Tetrahedron Vol. 43, No. 15, pp. 3421 to 3428, 1987
Printed in Great Britain.

0040-4020/87 $3.00+.00

REACTIVITY OF SUBSTITUTED 1,2-DITHIOLE-3-THIONES WITH SODIUM ETHANETHIOLATE: A CONVENIENT ROUTE TO A NOVEL HETEROCYCLE.

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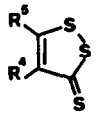
(*Received in Belgium* 19 *February* 1987)

Abstract - Sodium ethanethiolate reacts at the S-2 position of substituted 1,2-dithiole-3-thiones to give various products depending on the substituents at the C-4 and C-5 positions. In particular, the presence of a pyrimidinyl substituent induces some noticeable changes in the reaction pathway, yielding a novel heterocycle whose synthesis has not been previously reported.

This work is part of a program to elucidate the mechanism of the pharmacological action of 4-methyl-5-(2-pyrazinyl)-1,2-dithiole-3-thione (OLTIPRAZ, 35972 R.P.)[1]. This drug exhibits schistosomicidal activity[2] and is metabolized in mice to inactive pyrrolo [1,2-a] pyrazine derivatives[3]. In previous papers, a mechanistic interpretation of the biochemical process was proposed. These studies show that the same pyrrolo [1,2-a] pyrazine derivatives can be obtained in vitro by the use of nucleophiles[4] or by an electrochemical-reduction process[5].

It is notable that the major metabolites of OLTIPRAZ result from a 4e-reduction process and it is possible to distinguish several reduction steps which yield transient species that could be endowed with schistosomicidal activity. Thus, the isolation of such species is of particular interest from a pharmacological point of view.

The present paper deals with the chemical reactions of OLTIPRAZ analogues 1, 2 and 3 with sodium ethanethiolate, present in excess or in limited amounts, especially with respect to isolation of the transient metabolite and determination of its schistosomicidal activity in vitro.



1: R^5 = 2-pyridyl, R^4 = $COOC_2H_5$
2*: R^5 = 2-pyridyl, R^4 = CH_3
3: R^5 = 5-pyrimidinyl, R^4 = CH_3

*2 is devoid of schistosomicidal activity.

RESULTS AND DISCUSSION

The progress of the reaction was followed by U.V.-visible absorption spectrometry. The processes involved in the transformation are discussed according to the nature of the substituents at the C-4 and C-5 positions.

4-Ethoxycarbonyl-5-(2-pyridyl)-1,2-dithiole-3-thione 1 and 4-methyl-5-(2-pyridyl)-1,2-dithiole-3-thione 2.

The ability of 4-methyl-5-(2-pyrazinyl)-1,2-dithiole-3-thione (OLTIPRAZ) to produce the pyrrolo

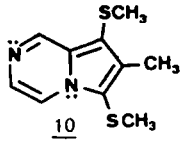
[1,2-a]pyrazine derivatives quantitatively in the presence of sodium ethanethiolate (EtS^-) has been previously reported[4].

The corresponding reactions of 1 and 2 give similar results. After methylation, the pyrrolo [1,2-a]pyridine species 4 and 5 (see scheme 1) are isolated in 80 and 50% yield respectively (see experimental section). Thus, replacement of pyrazine by pyridine at the C-5 position does not modify the reactivity of the dithiole-thione ring.

However, with limited amounts of EtS^-, the reaction of 2 gives three products all of which possess a pyrrolo[1,2-a]pyridine skeleton, as confirmed by ^1H N.M.R. and U.V.-visible absorption spectra (see experimental section). The major product, 6, is isolated in 70% yield. In addition, the reaction also gives compound 5 and the corresponding disulphide 7 in 10% yield (see scheme 1).

Compound 1 behaves similarly producing compounds 4, 8 and 9 in 5, 35 and 25% yield respectively. ^1H N.M.R., U.V.-visible absorption and mass spectroscopic data are consistent with the presence of pyrrolo[1,2-a]pyridine species.

