Electroorganic Synthesis. Reductive Alkylation of Functionalized 1,2-Dithiole-3-thiones [1]

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Two-electron reduction of some substituted 1,2-dithiole-3-thiones **1** followed by alkylation of the dianionic intermediates leads through electrosynthesis to mixture of *Z* and *E* isomers of the corresponding substituted alkyl-(3-thioalkyl)-2-propenedithioates **2, 3** in satisfactory yield. The structure of those products was established by ^{13}C and ^{1}H nmr and mass spectroscopy. The isomers ratios were determined by nmr spectroscopy.

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Electrochemistry has received much attention in organic synthesis. Exhaustive reviews gave recent [2] applications. The use of electrochemical reduction of dithiolethione has not been investigated to any appreciable extent, although it should have certain advantages over chemical reduction: (a) it is possible to start with a better understanding of the system; (b) a greater selectivity in reducing conditions is available; (c) the system is probably cleaner since the reducing agent is an inert electrode.

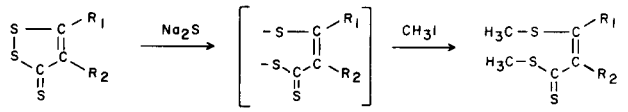
Recent papers [3] have shown that 1,2-dithiole-3-thiones of general structure **1** are compounds of pharmaceutical interest. Among these compounds 4-methyl-5-(2-pyrazinyl)-1,2-dithiole-3-thione (oltipraz ^{R}) has high schistosomicidal activity [4]. Its metabolic pathway follows a reductive methylation process [5] which was later confirmed by chemical reduction [6]. These results have prompted us to synthesize reduction derivatives of dithiolethiones **1a-c** which are also good antischistosomiasis [7a], to correlate eventually their activity with their electrochemical behavior and to test the new compounds **2**.

Sulfur-sulfur bonds are easily cleaved by various reducing agents [8]. Maignan and Vialle [9] have reported the reductive cleavage of the S-S bond of some 1,2-dithiole-3-thiones by using aqueous sodium sulfide, leading to the corresponding dithioesters **2** after methylation of the intermediates **4** (Scheme I). But the hitherto known method often requires excess amounts of the reagent and a skillful technique. This chemical reduction, under different reaction conditions of time and temperature, failed in our hands for compounds **1a-c**; it occurs as a side reaction of the oxazolinone ring which is very sensitive in an alkaline medium and which leads to the opening of the benzoxazolinyl heterocycle followed by polymerisation [18]. So this chemical technic cannot be generally applied to any type of substrate.

Oltipraz

Scheme I

Chemical Reduction of Dithiolethiones [7b]



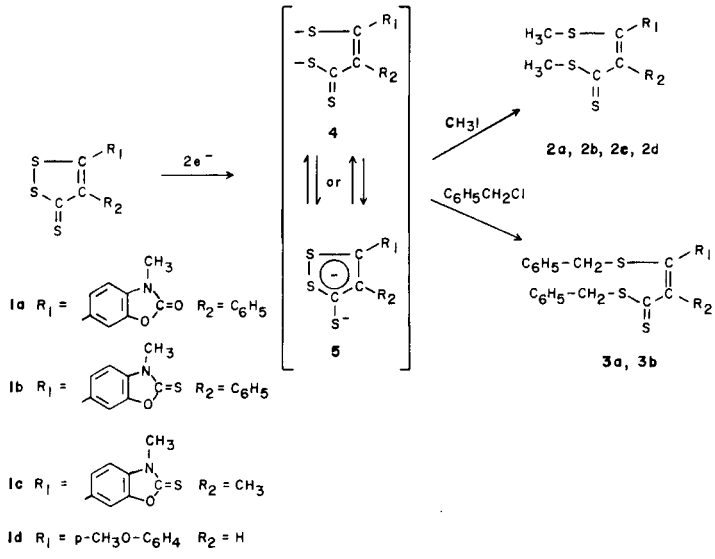
1 4 2

Therefore we performed a more selective electrochemical method which affords after methylation the expected products in satisfactory yields (Scheme II) (Table I) and shows the advantages and the superiority to a chemical reduction. To generalize in order to broaden the type of substrate, we also worked on the dithiolethione **1d** (sulfarlem^{R}). Previous studies have reported on the electrochemistry of 1,2-dithiole-3-thiones **1** in aqueous [10] or organic media [11]. The electroreduction has been largely studied from a mechanistic point of view. The results depend on the nature of substituents R^1, R^2 and of the electrode used. Reduction products have been rarely isolated or not fully characterized.

