Electro-organic Synthesis and *X*-Ray Crystal Structure of the Novel Complex 2,7-Dimethyl-6,8-bis(methylthio)pyrrolo[1,2-*a*]pyrazinium Tri-iodomercurate(II)

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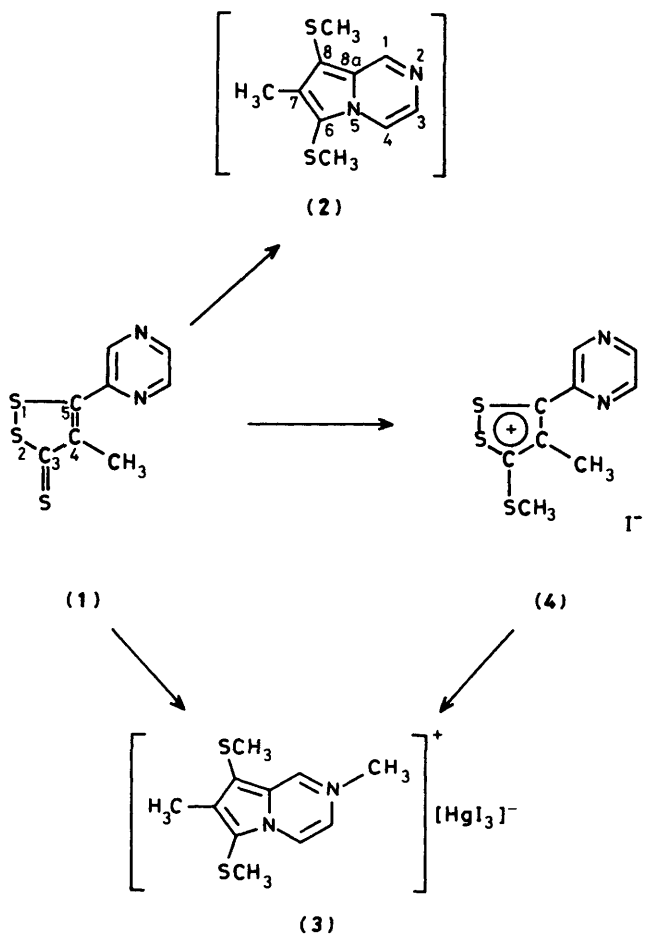
Electroreduction of oltipraz (INN), 4-methyl-5-(pyrazin-2-yl)-1,2-dithiole-3-thione and methylation leads to the known metabolite, 6,8-bis(methylthio)-7-methylpyrrolo[1,2-*a*]pyrazine on a glassy carbon cathode or to the novel mercury(II) title complex on a mercury cathode. The crystal structure of this complex is presented. The complex crystallizes in the triclinic space group $P\bar{1}$ with $a = 10.620(2)$, $b = 11.944(2)$, $c = 9.665(2)$ Å, $\alpha = 121.16(1)$, $\beta = 102.68(1)$, $\gamma = 95.38(1)°$, $Z = 2$. The structure was solved and refined on the basis of 3 162 significant data, to a final R value of 0.026. The electrochemical behaviour has been investigated by voltammetry.

Recent papers have shown that 1,2-dithiole-3-thiones are of pharmaceutical interest. One of the most potent antischistosomicidal compounds is oltipraz (INN), 4-methyl-5-(pyrazin-2-yl)-1,2-dithiole-3-thione (**1**).[1,2] Its metabolic pathway follows reductive alkylation leading to various pyrrolo[1,2-*a*]pyrazines.[3] The recent synthesis of 7-methyl-6,8-bis(methylthio)pyr-rolo[1,2-*a*]pyrazine (**2**),[4–7] the main metabolite formed by chemical reduction of (**1**), confirms the biological process but the question on its mode of action remains open. Recent studies have emphasized redox behaviour to help clarify the pharmaceutical activity of dithiolethiones.[5,6] In our investigations of the schistosomicidal activity[8] and electroreduction[9] of dithiolethiones compound (**1**) was used as starting compound. This molecule can lead to better understanding of the mechanism of the electroreductive reaction by providing information on the influence of the C(5) substituent and on the biological mechanism. Until now, the order of physiological activity of dithiolethiones could not be completely explained entirely in terms of their electrochemical behaviour although the schistosomicidal properties of (**1**) have been associated with particularly unusual electrochemistry.[6] More recently[10] a relationship between the shistosomicidal activity of (**1**) and parasite glutathione levels has been described. The involvement of (**1**) in enzymatic processes and ionic equilibria was demonstrated.