It is also worth mentioning that the reaction of OLTIPRAZ with a small amount of EtS^-, followed by methylation, gives similar results (see experimental section) and affords the same kind of compounds 10, 11 and 12 in 35, 40 and 5% yield respectively.



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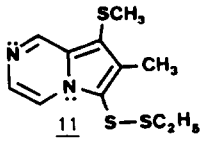

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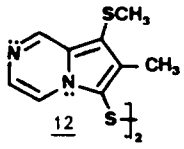

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Reaction pathway:

From these experimental results, we can conclude that attack by EtS^- at the S-2 position {eqn. (1), scheme 1} affords a convenient route to pyrrolo[1,2-a]pyridine (or pyrazine) species, a result which has been previously reported together with the alternative attack at the C-4 position[4]. We can now confirm that attack occurs at the S-2 position, since we have isolated compounds 6, 8 and 11, which could not have arisen from attack at the C-4 position. This attack is followed by intramolecular ring closure of 1'E (or 2'E) with elimination of molecular sulphur {eqn. (2) and (3)} yielding, after methylation, compound 6 (or 8), accompanied by compounds 5 and 7 (or 4 and 9).

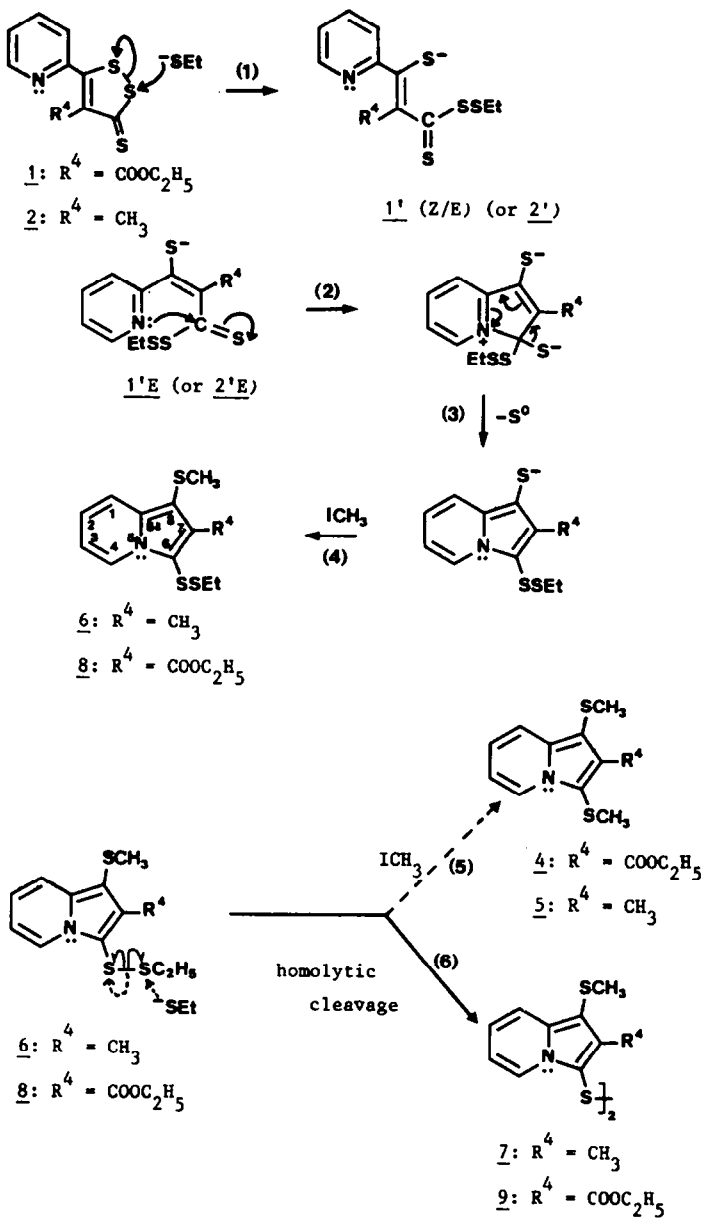
Compound 5 (or 4) most likely results from the reduction of 6 (or 8) with EtS^-. The fact that 5 (or 4) is the major product when using an excess of EtS^- is consistent with this hypothesis. Under these conditions, 6 (or 8) constitutes a transient species which is further reduced by EtS^- to give 5 (or 4). A homolytic cleavage of the disulphide bond may account for the formation of the disulphide 7 (or 9) {eqn. (6)}.

