)-**6**

	S	C-2	C-3	C-3a	N	C-9	C-9a
(*E*)-**6**	0.32	−0.33	−0.19	−0.05	−0.31	−0.13	−0.25
(*Z*)-**6**	0.33	−0.33	−0.19	−0.05	−0.30	−0.11	−0.31

m), 4.46–4.58 (1 H, m), 6.16 (1 H, dd, *J* 10.9, 7.6), 7.17 (1 H, dd, *J* 5.3, 3.6), 7.53 (1 H, dd, *J* 0.9, 5.3) and 7.61 (1 H, dd, *J* 0.9, 3.6).

Compound trans-**5**: yield 4.1 g (55%); mp 168–170 °C (Found: C, 40.8; H, 6.3; N, 3.3. $C_{13}H_{24}INSSi$ requires C, 40.9; H, 6.3; N, 3.7%); ν_{max}(KBr)/cm^{-1} 3100, 2950, 1250, 1208, 864 and 764; δ_H(400 MHz; $CDCl_3$) 0.31 (9 H, s), 2.36–2.44 (2 H, m), 2.45–2.54 (1 H, m), 2.69–2.72 (1 H, m), 2.78 (3 H, s), 2.83 (1 H, d, *J* 14.7), 3.83–3.85 (1 H, m), 3.86 (1 H, d, *J* 14.7), 4.42 (1 H, m), 5.87 (1 H, dd, *J* 11.1, 7.8), 7.17 (1 H, dd, *J* 3.7, 5.2), 7.54 (1 H, dd, *J* 5.2, 1.0) and 7.58 (1 H, m). NOE enhancement of N^+–CH_2–Si (7%, δ 4.47) and 5-H (4%, δ 4.42) was observed upon irradiation of 2-H (δ 5.87).

Reaction of *cis*-5 with CsF

(A). Compound *cis*-**5** (191 mg, 0.5 mmol) was placed in a 20-cm^3 flask equipped with a magnetic stirrer and a septum, and a test tube was connected to the flask by a short piece of rubber tubing. CsF (0.38 g, 2.5 mmol) was placed in the test tube. The apparatus was dried under reduced pressure and flushed with N_2. DMF (5 cm^3) was added to the flask with a syringe, and then CsF was added from the test tube. The mixture was stirred for 2 h at RT and then poured into water and extracted with Et_2O. The combined ethereal extracts were washed with water, dried ($MgSO_4$), and concentrated under reduced pressure to give (*E*)-2-methyl-3a,4,5,6,7,8-hexahydrothieno[3,2-*c*]azocine (*E*)-**6** (25 mg, 28%), a non-distillable oil (Found: C, 66.0; H, 8.3; N, 7.6. $C_{10}H_{15}NS$ requires C, 66.25; H, 8.3; N, 7.7%); ν_{max}(film)/cm^{-1} 2793, 1366, 1304, 797 and 683; δ_H(400 MHz; $CDCl_3$) 1.25–1.42 (1 H, m), 1.82–1.97 (1 H, m), 2.23 (2 H, m), 2.33–2.44 (1 H, m), 2.49 (3 H, s), 2.54–2.71 (3 H, m), 3.92 (1 H, m), 5.44 (1 H, ddd, *J* 6.3, 3.0, 1.2), 5.66 (1 H, m) and 6.24 (1 H, dd, *J* 6.3, 1.2); λ_{max}(hexane)/nm 282 (ε/dm^3 mol^{-1} cm^{-1} 4400), 261 (4800), 253 (5000) and 243 (6200).