Results and Discussion

Voltammetry.—Electrochemical reductive methylation of (**1**) led to (**2**), (Scheme). The reduction potential value and the procedure for the reduction of oltipraz were as follows. Cyclic voltammograms (0.2 V s^{-1}) of 2 × 10^{-3} mol dm^{-3} solutions of (**1**), in dry dimethylformamide [0.1 mol dm^{-3}-tetrabutylammonium fluoroborate (TBAP) as supporting electrolyte, s.c.e. as reference electrode, Pt as working electrode, and Pt as counter electrode] are shown in Figure 1. Two waves were observed. The peak potentials for anodic and cathodic waves were at *ca.*



Scheme.

−0.95 and −0.10 and at −1.00 and −1.50 V respectively. For the sake of comparison the cyclic voltammogram of a reference dithiolethione[9] showed only one anodic and one cathodic wave at *ca.* −0.45 and −1.07 V.

The electrochemical behaviour of some 1,2-dithiole-3-thiones has been reported.[5] These studies and those of chemical reduction[11] indicate that cleavage of the S–S bond occurs. The voltammetric curve of (**1**) at a platinum electrode shows complex behaviour, unusual for a chemically reversible cleavage of the S–S bond of a dithiolethione.[9] It seems likely that the pyrazine ring is involved in the primary reduction step. Electrochemical reduction of the pyrazine leading to dihydropyrazine[12] is in accord with this first step. After reductive cleavage of the S–S bond, ring closure occurs with formation of a cyclic thioamide before methylation by CH_3I. This reaction pathway determined by the electrochemical study is in accord with recent chemical investigations.[8]

Electrosynthesis.—Reduction of (**1**) at a glassy carbon cathode (−1.2 V *versus* s.c.e.) followed by addition of CH_3I at the end of electrolysis leads to a good yield of the pyrrolo[1,2-a]pyrazine (**2**) the parameters of which were in accord with published data.[3] The electrochemical method is a cleaner way and gives a satisfactory yield on a larger scale than chemical reduction by Na_2S[4] or by Bu^{t}OK.[7] This metabolite was prepared through electrosynthesis both by us[13] and by Moiroux *et al.*[14,15]

Reduction of (**1**), carried out at a mercury cathode (−1.8 V *versus* s.c.e.) followed by addition of CH_3I at the end of electrolysis, affords a mercury(II) compound (**3**) the structure of which has been fully established. Methylation of (**1**), leading to (**4**), prior to electrolysis, followed by reduction of a mercury cathode and then addition of CH_3I also affords (**3**).

Earlier studies[5,6,14] by polarography have shown the interaction of dithiolethiones with mercury during the electrolysis but mercury compounds have not previously been isolated. In fact electrochemical treatment of dithiolethiones at a mercury cathode does not lead to organometallic compounds.[9] Thus it appeared necessary to establish the structure of the first crystalline mercury(II) derivative of a reduced dithiolethione. The structure of (**3**) was established by comparison with (**1**). ^{1}H N.m.r. data are summarized in Table 1. The deshielding of H(1) and H(3) resulting from the quaternization of N(2) is confirmed by the presence of a three-proton singlet at δ *ca.* 4. Additional

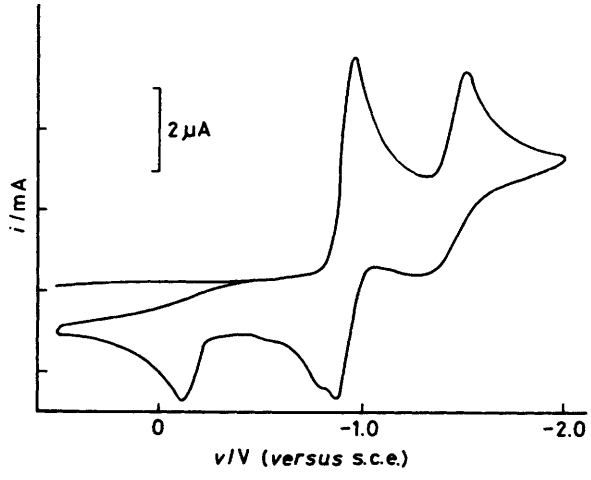


Figure 1. Cyclic voltammogram of (**1**) in dimethylformamide (scan rate 0.2 V s^{-1}).

