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Synthesis and X-Ray Crystal Structure of 8,9-Dimethoxy-4-methyl-3-phenyl-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinolinium Iodide

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Abstract

N-Methylation of 6,7-dimethoxy-1-(2′-phenylcyclopropyl)-3,4-dihydroisoquinoline (3b) with iodomethane in refluxing acetone gave the modified Cloke rearrangement product, 8,9-dimethoxy-4-methyl-3-phenyl-2,3,5,6-tetrahyropyrrolo[2,1-*a*]isoquinolinium iodide (5b), a new derivative of the pyrrolo[2,1-*a*]isoquinoline skeleton, together with the methiodide salt (4b) of (3b). The structure of (5b) was confirmed by X-ray crystallographic analysis.

Introduction

Pyrrolo[2,1-*a*]isoquinoline derivatives are generally accessed through Bischler–Napieralski technology[1] or cycloaddition reactions.[2–4] Rearrangement may also provide entry to this ring system, and recently the thermal rearrangement of a 1-cyclopropyl-substituted 3,4-dihydroisoquinolinium salt derivative to the pyrrolo[2,1-*a*]isoquinolinium system has been described[5] by de Meijere and coworkers. A further variation on this modified Cloke rearrangement has now been observed on heating of the 3,4-dihydroisoquinoline derivative (3b) with iodomethane, and the details are reported in this paper, together with results on the cyclopropyl analogue (3a).

Results and Discussion

The 3,4-dihyroisoquinolines (3a,b) were prepared through the Bischler–Napieralski cyclization. Treatment of homoveratrylamine with (1a,b) at elevated temperatures, between 140 and 170°C, gave (2a,b) in good yields as crystalline solids (Scheme 1). The cyclopropanecarboxamides (2a,b) were found to undergo cyclization

[1] Bremner, J. B., Engelhardt, L. M., White, A. H., and Winzenberg, K. N., *J. Am. Chem. Soc.*, 1985, **107**, 3910, and references therein.
[2] Dyke, S. F., and Kinsman, R. G., in 'The Chemistry of Heterocyclic Compounds—Isoquinolines Part 1' (Ed. G. Grethe) pp. 107–113 (John Wiley & Sons: New York 1981).
[3] Tominaga, Y., Shiroshita, Y., Kurokawa, T., Gotou, H., Matsuda, Y., and Hosomi, A., *J. Heterocycl. Chem.*, 1989, **26**, 477.
[4] Khlebnikov, A. F., Kostik, E. I., and Kostikov, R. R., *Synthesis*, 1993, 568.
[5] Giller, K., Baird, M. S., and de Meijere, A., *Synlett*, 1992, 524.