4-methyl-5-(5-pyrimidinyl)-1,2-dithiole-3-thione 3.

In this case, intramolecular ring-closure {eqn. (2)} can no longer occur and quite distinct behaviour can be expected in comparison with 1,2-dithiole-3-thiones 1, 2 and OLTIPRAZ.

After addition of an excess of EtS^- to the ethanolic stock solution of 3 at 20°C, a decrease of the absorption band at 425 nm, due to the starting material 3, is observed whilst two new bands develop at 345 and 510 nm. The absorption at 345 nm is compatible with a thiocarboxylate species[6]. Spectral changes show two isosbestic points at 390 and 480 nm, indicating that a simple reaction has taken place. However, after allowing the mixture to react for 20 min, a decrease of the absorption bands at 345 and 510 nm is observed and the isosbestic points disappear, indicating that the transient thiocarboxylate species 3" undergoes subsequent chemical reaction.

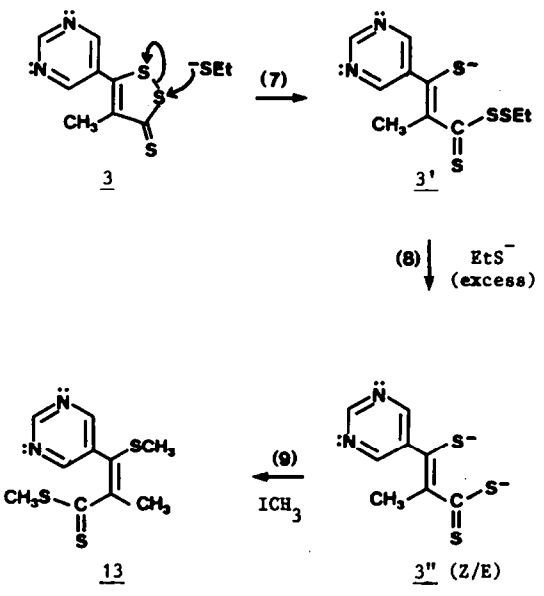
The reaction was stopped after 10 min in order to isolate the transient thiocarboxylate ion. Compound 13 was isolated, after methylation, as the E isomer, in 60% yield. ^1H and ^{13}C N.M.R., mass spectroscopic and U.V.-visible absorption data are consistent with structure 13 (see experimental section).



Scheme 1.

Assuming that the replacement of pyrazine or pyridine by pyrimidine does not strongly modify the reactivity of the dithiole-thione ring, nucleophilic attack at the S-2 position provides a satisfactory interpretation of these experimental results. This attack affords the transient species 3' {eqn. (7)} which cannot be isolated owing to its rapid reduction by excess EtS^- to give the thiocarboxylate transient species 3" {eqn. (8)}. Methylation of 3" yields 13 (scheme 2).

A different compound is isolated when the reaction is driven to completion at 35°C. After allowing the mixture to react for 5 min, a decrease in intensity of the absorption bands at 345 and 510 nm, characteristic of the transient thiocarboxylate ion 3", is observed whilst two new bands develop at 295 and 305 nm. Change in spectra shows an isosbestic point at 375 nm indicating that a simple reaction has taken place.



3 3' 13 3" (Z/E)

Scheme 2.

The reaction progresses slowly and is consistent with the following kinetics:

$$v = -dA_{510\ nm}/dt = k_{exp}|3''|\ ;\ k_{exp} = k|EtS^-| = 0.065\ min^{-1}\ \text{at}\ 35°C.$$

After methylation, the final compound was isolated in 80% yield. ^1H and ^{13}C N.M.R. and mass spectroscopic data are in agreement with structure 14. Raney Nickel desulphurization affords compound 15 {eqn. (14)} and allows us to confirm the structure of the final compound 14 which has not been previously described in the literature.