The aqueous layer after Et_2O extraction was concentrated on a rotary evaporator and extracted with $CHCl_3$. The extract was dried and concentrated *in vacuo* to give *cis-cisoid-cis*-5-methyl-3a,6,7,8,8a,8b-hexahydro-4*H*-thieno[2′,3′-*c*]pyrrolo[1,2-*a*]-pyrrolium salt **8** (66 mg, 60%, calculated for a counter anion of Cl). This salt dissolved in a solution of saturated aqueous KI (2.5 cm^3) was stirred for 3 h and then extracted with $CHCl_3$. The extract was evaporated and the residue was recrystallized from acetone to give pyrrolium iodide, mp 139–141 °C (Found C, 38.8; H, 5.24; N, 4.26. $C_{10}H_{16}INS$ requires C, 38.8; H, 5.2; N, 4.5%); ν_{max}(Nujol)/cm^{-1} 1377 and 1088; δ_H(500 MHz; $CDCl_3$) 2.22–2.28 (1 H, m, 8-H), 2.30–2.42 (2 H, m, 7-H), 2.49–2.57 (1 H, m, 8-H), 3.58 (3 H, s, 5-Me), 3.83 (1 H, dd, *J* 4.28, 10.38, 4-H), 3.88–3.94 (2 H, m, 6-H), 4.32–4.40 (2 H, m, 3a-H, 4-H), 4.92 (1 H, dt, *J* 8.5, 4.9, 8a-H), 5.01 (1 H, t, *J* 8.5, 8b-H), 5.67 (1 H, dd, *J* 2.5, 5.5, 3-H) and 6.24 (1 H, dd, *J* 1.8, 6.1, 2-H); δ_C(126 MHz; $CDCl_3$) 23.32 (7-C), 27.23 (8-C), 51.81 (5-Me), 51.53 (3a-C), 53.23 (8b-C), 64.91 (6-C), 67.35 (4-C), 81.34 (8a-C), 122.85 (3-C) and 128.00 (2-C).

(B). After a repeat of the reaction described for (A) the reaction mixture was diluted with Et_2O (50 cm^3), washed with water (3 × 50 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure to give a mixture (82 mg, 91%) of (*E*)-**6** and (*Z*)-**6**. Chromatographic separation of both compounds failed because of their instability at RT; the structure was determined by ^{1}H NMR analysis of the mixture. The product ratio was calculated on the basis of the proton ratios in the ^{1}H NMR spectrum of the mixture.

Compound (*Z*)-**6**: δ_H(270 MHz; $CDCl_3$) 2.04 (1 H, dd, *J* 13.2, 8.2), 2.50 (3 H, s), 3.04 (1 H, dd, *J* 13.2, 5.9), 3.50 (1 H, m), 5.59 (1 H, dt, *J* 11.9, 1.7), 5.77 (1 H, dd, *J* 5.9, 3.7) and 6.38 (1 H, dd, *J* 5.9, 1.0).

Reaction of *trans*-5 with CsF

(A). Compound *trans*-**5** (191 mg, 0.5 mmol) and CsF (0.38 g, 2.5 mmol) were treated in DMF (5 cm^3) in a manner similar to that described for (A) above to give a mixture of (*E*)-**6** and 1-methyl-3-(2-thienyl)piperidine **7** (58 mg, total 64%). The products were separated on alumina columns (hexane–Et_2O). The ratio was determined on the basis of the proton ratios in the ^{1}H NMR spectrum of the mixture.

Compound **7**; bp 140 °C (15 mmHg) (Found: C, 66.55; H, 8.4; N, 7.6. $C_{10}H_{15}NS$ requires C, 66.25; H, 8.3; N, 7.7%); ν_{max}(Nujol)/cm^{-1} 2940, 2780, 1440, 1370, 1198 and 692; δ_H(270 MHz; $CDCl_3$) 1.33–1.48 (1 H, m), 1.64–1.83 (2 H, m), 1.94 (1 H, dd, *J* 10.9, 4.1), 2.01 (1 H, t, *J* 10.9), 2.08 (1 H, m), 2.31 (3 H, s), 2.87 (1 H, m), 3.07 (1 H, m), 3.15 (1 H, m), 6.83 (1 H, dd, *J* 3.5, 1.0), 6.94 (1 H, dd, *J* 5.0, 3.5) and 7.13 (1 H, dd, *J* 5.0, 1.0).

The aqueous layer after ether extraction was concentrated to give **8** (22 mg, 20%, calculated for a counter ion of Cl).