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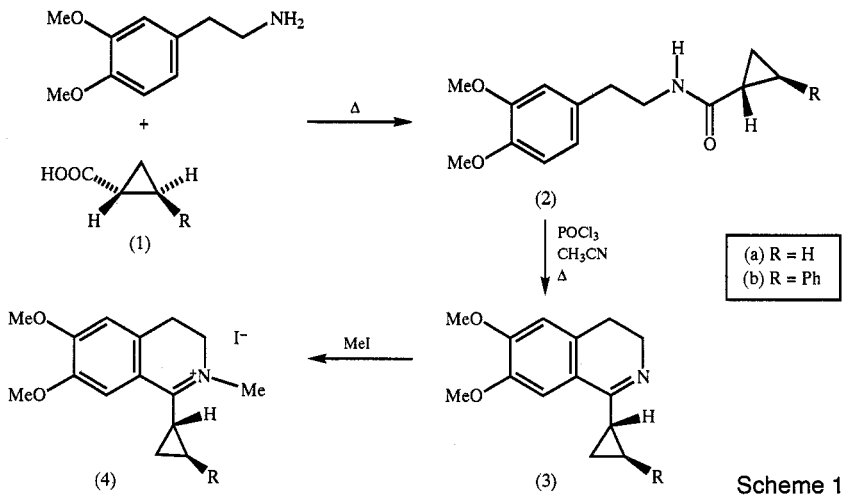
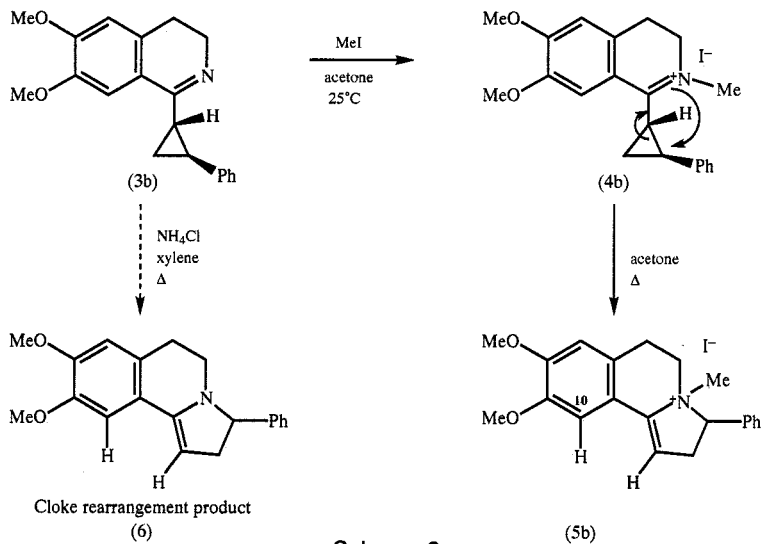
smoothly on relatively mild treatment by phosphorus oxychloride in refluxing acetonitrile. The 1-cyclopropyldihydroisoquinolines (3a,b) were isolated in excellent yields after basification, and their structures were confirmed spectroscopically. The Bischler–Napieralski cyclization of cyclopropanecarboxamides does not appear to have been reported previously.



Scheme 1

The imines (3a,b) were converted into the crystalline iminium salts (4a,b) by *N*-methylation with iodomethane in acetone, and satisfactory microanalyses were obtained on these salts. While the *N*-methylation of (3a) was conducted in refluxing acetone, the *N*-methylation of (3b) proceeded to the desired salt only at or below room temperature. At higher temperatures an alternative salt predominated (Scheme 2).



Scheme 2

The *N*-methylation of the imine (3b) with iodomethane in refluxing acetone produced a precipitate which, when isolated, proved not to be the expected methiodide salt (4b), which was instead present in the filtrate.

The precipitate was found to be an isomer of (4b), with an ion at *m/z* 322 for the cationic component, as determined by positive ion electrospray m.s. The reduced pyrrolo[2,1-*a*]isoquinoline structure (5b) was proposed after examination of the ^1H and ^{13}C n.m.r. spectra and on mechanistic considerations. An n.O.e. difference experiment demonstrated an effect between H 10 and the olefinic signal and the compound was thus assigned the structure (5b), with COSY and X–H correlation experiments allowing the assignment of the n.m.r. signals shown in Fig. 1. Elemental microanalyses on (5b) and the analogous tetrafluoroborate salt derived from the iodide salt, confirmed the molecular formula.

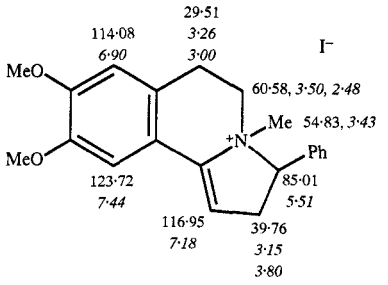


Fig. 1. ^{13}C and ^1H (*italics*) assignments for (5b).

The structure of (5b) was confirmed unambiguously by a single-crystal X-ray structure determination. The compound was identified as the diastereomer of (5b) with the 3-phenyl and 4-methyl substituents *trans* to each other (Fig. 2).