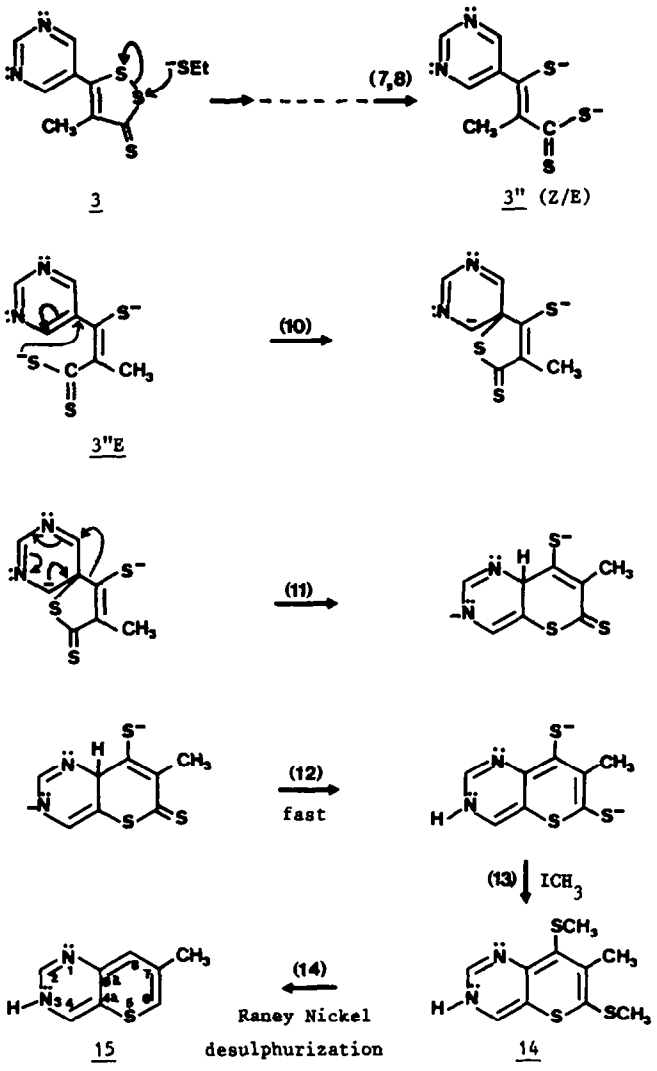
Reaction pathway:

From these experimental results, it can be deduced that 3 is transformed via attack by EtS^- at the S-2 position, according to the mechanistic pathway reported above (scheme 2). This attack yields the transient thiocarboxylate ion 3" which can exist as an E/Z mixture {eqn. (7) and (8)}. Intramolecular ring-closure of 3" (E) involves nucleophilic attack by the negative charge of the thiocarboxylate group to afford the spiro cycle {eqn. (10), scheme 3} which then undergoes a rearrangement {eqn. (11)}. Note that an analogous rearrangement is observed in the Smiles transposition[7]. After methylation, rearrangement yields compound 14 {eqn. (12) and (13)}.

It is possible to distinguish two kinds of behaviour, in the reaction of 1,2-dithiole-3-thiones 1, 2, 3 and OLTIPRAZ with sodium ethanethiolate in alcoholic medium:

1) Using 1, 2 or OLTIPRAZ as starting material, attack by EtS^- occurs at the S-2 position, providing a convenient route to pyrrolo [1,2-a] pyridine (or pyrazine) species 4 and 5 (or 10). 4 and 10 constitute the inactive metabolites of 1 and OLTIPRAZ respectively. It is worth mentioning that the transient species 8 and 11 which have not been previously described in the literature, are endowed with schistosomicidal activity in vitro. In contrast, the transient species 6 which is prepared from the inactive 1,2-dithiole-3-thione 2 is devoid of such activity. These results are of interest from a biological point of view as they may contribute to the understanding of the pharmacological activity of OLTIPRAZ.