To test the generality of our electrosynthesis method as a route to differently substituted propenedithioates, the intermediates **4** were treated with benzyl chloride to furnish compounds **3**. To the best of our knowledge derivatives **3** have never been described. The benzyl group has a more lipophilic character than a methyl group and can lead to more active compounds.

Scheme II

Electroreduction and Alkylation of Dithiolethiones



Prior to electrosynthesis voltammetric studies of compounds **1** in dimethylformamide-tetrabutylammonium tetrafluoroborate (0.1 *M*) at the platinium electrode are in accordance with the chemically reversible cleavage of the S-S bond and show the following electrochemical behavior. A two-electrons irreversible reduction appears near −1.1 V SCE (Ep_c in Table I); during the reverse scan the oxidation of the corresponding dianoinic intermediate **4**⇌**5** occurs at −0.3 V SCE (Ep_a in Table I). Polarographic curves at the dropping mercury electrode shows two one electron-waves for compounds **1a, 1b** and **1d** but only one two electrons-wave for **1c** (Table I). The half-wave potentials $E^{1/2}$ (at the mercury cathode) are less negative than the cathodic peak potentials Ep_c (at the platinum electrode) in cyclic voltametry. It is well known [17] that the electroactivity of sulfur compounds depends upon the nature of the electrode. Interaction with mercury facilitates reduction of dithiolethiones.

Reduction of dithiolethione **1** in dimethylformamide-lithium perchlorate was carried out at controlled potential (− 1.2 V SCE) at the mercury cathode. The current consumption was consistent with the donation of two electrons per molecule of **1**. The solution was then alkylated. One-step electroreductive alkylation may be carried out in the presence of methyl iodide or benzyl chloride. However, in the two-step process, the chemical stability of the dianionic species **4** allows the use of electrophiles which are more easily reducible than the starting dithiolethione. After alkylation the solution was poured into water and extracted with toluene. The product was isolated by column

Table I

Data of Electrochemistry

Compound	Cyclic Voltammetry		Polarography			Electrolysis	
	Ep_c [a] V (SCE)	Ep_a [a] (V SCE)	E_1 1/2 [b] (V SCE)	E_2 1/2 [b] (V SCE)	n [c] (e^-/molecule)	alkylating agent	yield [d] %
1a	−1.15	−0.35	−0.88	−1.00	1.85	CH_3I	34
					1.88	$C_6H_5CH_2Cl$	54
1b	−1.10	−0.32	−0.81	−0.95	1.93	CH_3I	42
					1.82	$C_6H_5CH_2Cl$	61
1c	−1.15	−0.33	−0.93	—	1.66	CH_3I	25
1d	−1.15	−0.45	−0.91	−1.35	2.10	CH_3I	61

[a] Values obtained in dimethylformamide-tetrabutylammonium tetrafluoroborate (0.1 *M*) at Scan rate 0.2 $V.s^{-1}$. Ep_a and Ep_c refer to peak potentials for anodic and cathodic waves, respectively. [b] Values obtained in dimethylformamide-tetrabutylammonium tetrafluoroborate (0.1 *M*) at Hg electrode. [c] Values for the reduction at Hg electrode in dimethylformamide-lithium perchlorate (0.2 *M*) at − 1.2 V SCE. [d] Yields are not optimized.

Table II

^1H and ^{13}C Chemical Shifts for Compounds **2, 3**. Spectra were recorded in deuteriochloroform with TMS as internal standard. Values in brackets (lit [7]) in carbontetrachloride.

Compound	SCH_3 or SCH_2	CS_2CH_3 or CS_2CH_2	ratio Z/E	SCH_3 or SCH_2	CS_2CH_3 or CS_2CH_2	CS_2
2a	1.80 (Z) and 1.90 (E)	2.40 (E) and 2.75 (Z)	50/50	16.19 and 16.77	20.14 and 20.31	231.31
2b	1.78 (Z) and 1.90 (E)	2.36 (E) and 2.71 (Z)	50/50	16.21 and 16.80	20.09 and 20.28	231.99
2c	1.77 (Z) and 1.90 (E)	2.38 (E) and 2.75 (Z)	40/60	15.68 and 16.76	19.84 and 20.21	226
2d	1.97 (Z) (1.88) and 2.35 (E) (2.34)	2.45 (E) (2.42) and 2.55 (Z) (2.55)	75/25	16.35 and 17.42	18.87 and 20.10	215.53
3a	3.45 (Z) and 3.50 (E)	4.25 (E) and 4.50 (Z)	50/50	37.42 and 38.00	40.53 and 41.54	230.55 and 231.15
3b	3.43 (Z) and 3.50 (E)	4.22 (E) and 4.50 (Z)	50/50	37.35 and 37.96	50.39 and 41.47	230.01 and 230.69