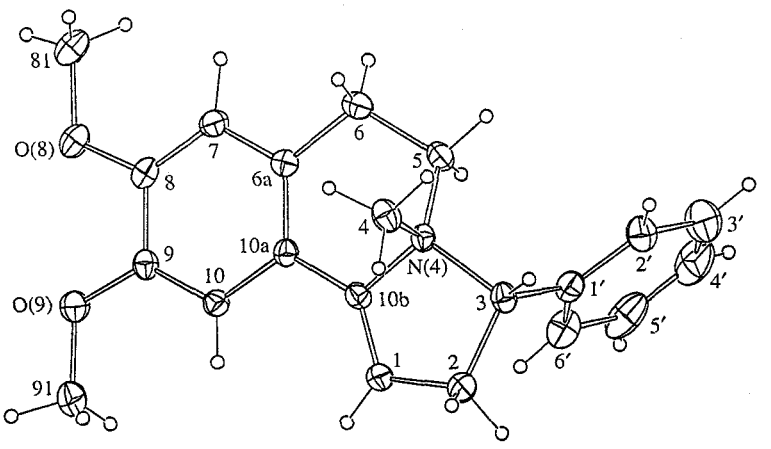


Fig. 2. Projection of the cation of (5b); 20% thermal ellipsoids are shown for the non-hydrogen atoms, hydrogen atoms having arbitrary radii of 0·1 Å.

Further experiments demonstrated that (5b) was formed through the initial conversion of (3b) into (4b), followed by cyclopropane ring opening and rearrangement, rather than the alternative sequence; the phenyl substituent in

the cyclopropane ring would facilitate ring opening by charge stabilization. At low temperatures the methylation of (3b) proceeded selectively to give (4b). This salt, after isolation and removal of excess iodomethane, was isomerized to (5b) in good yield by refluxing in acetone for 24 h. Attempts to dry (4b) at elevated temperatures also produced the partial isomerization of (4b) to (5b).

The formation of (5b) is a variation of the Cloke rearrangement[6] of cyclopropylimines. In this rearrangement the heteroatom may act as either a nucleophile or an electrophile to initiate ring opening of the cyclopropane and formation of a pyrroline. The promotion of this rearrangement by iodomethane does not appear to have been reported previously. The Cloke rearrangement normally proceeds from an imine by acid catalysis at elevated temperatures, typically by heating the substrate as a melt, or in xylene, with ammonium chloride above 130°C. The treatment of (3b) under these conditions, at temperatures up to 195°C, failed to afford the expected enamine (6), and in each case a complex mixture of products was obtained. However, the Cloke rearrangement of a substituted 1-(1′-methylcyclopropyl)-3,4-dihydroisoquinoline hydrochloride salt in acetonitrile at 85–90°C in the presence of sodium iodide did give,[5] after further reduction, unstable hexahydropyrrolo[2,1-*a*]isoquinoline derivatives in good overall yield. This result and the iodomethane-induced rearrangement suggests potential for the development of a new route to pyrrolo[2,1-*a*]isoquinoline derivatives based on 1-cyclopropyl-3,4-dihydroisoquinoline precursors.

Experimental

General

Most of the general notes covering this experimental have been given[7] previously. Additionally, elemental analyses were performed by the Central Science Laboratory (C.S.L.), University of Tasmania, Hobart, Tasmania, by using a Carlo Erba EA1108 CHN analyser and the Department of Chemistry, University of Queensland, by using a Carlo Erba EA1106 CHN analyser. The electrospray mass spectra (positive ion) were determined on a VG Quattro triple quadrupole mass spectrometer. The ^{1}H nuclear magnetic resonance spectrum of the tetrafluoroborate salt was determined at 400 MHz with a Varian Unity 400 spectrometer. ^{13}C n.m.r. assignments indicated by superscript letters may be interchanged as defined by those letters. Melting points are uncorrected.