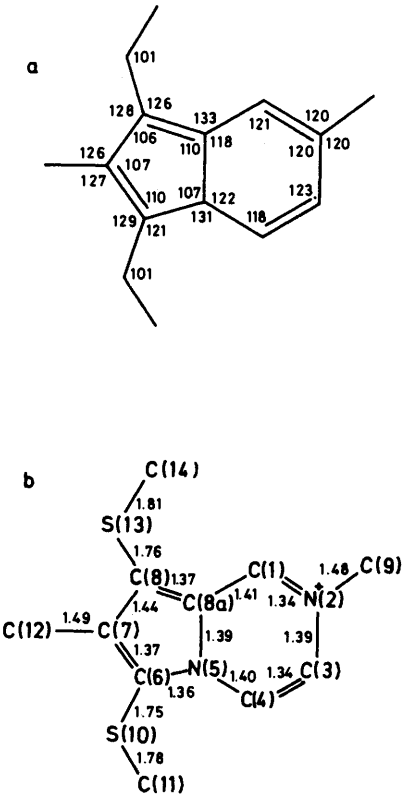


Figure 2. a, Atom numbering, bond lengths (Å) and valence angles (°); b, max. e.s.d.s 0.012 Å and 0.7°.

Table 1. ^{1}H N.m.r. spectral data (chemical shift δ from $SiMe_4$).[a]

Compound	N^+CH_3	7-(CH_3)	6-(SCH_3)	8-(SCH_3)	H(1)	H(3)	H(4)	Solvent
(**2**)		2.49 (s)	2.28 (s)	2.21 (s)	8.96 (d) J_m 1.4 Hz	7.68 (d) J_o 5.8 Hz	8.19 (dd) J_m 1.4, J_o 5.8 Hz	$CDCl_3$
		2.45 (s)	2.30 (s)	2.25 (s)	8.85 (d)	7.70 (d)	8.38 (d)	[$^2H_6$]DMSO
(**3**)	4.35 (s)	2.50 (s)	2.60 (s)	2.32 (s)				$CDCl_3$
	4.18 (s)	2.50 (s)	2.45 (s)	2.41 (s)	9.45 (d) J_m 1.4 Hz	8.87 (d) J_o 5.8 Hz	7.87 (dd) J_m 1.4, J_o 5.8 Hz	[$^2H_6$]DMSO
	4.12 (s)	2.56 (s)	2.42 (s)	2.38 (s)	8.95 (d)	8.55 (d)	7.50 (dd)	CD_3CN
Δδ[b]		+0.01	+0.42	+0.11				$CDCl_3$
Δδ[b]		+0.05	+0.15	+0.16				[$^2H_6$]DMSO

[a] s = Singlet; d = doublet; dd = double doublet. [b] Δδ is defined as positive if the change in shift is from low to high frequency.

Table 2. ^{13}C N.m.r. spectral data [chemical shift δ (p.p.m.) from $SiMe_4$].

Compound	C(9) N^+CH_3	C(12) 7-CH_3)	C(11) 6-(SCH_3)	C(14) 8-(SCH_3)	C(1)	C(3)	C(4)	C(6)	C(7)	C(8)	C(8a)	Solvent
(2)		10.66	20.52	17.86	143.16	128.54	116.32	136.06	115.95	108.18	131.31	$CDCl_3$
(3)	45.84	11.06	19.44	16.88	138.55	120.21	119.89	139.96	126.16	121.49	128.03	[$^2H_6$]DMSO
	45.85	10.54	19.05	16.66	136.79	120.26	119.41	141.50			127.85	$CDCl_3$–CD_3CN (1:1)
Δδ[a]		+0.12	−1.47	−1.20								

[a] Δδ is defined as positive if the change in shift is from low to high frequency.

Table 3. Final atomic co-ordinates for non-hydrogen atoms (× 10^4).

	x	*y*	*z*
Hg	1 922(1)	4 880(1)	260(1)
I(1)	3 729(1)	6 646(1)	3 375(1)
I(2)	2 810(1)	2 922(1)	7 991(1)
I(3)	355(1)	6 211(1)	9 071(1)
C(1)	7 814(5)	3 652(6)	3 855(8)
N(2)	7 006(5)	4 386(5)	3 655(6)
C(3)	6 022(6)	3 840(8)	2 114(9)
C(4)	5 838(6)	2 581(8)	774(9)
N(5)	6 685(5)	1 815(5)	974(5)
C(6)	6 790(6)	553(8)	−157(8)
C(7)	7 809(6)	236(6)	601(9)
C(8)	8 388(6)	1 383(6)	2 332(8)
C(8a)	7 694(5)	2 329(6)	2 497(8)
C(9)	7 157(9)	5 777(8)	5 092(10)
S(10)	5 694(1)	−439(1)	−2 246(1)
C(11)	6 650(10)	−98(9)	−3 343(9)
C(12)	8 281(12)	−1 024(9)	−199(12)
S(13)	9 779(1)	1 604(2)	3 905(2)
C(14)	8 963(9)	1 201(10)	5 105(12)

structural evidence is provided by off-resonance decoupled ^{13}C n.m.r. spectra (Table 2). The pyrrolo[1,2-*a*]pyrazine skeleton is clearly demonstrated by the absence of the thiocarbonyl group and from a comparison with literature data[3] which permitted the assignment of each carbon. The *N*-methyl group resonates at δ 45.85 p.p.m. The structure assigned to the product obtained was supported by elemental analysis although only one iodine atom was suggested. The mass spectra obtained by electronic ionization agreed with the proposed structure. Fragments at *m/z* 456 (HgI_2) and 224 (pyrrolopyrazine ring) were observed. These results were corroborated by crystallographic analysis.