(B). After a repeat of the reaction, the reaction mixture was diluted with Et_2O (50 cm^3) and worked up to give a mixture of (*E*)-**6**, (*Z*)-**6** and **7** (78 mg, total 87%). The product ratio was determined on the basis of the proton ratios in the ^{1}H NMR spectrum of the mixture.

Conversion of (*Z*)-6 into 8

A mixture of (*E*)-**6**, (*Z*)-**6** and **7** in a ratio of 11 : 26 : 63 (1.114 g) obtained from *trans*-**5** by method (B) was added to a mixture of DMF (15 cm^3) and 0.5 M aqueous $MgCl_2$ (10 cm^3). After the mixture had been stirred at RT for 0.5 h it was treated with water (100 cm^3) and washed with Et_2O (3 × 100 cm^3). The aqueous layer was concentrated under reduced pressure and the residue was extracted with $CHCl_3$ to give **8** (160 mg, 46%, calculated for a counter ion of Cl). The ether layer was dried and concentrated to give a mixture of (*E*)-**6** and **7** in a ratio of 15 : 85 (626 mg, 76%).

Crystal structure analysis of 8

Crystals suitable for X-ray analysis were obtained by slow evaporation of the acetone solution.

Crystal data. $C_{10}H_{16}INS$, $M = 309.2$ Monoclinic, $a = 15.007(3)$, $b = 20.921(2)$, $c = 12.555(2)$ Å, $\beta = 113.98(1)°$, $U = 3601.2(20)$ Å^3, space group $P2_1/c$, $Z = 12$, $D_c = 1.711$ g cm^{-3}, colourless block 0.48 × 0.48 × 0.54 mm, μ(Mo-Kα) = 27.66 cm^{-1}.

Data collection and processing. Enraf-Nonius CAD4 diffractometer, graphite-monochromated Mo-Kα radiation (λ = 0.710 73 Å), ω–2θ scans with (0.86 + 1.04 tan θ)°; 11 532 reflections measured ($4 \leqslant 2\theta \leqslant 60°$, h, k, $\pm l$), 5523 unique with $F_o \geqslant 3\sigma(F_o)$, which were retained in all of the calculations. Net intensities were reduced to a set of relative structure factors by the application of the standard Lorentz and polarization factors. An empirical absorption correction was made (transmission factors: 0.80–1.00).

Structure analysis and refinement. The structure was solved by the Patterson method, initially for two iodine atoms, and then refined by the difference Fourier (DF) and least-squares techniques.[6] The third iodine atom and many non-hydrogen atoms of three independent molecular cations in an asymmetric unit were found in an initial DF-map. Subsequent DF syntheses revealed all non-hydrogen atomic positions. One of the three molecular cations showed an ordered structure, but the others had disorders in some of their five-membered rings. The disorders were basically treated with two atomic positions for one carbon (static model). The non-hydrogen atoms were refined with anisotropic thermal parameters, and hydrogen atoms bound to carbons except for the disordered carbons were included in calculated positions as fixed parameters. Final

cycles of full-matrix least-squares refinement were carried to convergence at $R = 0.076$ and $R_w = 0.077$.‡ The final DF map showed a residual peak of 2.3 Å^3 near the inversion centers, which could not be attributed to any significant chemical species (even a partly occupied water) thus left alone. Several residual peaks of 1.7–1.0 Å^3 near iodine atoms were also there, but these were judged to be essentially featureless. Structure of an ordered molecular cation is displayed in Fig. 1 with the atomic labels. Owing to the above mentioned disorder, some unusual bond lengths and angles are found around the disordered atoms. No other abnormal bond parameter has been found in the molecular ions. Atomic coordinates, thermal parameters, and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre. Any request to the CCDC for this material should quote the full literature citation together with the reference number 207/145.§

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‡ $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, $R_w = [\Sigma w(|F_o| - |F_c|)^2/\Sigma wF_o^2]^{\frac{1}{2}}$
§ For details of the scheme see Instructions for Authors (1997), *J. Chem. Soc.*, *Perkin Trans. 1*, 1997, Issue 1.

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