N-[2′-(3″,4″-Dimethoxyphenyl)ethyl]cyclopropanecarboxamide (2a)

Homoveratrylamine (30·03 g, 165·7 mmol) and cyclopropane carboxylic acid (1a) (20·40 g, 237·0 mmol) were combined and stirred as a melt at 160° for 4·25 h under a slow stream of nitrogen to remove water vapour, then allowed to cool to a solid which was taken up in chloroform (300 ml). The chloroform solution was washed with 2 M sodium hydroxide (3×80 ml), 3 M hydrochloric acid (2×80 ml), 0·5 M hydrochloric acid (3×60 ml), and water (60 ml), then dried, and concentrated under vacuum, and the residue was recrystallized from ethyl acetate to give the *cyclopropyl carboxamide* (2a) (28·59 g, 69%) as a colourless powder, m.p. 94–95° (Found: C, 67·7; H, 7·9; N, 5·7. $C_{14}H_{19}NO_3$ requires C, 67·4; H, 7·7; N, 5·6%). Mass spectrum *m/z* 249 (M, 9%) (Found: 249·1357. $C_{14}H_{19}NO_3$ requires $M^{+\bullet}$, 249·1364), 165 (11), 164 (100), 151 (25), 149 (10), 69 (17). ^{1}H n.m.r. δ 6·82, d, *J* 8·4 Hz, ArH; 6·74, d, *J* 8·2 Hz, ArH; 6·73, *s*, ArH; 5·84, br s, NH; 3·87, s, OCH_3; 3·86, s, OCH_3; 3·50, q, *J* 6·7 Hz, CH_2, $(H1')_2$; 2·77, t, *J* 7·1 Hz, CH_2, $(H2')_2$; 1·32–1·27, m, H1; 0·98–0·93, m,

[6] Hudlicky, T., and Reed, J. W., in 'Comprehensive Organic Synthesis—Selectivity, Strategy and Efficiency in Modern Organic Chemistry' (Eds B. M. Trost and I. Fleming) Vol. 5, pp. 945–947 (Pergamon Press: Oxford 1991).

[7] Bailey, T. S., and Bremner, J. B., *Aust. J. Chem.*, 1993, **46**, 1965.

2H; 0·74–0·67, m, 2H. ^{13}C n.m.r. δ 174·15, CO; 149·63, ^{A}C3″; 148·26, ^{A}C4″; 132·12, C1″; 121·24, ^{B}C6″; 112·55, ^{B}C2″; 111·95, ^{B}C5″; 56·50, 2OCH$_3$; 41·55, C1′; 35·96, C2′; 15·31, C1; 7·63, C2, C3. ν_{max} (thin film from CDCl$_3$) 3309 (NH), 1636 (CO), 1028 cm^{-1}.

*N-[2′-(3″,4″-Dimethoxyphenyl)ethyl]-*trans*-2-phenylcyclopropanecarboxamide (2b)*

Homoveratrylamine (12·2 g, 67·3 mmol) and *trans*-2′-phenylcyclopropane carboxylic acid (1b) (13·14 g, 81·02 mmol) were combined and stirred as a melt between 140 and 160° for 5 h under a slow stream of nitrogen to remove water vapour, then allowed to cool to a solid which was taken up in chloroform (150 ml). The chloroform solution was washed with 2 M sodium hydroxide (3×35 ml), 3 M hydrochloric acid (3×30 ml), water (20 ml), and saturated aqueous sodium chloride (20 ml) then dried, concentrated under vacuum, and the residue was recrystallized from ethyl acetate to give the trans-*phenylcyclopropyl carboxamide* (2b) (16·51 g, 75%) as a colourless powder, m.p. 116–117°. Mass spectrum *m/z* 325 (M, 15%) (Found: 325·1674. $C_{20}H_{23}NO_3$ requires $M^{+\bullet}$, 325·1677), 165 (12), 164 (100), 151 (16), 91 (6). ^{1}H n.m.r. δ 7·27–7·17, m, 3ArH; 7·06–7·03, m, 2ArH; 6·80–6·70, m, 3ArH; 5·85, br s, NH, 3·84, s, OCH$_3$, 3·82, s, OCH$_3$; 3·50, q, *J* 5·6 Hz, CH$_2$, (H1′)$_2$; 2·76, t, *J* 7·0 Hz, CH$_2$, (H2′)$_2$; 2·48–2·42, m, H2; 1·60–1·52, m, 2H, H1 and H3; 1·23–1·17, m, 1H, H3. ^{13}C n.m.r. δ 172·53, CO; 149·58, ^{A}C3″; 148·23, ^{A}C4″; 141·43, ^{B}C1″; 131·92, ^{B}C1‴; 129·03, ^{C}2C‴; 126·84, ^{C}1C‴; 126·55, ^{C}2C‴; 121·21, ^{D}C6″; 112·43, ^{D}C2″; 111·91, ^{D}C5″; 56·47, OCH$_3$; 56·39, OCH$_3$; 41·64, C1′; 35·87, C2′; 27·31, ^{E}C2; 25·58, ^{E}C1; 16·52, C3. ν_{max} (KBr disk) 3323 (NH), 1638 (CO), 1028 cm^{-1}.