X-*Ray Crystallography*.—The atomic co-ordinates are given in Table 3. Figure 2a and b illustrate the atomic numbering, bond lengths and angles of the organic moiety. This is planar, within the e.s.d. range, except for the methyl substituents on the sulphur atoms; the two methyl groups C(11) H_3 and C(14) H_3 adopt a '*trans*' conformation with respect to the mean plane of the molecule (deviations from plane +1.76 and −1.72 Å, respectively). The observed bond lengths are in accord with the planar structure of (3) with alternating single and double bonds in the pyrrolopyrazinium ring.

Figure 3 shows the Hg^{2+} ion tetrahedrally co-ordinated by the I^- ions. Moreover, two cations are linked by means of two I^- ions leading to the formation of inorganic pseudodimers.

The organic fragments are parallel to each other and form columns in which the inorganic dimers are inserted in a sandwich layer, with the triangular I_3^- in front of the pyrazinium ring. The shortest intermolecular distances are I(1)–C(1) 3.576(5), I(1)–S(10) 3.719(5), I(2)–C(4) 3.913(5), I(2)–S(13) 3.936(5), I(3)–C(8a) 3.613(5), and I(3)–C(9) 3.928(5) Å.

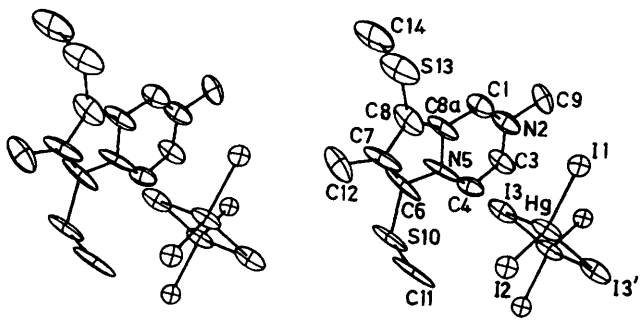


Figure 3. Stereoview (ORTEP) of the organic moiety and the inorganic pseudo dimer.

Experimental

^1H (80.13 MHz) and ^{13}C (20.15 MHz) n.m.r. spectra were recorded on a Bruker WP 80 spectrometer. Mass spectra (electronic impact) were performed on a Ribermag R-10-10 or VG 30 F (C.N.R.S.) instrument. M.p.s were measured with a Büchi SMP-20 capillary apparatus. Combustion analysis were performed by the C.N.R.S. (Vernaison). 4-Methyl-5-(2-pyrazin-2-yl)-1,2-dithiole-3-thione (oltipraz DC) was a loan from Rhône–Poulenc.

Electrochemistry.—Voltammetric studies were carried out in dimethylformamide (DMF) with the standard three electrode configuration [a platinum disc as working electrode, a platinum wire as counter electrode, and a standard calomel reference electrode (s.c.e.)]. The electrolyte was 0.1 mol dm^{-3}-tetrabutylammonium fluoroborate (TBAP).

General electrolysis procedure. Electrolyses were carried out in a cell (1 g, 5 mmol) with compartments separated by a porous glass diaphragm. A mercury pool (or a glassy carbon electrode) was used as the cathode and a platinum plate as the anode. Stirring was by magnet. The electrolyte was 0.2 mol dm^{-3} anhydrous lithium perchlorate in anhydrous DMF. Electrolysis were carried out with a controlled cathodic potential and coulometric measurements were made with an IG5 Tacussel electronic integrator coupled to a PRT 20-2 Tacussel potentiostat. The solution turned red-brown. At the end of electrolysis, which needed 2 electrons per mole of dithiolethione, a large excess of methyl iodide was added. The colour slowly faded. The solution was left overnight and a large excess of cold water was then added. The aqueous layer was extracted with toluene. The organic layer was washed (H_2O) to eliminate residual DMF, dried (Na_2SO_4), and evaporated *in vacuo*. The oily residue was purified by being passed through a silica gel column (monitoring by t.l.c. on silica gel plates) and re-crystallized.