2) Using 3 as starting material, attack by EtS^- occurs at the same S-2 position but is followed by a specific rearrangement affording compounds 14 and 15 whose syntheses have not yet been reported, to the best of our knowledge.



Scheme 3.

Acknowledgements: We are grateful to the RHONE-POULENC-society for providing us with the 1,2-dithiole-3-thiones. The authors would also like to thank Drs. M. BARREAU, M. MESSER and M. VUILHORGNE for fruitful discussions.

EXPERIMENTAL

General: 1,2-dithiole-3-thiones 1, 2, 3 and OLTIPRAZ, substituted at the C-4 and C-5 positions, were supplied by RHONE-POULENC-SANTE.

The solvents used for extractions and chromatography were obtained from S.D.S. (puran purity grade). Methyl iodide was a MERCK product and Raney Nickel was obtained from ALDRICH. Sodium ethanethiolate (EtS$^-$) was prepared by a previously described procedure[4].

U.V.-visible absorption spectra were recorded using a VARIAN DMS 90 spectrophotometer.

U.V.-visible absorption spectra data of substituted 1,2-dithiole-3-thiones at 20°C (100% ethanol):

1: λ_{nm} (ε_M-1 $_{cm}$-1): 220 (13000), 235 (10000, sh), 278 (11500), 312 (14000), 445 (7500);

2: 224 (12500), 240 (9000, sh), 275 (9500), 310 (12500), 435 (8500);

3: 225 (11500), 235 (10500, sh), 275 (10500), 320 (5000), 425 (8500);

^{1}H N.M.R. spectra were recorded on a BRUKER W.M. 270 (270 MHz) spectrometer. Chemical shifts are reported in p.p.m. relative to internal T.M.S. The multiplicity of the signal, the number of protons and the coupling constant are listed in that order.

^{13}C N.M.R. spectra were recorded on a BRUKER W.P. 200 SY spectrometer. The multiplicity of the signals was determined by off-resonance or by spin echo J. modulation sequence[8].

Mass spectra were recorded on a RIBER R 10-10 C spectrometer.

Chromatography was conducted on MERCK silica gel type 60 N° 9385. T.L.C. and preparative T.L.C. were performed using MERCK silica gel 60 F 254 N° 5714 and 5715 respectively.

6,8-Dimethythio-7-ethoxycarbonyl-pyrrolo [1,2-a] pyridine 4.

Sodium ethanethiolate (EtS^-) (1 mmol) was added to a solution of 1 (0.1 mmol) in ethanol (100 ml) under nitrogen, at 35°C. The reaction was allowed to go to completion and the resulting mixture methylated with an excess of methyl iodide (10 mmol). The solution was neutralised with dry-ice and evaporated to dryness in vacuo at 35°C. The residue was poured into water (20 ml) and then extracted with ethyl acetate (20 ml). The organic phase was dried over anhydrous sodium sulphate and evaporated to dryness in vacuo.

Chromatography (hexane-acetone 95:5 v/v) permitted separation of compound 4 as a colourless solid (23 mg; 80% yield; m.p. 64°C ±2°C).

^{1}H N.M.R., 270 MHz, $CDCl_3$, δ: 1.50 {t, 3H, CH_3 (7), ethyl}, 2.40 {s, 6H, SCH_3 (6) and SCH_3 (8)}, 4.50 {q, 2H, CH_2 (7), ethyl}, 6.80 {td, 1H, H (3), J (H_3-H_4) = 6.5 Hz, J (H_3-H_2) = 6.5 Hz, J (H_2-H_1) = 1 Hz}, 7.00 {ddd, 1H, H (2), J (H_2-H_1) = 9 Hz, J (H_2-H_3) = 6.5 Hz, J (H_2-H_4) = 1 Hz}, 7.80 {dd, 1H, H (1), J (H_1-H_2) = 9 Hz, J (H_1-H_3) = 1 Hz}, 8.55 {dd, 1H, H (4), J (H_4-H_3) = 6.5 Hz, J (H_4-H_2) = 1 Hz}.

mass spectrum (E.I.): m/z = 281 ($M^{+\cdot}$) (100%); m/z = 266 (M - CH_3); m/z 236 (M - OC_2H_5); m/z = 146 m/z = 122; m/z = 78.