1-Cyclopropyl-6,7-dimethoxy-3,4-dihydroisoquinoline (3a)

The carboxamide (2a) (32·44 g, 130·1 mmol) in dry acetonitrile (500 ml) was refluxed with phosphorus oxychloride (48 ml, 510 mmol) for 3 h and cooled, and excess reagent was decomposed with ice. The resultant solution was concentrated under vacuum until the majority of organic solvent was removed, water (700 ml) was added, and the aqueous solution was extracted with diethyl ether (3×100 ml). Basification of the aqueous solution with concentrated aqueous ammonia and extraction with chloroform (4×300 ml) gave pale red organic extracts which, when combined, were dried and concentrated under vacuum to give, crude *1-cyclopropyl imine* (3a) (26·50 g), as a grey solid. Recrystallization of a small portion of this material from ethanol gave a colourless powder, m.p. 80–81°. Mass spectrum *m/z* 231 (M, 88%) (Found: 231·1241. $C_{14}H_{17}NO_2$ requires $M^{+\bullet}$, 231·1259), 230 (100), 216 (28), 214 (14), 200 (37), 184 (13). ^{1}H n.m.r. δ 7·31, s, ArH; 6·70, s, ArH; 3·94, s, OCH$_3$; 3·93, s, OCH$_3$; 3·56, t, *J* 7·4 Hz, CH$_2$, (H3)$_2$; 2·60, t, *J* 7·4 Hz, CH$_2$, (H4)$_2$; 2·02–1·90, m, H1′; 1·01–0·97, m, H2′; 0·91–0·86, m, H3′. ^{13}C n.m.r. δ 167·22, C1; 151·33, ^{A}C6; 148·09, ^{A}C7; 131·80, ^{B}C4a; 123·59, ^{B}C8a; 110·74, ^{C}C5; 109·52, ^{C}C8; 56·83, OCH$_3$; 56·58, OCH$_3$; 47·41, C3; 26·48, C4; 15·24, C1′; 7·66, C2′, C3′. ν_{max} (thin film from CDCl$_3$) 3001, 2936, 2832, 1512, 1281, 1142 cm^{-1}.