7-Methyl-6,8-bis(methylthio)pyrrolo[1,2-a]*pyrazine* (2). This was eluted with benzene and then recrystallized from light petroleum (b.p. 40–60 °C) to yield a pale yellow solid (40%),

m.p. 64–66 °C, *m/z* 224 (M^+, 86.3%), 209 (100.0), 194 (16.4), and 123 (24.6).

2,7-*Dimethyl*-6,8-*bis*(*methylthio*)*pyrrolo*[1,2-a]*pyrazinium triiodomercurate*(II) (**3**). This was eluted with acetonitrile in 55% yield, m.p. 165 °C (from CH_3OH or $CH_3CO_2C_2H_5$) (Found: C, 16.7; H, 1.85; Hg, 24.3; I, 16.8; N, 3.7; S, 7.55. $C_{11}H_{15}HgI_3N_2S_2$ requires C, 16.1; H, 1.8; Hg, 24.3; I, 46.5; N, 3.4; S, 7.8%).

4-*Methyl*-3-*methylthio*-5-*pyrazin*-2-*yl*-1,2-*dithiolium iodide* (**4**). A solution of (**1**) (2.26 g, 0.01 mol) and methyl iodide in large excess (14.2 g, 0.10 mol) in acetone was refluxed overnight. The precipitate was filtered off and washed with acetone and used without further purification, yield 90%; m.p. 170 °C (decomp.) (Found: C, 29.5; H, 2.55; I, 34.9; N, 7.2; S, 25.7. $C_9H_9IN_2S_3$ requires C, 29.35; H, 2.45; I, 34.5; N, 7.6; S, 26.1%); δ(D_2O) 2.65 (3 H, s, CH_3), 3.20 (3 H, s, SCH_3), 8.85 (2 H, s, aromatic), and 9.22 (1 H, s, aromatic).

X-*Ray Crystallography*.—The crystals were grown from a methanol solution.

Crystal data. $C_{11}H_{15}N_2S_2HgI_3$, M = 820.7. Triclinic, a = 10.620(2), b = 11.944(2), c = 9.665(2) Å, α = 121.16(1), β = 102.68(1), γ = 95.38(1)°, V = 991.4 Å^3 (by least-squares refinement on diffractometer angles for 25 medium angle reflections, Mo-K_α, λ = 0.710 69 Å), space group $P\bar{1}$, Z = 2, 2.2 < D_m < 2.9 g cm^{-3}, D_x = 2.75 g cm^{-3}. Yellowish transparent plates, crystal dimensions (distance to faces from centre): 0.090 (001, 001), 0.035 (110, 110), 0.113 (010, 010), 0.125 (111) mm, μ(Mo-K_α) = 120.42 cm^{-1}.

Data collection and processing. CAD4 diffractometer, ω–θ mode with ω scan width = 0.70 + 0.35 tanθ, graphite-monochromated Mo-K_α radiation; 5 962 reflections measured ($2 \leqslant \theta \leqslant 30°$, $-14 \leqslant h \leqslant 14$, $-7 \leqslant k \leqslant 16$, $-13 \leqslant l \leqslant 13$), 5 768 unique [$R$ = 0.007 after numerical absorption correction[16] (maximum and minimum transmission factors 0.47 and 0.16)], 3 162 with $I > 2.5\ \sigma(I)$ used for all calculations. Intensity variation of standard reflection (423) < 2%.

Structure analysis and refinement. The positions of the heavy atoms (Hg, 3 I, 2 S) were taken from the Patterson map (SHELXS 86).[17] Subsequent normal heavy-atom procedures revealed the C and N atoms. Full-matrix least-squares refinement on F using SHELX 76,[14] located 13 H atoms on a difference Fourier map; 8 Hs have calculated and not refined locations. Anisotropic temperature factors (U_{ij}) for all non-H atoms and isotropic ones for H atoms (corresponding to the isotropic temperature factors of the carrier atoms incremented by 0.02) were taken. The weighting scheme is $W = 1/[\sigma 2(F_o) + 0.007F_o 2]$ with $\sigma(F_o)$ from counting statistics. Final R and R_w values are 0.026 and 0.035; $(\Delta/\sigma)_{max.} = -0.433$ [Z/C of C(07)], S = 0.85; maximum and minimum heights in final difference Fourier map were −1.24 and 1.03 e Å^{-3}. Scattering factors were from refs. 16 and 18 (Hg^{2+}, I^-). Structural analysis used SHELX 76 and *X*-RAY 76.[19] Calculations were performed on IBM 4341 computer at Namur-SCF.[20]

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