U.V.-visible (100% ethanol), λ_{max} (ε_M cm^{-1} mm^{-1}): 240 (25000), 315 (4700), 350 (2700).

Elemental analysis: found (C, 55.23; H, 5.43; N, 4.80; S, 22.51%) $C_{13}H_{15}NO_2S_2$ requires (C, 55.52, H, 5.34; N, 4.98; S, 22.78%).

6,8-Dimethylthio-7-methyl-pyrrolo [1,2-a] pyridine 5, 7-methyl-8-methylthio-pyrrolo [1,2-a] pyridine unsymmetrical disulphide 6 and 7-methyl-8-methylthio-pyrrolo [1,2-a] pyridine disulphide 7.

a) Using the above mentioned method, 2 yielded a mixture of products. Preparative T.L.C. (hexane-acetone 10:1 v/v) provided a major product 5 (12 mg, 50% yield) and a minor product 6 (6 mg, 20% yield).

Compound 5 was a yellow oil:

^{1}H N.M.R., 270 MHz, $CDCl_3$, δ: 2.18 {s, 3H, SCH_3 (6) or SCH_3 (8) or CH_3 (7)}, 2.22 {s, 3H, SCH_3 (6) or SCH_3 (8) or CH_3 (7)}, 2.50 {s, 3H, SCH_3 (6) or SCH_3 (8) or CH_3 (7)}, 6.65 {td, 1H, H (3), J (H_3-H_4) = 6.5 Hz, J (H_3-H_2) = 6.5 Hz, J (H_3-H_1) = 1.5 Hz}, 6.90 {ddd, 1H, H (2), J (H_2-H_1) = 9 Hz, J (H_2-H_3) = 6.5 Hz, J (H_2-H_4) = 1.5 Hz}, 7.65 {dd, 1H, H (1), J (H_1-H_2) = 9 Hz, J (H_1-H_3) = 1.5 Hz}, 8.40 {dd, 1H, H (4), J (H_4-H_3) = 6.5 Hz, J (H_4-H_2) = 1.5 Hz}.

mass spectrum, (E.I.): m/z = 223 ($M^{+\cdot}$); m/z = 208 (M - CH_3) (100%); m/z = 193 (M - CH_3 - CH_3).
(D.C.I.): m/z = 224 (MH^+).

U.V.-visible (100% ethanol), λ_{max} (ε_M cm^{-1} mm^{-1}): 254 (20000), 300 (3700), 314 (4700), 346 (2200).

Elemental analysis: found (C, 59.00; H, 5.72; N, 6.14; S, 28.97%) $C_{11}H_{13}NS_2$ requires (C, 59.19; H, 5.83; N, 6.28; S, 28.70%).

Compound 6 was a colourless oil:

^{1}H N.M.R., 270 MHz, $CDCl_3$, δ: 1.40 {t, 3H, CH_2, ethyl}, 2.20 {s, 3H, CH_3 (7) or SCH_3 (8)}, 2.55 {s, 3H, CH_3 (7) or SCH_3 (8)}, 2.80 {q, 2H, CH_2 (ethyl)}, 6.75 {td, 1H, H (3), J (H_3-H_4) = 7 Hz, J (H_3-H_2) = 7 Hz, J (H_3-H_1) = 1 Hz}, 7.00 {ddd, 1H, H (2), J (H_2-H_1) = 9 Hz, J (H_2-H_3) = 7 Hz, J (H_2-H_4) = 1 Hz}, 7.70 {dd, 1H, H (1), J (H_1-H_2) = 9 Hz, J (H_1-H_3) = 1 Hz}, 8.45 {dd, 1H, H (4), J (H_4-H_3) = 7 Hz, J (H_4-H_2) = 1 Hz}.

mass spectrum (E.I.): m/z = 269 ($M^{+\cdot}$); m/z = 208 (M - SC_2H_5) (100%); m/z = 193 (M - SC_2H_5 - CH_3).