*6,7-Dimethyoxy-1-(*trans*-2′-phenylcyclopropyl)-3,4-dihydroisoquinoline (3b)*

The carboxamide (2b) (16·50 g, 50·70 mmol) in dry acetonitrile (300 ml) was refluxed with phosphorus oxychloride (20 ml) for 3 h and cooled, and ice (50 g) was added to destroy excess reagent. The resultant solution was concentrated under vacuum until the majority of organic solvent was removed, water (300 ml) was added, and the aqueous solution was extracted with diethyl ether (3×75 ml). Basification of the aqueous solution with concentrated aqueous ammonia and extraction with chloroform (3×75 ml) gave a yellow organic solution which developed a red colour during drying and concentration under vacuum to the crude *phenylcyclopropyl imine* (3b) (15·50 g, 98%), obtained and used as a red oil. Mass spectrum *m/z* 307 (M, 50%) (Found: 307·1586. $C_{20}H_{22}NO_3$ requires $M^{+\bullet}$, 307·1572), 306 (83), 305 (100), 304 (63), 290 (21), 276 (12), 201 (18). ^{1}H n.m.r. δ 7·32–7·16, m, 5ArH″; 7·07, s, ArH; 6·68, s, ArH; 3·89, s, OCH$_3$; 3·81–3·74, m, 1H, H3; 3·64, s, OCH$_3$; 3·51–3·42, m, 1H, H3; 2·68–2·58, m, H4; 2·29–2·19, m, 2H′; 1·86–1·80, m, 1H′; 1·39–1·33, m, 1H′. ^{13}C n.m.r. δ 165·90, C1; 151·29, ^{A}C6; 148·05, ^{A}C7; 142·60, ^{B}C4a; 131·56, ^{B}C8a; 129·03, 2C‴ 127·94, C4″; 126·39, 2C″; 123·23, ^{B}C1″; 110·69, ^{C}C5; 109·36, ^{C}C8; 56·52, OCH$_3$; 56·39, OCH$_3$; 47·58, C3; 28·32, ^{D}C1′; 26·68, ^{D}C2′; 26·39, C4; 15·55, C3′.

Conversion of (4b) into (5b)

The 1-(*trans*-2′-phenylcyclopropyl)isoquinoline salt derivative (4b) (110 mg) in dry acetone (5 ml) was refluxed for 24 h. Filtration of the solution after cooling gave the salt (5b) (74 mg, 64%).

Structure Determination

A unique room-temperature diffractometer data set ($T \approx 295$ K; monochromatic Mo Kα radiation, λ 0·7107$_3$ Å; $2\theta/\theta$ scan mode, $2\theta_{max}$ 50°) yielded 3688 independent reflections, 2731 with $I > 3\sigma(I)$ being considered 'observed' and used in the full-matrix least-squares refinement after Gaussian absorption correction. Anisotropic thermal parameters were refined for the non-hydrogen atoms; (x, y, z, U_{iso}) were refined for all hydrogen atoms except those on the solvent molecule, the latter modelling difference map artefacts as a half-weighted acetonitrile disordered about a crystallographic 2-axis after trial refinement. Conventional residuals on $|F|$ at convergence were R 0·033, R_w 0·035 (statistical weights derivative of $\sigma^2(I) = \sigma^2(I_{diff}) + 0{\cdot}0004\sigma^4(I_{diff})$). Neutral atom complex scattering factors were employed; computation used the XTAL 3.2 program system[8] implemented by S. R. Hall. Pertinent results

Table 2. Molecular core geometries in (5b)

In the ring torsion angles atoms are denoted by number only, *O*, *N* italicized. Distances in Å, bond angles and torsion angles in degrees