chromatography and is roughly an equimolar mixture of *E* and *Z* isomers identified by ^1H and ^{13}C nmr (Table II). These results are in contrast with the assumption [11b] that the amount of *E* isomer is negligible. In ^1H nmr spectrum the *E* and *Z* isomers were characterized by four singlets [9,12,13] in the correct intensity ratio corresponding to methylthio (or benzylthio) and methyl dithioester (or benzyl dithioester) groups. The methylthio group appeared at a higher field than the corresponding methyl dithioester group. A thermal $E \rightleftharpoons Z$ isomerization in the compound was previously proposed [9,12].

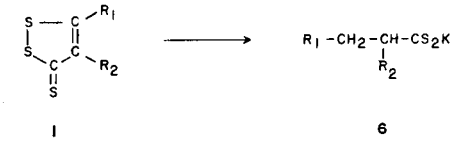
The ^{13}C nmr spectroscopy allows us also to distinguish the two isomers. The methyl dithioester (or benzyl dithioester) group is expected at a lower field in comparison with the methylthio (or benzylthio) group (Table II). Moreover for benzyl derivatives **3** the thiocarbonyl groups are split into two signals. The *N*-methyl signal resonates at *ca.* 28 ppm for oxobenzoxazolinyl **2a** and **3a**, and *ca.* 32 ppm for thioxobenzoxazolinyl **2b, 2c** and **3b.**

The ^{13}C nmr signals were assigned in accordance with related data [13,16]. Moreover the structural assignment was substantiated by a mass spectroscopic examination on desorption chemical ionisation.

The formation of a methyl dithioester group was suspected [11b] when an excess of methyl iodide is added to the exhaustive electrolyzed solution with the help of uv-visible absorption. Recently [10c] compounds **6** (Scheme III) corresponding to the loss of CS_2^- or HS^- group (after exhaustive electrolysis: 4 of 6 e^-/molecule) were characterized as potassium salts by ^1H and ^{13}C nmr. No yield was described.

Scheme III

Exhaustive Electrolysis of Dithiolethiones [11c]



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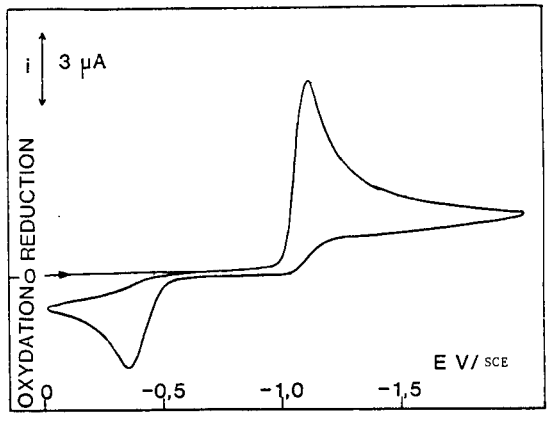

Figure 1. Cyclic voltammetry for **1b**, $2\text{-}10^{-3}$ *M* in dimethylformamide-tetrabutylammonium tetrafluoroborate (0.1 *M*) at platinium electrode, potential scan rate 1V S^{-1}; scan initiated at arrowhead.

Our technique may be a useful and simple approach in the synthesis of dithioesters [19]. It is a method which can be generalized to any kind of substrate and alkylating agent which differs with chemical synthesis. Compounds of antiparasitic potential value can be prepared. Up to now, the order of physiological activity of dithiolethiones cannot be completely explained by a particular electrochemical behavior. The schistosomicidal property of oltipraz^R has been associated with an unusual electrochemical behavior by Fleury *et al* [10c] and we agreed with this argument when we isolated its metabolite through electrosynthesis [14]. We shall further investigate in this way and will try to establish a possible relationship between electrochemical and biological properties.

EXPERIMENTAL

Infrared spectra were recorded with a Beckman-Acculab IV spectrometer. The ^1H and ^{13}C nmr spectra were recorded on a Bruker WP 80 pulsed Fourier transform spectrometer. Mass spectra were performed on a Riberman R-10-10 or a VG 30 F (CNRS) on desorption chemical ionisation (ammonia). Melting points were measured with a Büchi SMP-20 capillary melting point apparatus. Combustion analysis were performed by the CNRS.