Atoms	Distance	Atoms	Angle	Atoms	Torsion
C(1)–C(2)	1·494(4)	C(2)–C(1)–C(10b)	113·2(4)	10b–1–2–3	−16·8(6)
C(1)–C(10b)	1·312(6)	C(1)–C(2)–C(3)	103·4(4)	1–2–3–*4*	27·0(5)
C(2)–C(3)	1·532(7)	C(2)–C(3)–N(4)	101·5(3)	2–3–*4*–10b	−28·7(5)
C(3)–N(4)	1·565(4)	C(2)–C(3)–C(1′)	114·6(4)	3–*4*–10b–1	20·2(5)
N(4)–C(4)	1·514(7)	N(4)–C(3)–C(1′)	112·6(4)	*4*–10b–1–2	−2·4(6)
N(4)–C(5)	1·502(6)	C(3)–N(4)–C(5)	114·3(3)	10b–*4*–5–6	59·7(5)
N(4)–C(10b)	1·504(5)	C(3)–N(4)–C(10b)	103·7(3)	*4*–5–6–6a	−49·5(6)
C(5)–C(6)	1·503(6)	C(5)–N(4)–C(10b)	111·0(3)	5–6–6a–10a	20·8(8)
C(6)–C(6a)	1·510(6)	C(4)–N(4)–C(3)	108·5(4)	6–6a–10a–10b	−1·1(8)
C(6a)–C(7)	1·401(5)	C(4)–N(4)–C(5)	110·6(3)	6a–10a–10b–*4*	11·0(6)
C(6a)–C(10a)	1·382(6)	C(4)–N(4)–C(10b)	108·3(3)	10a–10b–*4*–5	−40·2(5)
C(7)–C(8)	1·369(6)	N(4)–C(5)–C(6)	110·6(4)	10a–10b–1–2	−178·0(5)
C(8)–C(9)	1·417(6)	C(5)–C(6)–C(6a)	112·3(4)	3–*4*–5–6	176·6(4)
C(8)–O(8)	1·358(5)	C(6)–C(6a)–C(7)	119·3(4)	5–*4*–10b–1	143·4(4)
C(9)–C(10)	1·375(5)	C(6)–C(6a)–C(10a)	121·5(3)	3–*4*–10b–10a	−163·4(4)
C(9)–O(9)	1·359(5)	C(7)–C(6a)–C(10a)	119·2(4)	7–8–*8*–81	1·0(7)
C(10)–C(10a)	1·410(6)	C(6a)–C(7)–C(8)	121·2(4)	9–8–*8*–81	−177·9(5)
C(10a)–C(10b)	1·461(5)	C(7)–C(8)–C(9)	119·9(3)	8–9–*9*–91	177·7(5)
		C(7)–C(8)–O(8)	125·4(4)	10–9–*9*–91	−2·4(8)
		C(9)–C(8)–O(8)	114·7(4)		
		C(8)–C(9)–C(10)	119·1(4)		
		C(8)–C(9)–O(9)	114·8(3)		
		C(10)–C(9)–O(9)	126·0(4)		
		C(9)–C(10)–C(10a)	120·6(4)		
		C(10)–C(10a)–C(10b)	119·0(3)		
		C(6a)–C(10a)–C(10b)	121·1(3)		
		C(10)–C(10a)–C(6a)	119·9(3)		
		C(1)–C(10b)–N(4)	109·3(3)		
		C(1)–C(10b)–C(10a)	134·2(4)		
		N(4)–C(10b)–C(10a)	116·3(3)		

[8] Hall, S. R., Flack, H. D., and Stewart, J. M., (Eds) 'The XTAL 3.2 Reference Manual' Universities of Western Australia, Geneva and Maryland, 1992.

are given in Fig. 2 and Tables 1 and 2; material deposited comprises thermal and hydrogen atom parameters, full molecular non-hydrogen geometries, and structure factor amplitudes.†

Crystal/Refinement Data

$C_{21}H_{24}NO_2^+ I^-.0{\cdot}5CH_3CN$, compound (5b), M 470·0. Monoclinic, space group $C2/c$ (C_{2h}^6, No. 15), a 30·86(1), b 10·257(4), c 14·609(8) Å, β 114·19(4)°, V 4218 Å^3. $D_c(Z = 8)$ 1·48 g cm^{-3}; $F(000)$ 1896. μ_{Mo} 15·4 cm^{-1}; specimen: 0·33 by 0·27 by 0·33; $A^*_{min,max}$ 1·32, 1·46.

Structural Commentary

The results of the single-crystal X-ray study are consistent in stoichiometry, connectivity and stereochemistry with (5b) as given above. The methoxy substituents are essentially coplanar with the associated aromatic ring, with the usual angular distortions at their points of attachment, with a tangible degree of alternant bond localization in the ring, with a shortening of C(10a)–C(10b) exocyclically indicative of some conjugation to C(10b)–C(1). Substantial angular distortions about C(10b) are evident with C(10a)–C(10b)–C(1) particularly enlarged to 134·2(4)°, while C(1)–C(10b)–N(4) is reduced to 109·3(3)°. C(10b)–C(1)–C(2) (113·2(4)°) is also reduced well below the trigonal norm, the associated strain accumulation being evident in the elongation of C(3)–N(4) (1·565(4) Å).

Acknowledgments

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