Starting Compounds **1a** and **1b** have been previously described [7a]. Compound **1c** was prepared according to the same process [7].

4-Methyl-5-(3-methyl-2-thioxo-6-benzoxazolinyl)-1,2-dithiole-3-thione (**1c**).

This compound was obtained in a yield of 37%, mp 173-174° (ethanol-acetone 1-1); ^{1}H nmr (deuteriochloroform): δ 2.20 (s, 3H, C=C-CH_3), 3.75 (s, 3H, NCH_3), 7.00-7.55 (m, 3H, aromatic protons).

Anal. Calcd. for $C_{12}H_9NOS_4$ (M = 311.1): C, 46.30; H, 2.89; N, 4.50; O, 5.14; S, 41.16. Found: C, 46.62; H, 2.92; N, 4.34; O, 5.53; S, 40.77.

Compound **1d** (5-(4-methoxy-phenyl)-1,2-dithiole-3-thione, sulfarlem^R) was a loan of Latema.

Electrochemistry Equipment.

Voltammetric studies were carried out in dimethylformamide with the standard three electrode configuration [a platinium working electrode, a platinium auxilary electrode, and a standard calomel reference electrode (SCE)] with a system composed of a Tacussel VAP 4 signal generator. The electrolyte was 0.1 *M* tetrabutylammonium tetrafluoroborate.

Polarograms in dimethylformamide were recorded on a Tacussel EPL 2. The recorder was equipped with a TIPOL plug-in.

General Electrolysis Procedure.

Electrolysis was carried out in a cell (10^{-3} mole of **1** *ca.* 1 g) with compartments separated by a porous glass diaphragm. A mercury pool was used as the cathode and a platinium plate as the anode. Stirring was magnetic. Studies were run at room temperature and in a nitrogen atmosphere. The electrolyte was 0.2 *M* anhydrous lithium perchlorate in anhydrous dimethylformamide. Electrolysis was carried out under controlled cathodic potential (− 1.2 V SCE) and coulometric measurements were made with an electronic integrator IG5 Tacussel coupled to the potentiostat PRT 20-2 Tacussel.

The solution turned red-brown. At the end of the electrolysis which needed 2 electrons per mole of dithiolethione, a large excess of methyl iodide (or benzyl chloride) was added. The solution slowly faded. After one hour (or one night) a large excess of cold water was added. The aqueous layer was extracted with toluene. The organic layer was washed with water to eliminate residual dimethylformamide, dried over sodium sulfate and evaporated in vacuum. The oily residue was purified through silica gel chromatography (benzene as eluent). An analytical sample was recrystallized.

Methyl (3-Methylthio)-3-(3-methyl-2-oxo-6-benzoxazolinyl)-2-phenyl-2-propenedithioate (**2a**) (*E, Z* mixture).

This compound was obtained in a yield of 34%, mp 117-120° (methanol); ir (potassium bromide): 1775 cm^{-1} (O-CO-N); ^{1}H nmr (deuteriochloroform): δ 1.80 (s, 3H, SCH_3 *Z*), 1.90 (s, 3H, SCH_3 *E*), 2.40 (s, 3H, CS_2CH_3 *E*), 2.75 (s, 3H, CS_2CH_3 *Z*), 3.35, 3.42 (2 singlets, 6H, NCH_3 *Z,E*), 6.70-7.60 (m, 8H, aromatic protons); ms: m/e 388 (M^+ + 1, base peak).

Anal. Calcd. for $C_{19}H_{17}NO_2S_3$ (M = 387.3): C, 58.92; H, 4.42; N, 3.61; O, 8.26; S, 24.79. Found: C, 58.85; H, 4.18; N, 3.79; O, 8.53; S, 24.39.

Methyl (3-Methylthio)-3-(3-methyl-2-thioxo-6-benzoxazolinyl)-2-phenyl-2-propenedithionate (**2b**) (*E, Z* mixture).

This compound was obtained in a yield of 42%, mp 128-129° (methanol); ^{1}H nmr (deuteriochloroform): δ 1.78 (s, 3H, SCH_3 *Z*), 1.90 (s, 3H, SCH_3 *E*), 2.36 (s, 3H, CS_2CH_3 *E*), 2.71 (s, 3H, CS_2CH_3 *Z*), 3.64, 3.70 (2 singlets, 6H, NCH_3 *Z,E*), 6.80-7.60 (m, 8H, aromatic protons); ms: m/e 404 (M^+ + 1, base peak).

Anal. Calcd. for $C_{19}H_{17}NOS_4$ (M = 403.6): C, 56.54; H, 4.24; N, 3.47; O, 3.97; S, 31.76. Found: C, 56.54; H, 4.30; N, 3.58; O, 4.28; S, 31.39.

Methyl (3-Methylthio)-3-(3-methyl-2-thioxo-6-benzoxazolinyl)-2-methyl-2-propenedithioate (**2c**) (*E, Z* mixture).

This compound was obtained in a yield of 25%, mp 101-102° (methanol); ^{1}H nmr (deuteriochloroform): δ 1.78 (s, 3H, SCH_3, *Z*), 1.90 (s, 3H, SCH_3 *E*), 2.35, 2.40 (2 singlets, 6H, C=C-CH_3, *Z,E*), 2.40 (s, 3H, CS_2CH_3, *E*), 2.72 (s, 3H, CS_2CH_3 *Z*), 3.64, 3.70 (2 singlets, 6H, NCH_3 *Z,E*), 6.70-7.55 (m, 3H, aromatic protons); ms: m/e 342 (M^+ + 1).

Anal. Calcd. for $C_{14}H_{15}NOS_4$ (M = 341.3): C, 49.28; H, 4.43; N, 4.10; O, 4.69; S, 37.51. Found: C, 48.93; H, 4.63; N, 4.25; O, 5.01; S, 37.18.

Methyl (3-Methylthio)-3-(4-methoxyphenyl)-2-propenedithioate (**2d**) (*E, Z* mixture) (lit [7]).

This compound was obtained in a yield of 62%, mp 78-80° (methanol) lit 79°; ^{1}H nmr (deuteriochloroform): δ 1.97 (s, 3H, SCH_3 *Z*), 3.35 (s, 3H, SCH_3 *E*), 2.45 (s, 3H, CS_2CH_3 *E*), 2.55 (s, 3H, CS_2CH_3 *Z*), 3.80 (s, 3H, OCH_3), 6.50-7.50 (m, 4H, aromatic protons and C=C-H).

Benzyl (3-Benzylthio)-3-(3-methyl-2-oxo-6-benzoxazolinyl)-2-phenyl-2-propenedithioante (**3a**) (*E, Z* mixture).

This compound was obtained in a yield of 54%, mp 119-121° (methanol); ir (potassium bromide): 1785 cm^{-1}, (O-CO-N); ^{1}H nmr (deuteriochloroform): δ 3.37, 3.42 (2 singlets, 6H, NCH_3 *Z,E*), 3.45 (s, 2H, SCH_2 *Z*), 3.50 (s, 2H, SCH_3 *E*), 4.25 (s, 2H, CS_2CH_2 *E*), 4.50 (s, 2H, CS_2CH_2 *Z*), 6.75-7.50 (m, 18H, aromatic protons); ms: m/e 540 (M^+ + 1), 358 (base peak).

Anal. Calcd. for $C_{31}H_{25}NO_2S_3$ (M = 539.5): C, 69.01; H, 4.67; N, 2.59; O, 5.93; S, 17.80. Found: C, 68.77; H, 5.03; N, 2.65; O, 6.25; S, 17.42.

Benzyl (3-Benzylthio)-3-(3-methyl-2-thioxo-6-benzoxazolinyl)-2-phenyl-2-propenedithioate (**3b**) (*E, Z* mixture).

This compound was obtained in a yield of 61%, mp 110-111° (methanol); ^{1}H nmr (deuteriochloroform): δ 3.43 (s, 2H, SCH_2 *Z*), 3.50 (s, 2H, SCH_2 *E*), 3.64, 3.70 (2 singlets, 6H, NCH_3 *Z,E*), 4.22 (s, 2H, CS_2CH_2 *E*), 4.50 (s, 2H, CS_2CH_2 *Z*), 6.75-7.50 (m, 18H, aromatic protons); ms: m/e 556 (M^+ + 1), 374 (base peak).

Anal. Calcd. for $C_{31}H_{25}NOS_4$ (M = 555.5): C, 67.03; H, 4.53; N, 2.52; O, 2.88; S, 23.04. Found: C, 66.83; H, 4.53; N, 2.39; O, 3.22; S, 22.79.

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