U.V.-visible (100% ethanol), λ_{max} (ε_M cm^{-1} mm^{-1}): 245 (20000), 302 (6500), 316 (7000), 345 (4900).

Elemental analysis: found (C, 53.26; H, 5.60; N, 5.00; S, 35.70%) $C_{12}H_{15}NS_3$ requires (C, 53.53; H, 5.58; N, 5.20; S, 35.89%).

b) The above method with 2 = 0.1 mmol, EtS^- = 0.4 mmol and ICH_3 = 10 mmol yielded a mixture of products. Preparative T.L.C. (hexane-acetone 10:1 v/v) provided a major product 6 (19 mg, 70% yield) and two minor products 5 (2.5 mg, 10% yield) and 7 (4 mg, 10% yield).

Compound 7 was a yellow solid (m.p. 100°C ±2°C):

^{1}H N.M.R., 270 MHz, $CDCl_3$, δ: 2.15 {s, 3H, CH_3 or SCH_3}, 2.20 {s, 3H, CH_3 or SCH_3}, 6.60 {m, 2H, H (2) and H (3)}, 6.90 {dd, 1H, H (1), J (H_1-H_2) = 8.5 Hz, J (H_1-H_3) = 1.5 Hz}, 8.30 {dd, 1H, H (4), J (H_4-H_3) = 6.5 Hz, J (H_4-H_2) = 1 Hz}.

mass spectrum (D.C.I.): m/z = 417 (MH^+).

U.V.-visible (100% ethanol), λ_{max} (ε_M cm^{-1} mm^{-1}): 250 (22000), 315 (8000), 360 (6500, broad band).

Elemental analysis: found (C, 57.49; H, 4.81; N, 6.40; S, 29.92%) $C_{20}H_{20}N_2S_4$ requires (C, 57.69; H, 4.81; N, 6.73; S, 30.77%).

7- Ethoxycarbonyl-8-methylthio-pyrrolo [1,2-a] pyridine unsymmetrical disulphide 8 and 7-ethoxycarbonyl-8-methylthio-pyrrolo [1,2-a] pyridine disulphide 9.

The above method with 1 = 0.1 mmol, EtS^- = 0.2 mmol and ICH_3 = 10 mmol yielded a mixture of products.

Preparative T.L.C. (hexane-acetone 3:1) provided compounds 4 (1.5 mg, 5% yield), 8 (11.5 mg, 35% yield) and 9 (13.5 mg, 25% yield).
Spectroscopic data for 4 have been reported above.
Compound 8 was a yellow oil:

^{1}H N.M.R., 270 MHz, $CDCl_3$, δ: 1.40 {t, 3H, CH_2 (6), ethyl}, 1.50 {t, 3H, CH_3 (7), ethyl}, 2.40 {s, 3H, SCH_3 (8)}, 2.80 {q, 2H, CH_2 (6), ethyl}, 4.50 {q, 2H, CH_2 (7), ethyl}, 6.90 {ddd, 1H, H (3), J (H_3-H_2) = 7 Hz, J (H_3-H_4) = 7 Hz, J (H_3-H_1) = 1.5 Hz}, 7.10 {ddd, 1H, H (2), J (H_2-H_3) = 7 Hz, J (H_2-H_1) = 9 Hz, J (H_2-H_4) = 1.5 Hz}, 7.85 {dd, 1H, H (1), J (H_1-H_2) = 9 Hz, J (H_1-H_3) = 1.5 Hz}, 8.55 {dd, 1H, H (4), J (H_4-H_3) = 7 Hz, J (H_4-H_2) = 1.5 Hz}.
mass spectrum (E.I.): m/z = 327 ($M^{+\cdot}$); m/z = 266 (M - SC_2H_5) (100%).
U.V.-visible (100% ethanol), λ_{nm} (ε_M cm^{-1}): 240 (26000), 315 (6000), 350 (4000).
Elemental analysis: found (C, 51.00; H, 5.85; N, 4.20; S, 29.32%) $C_{14}H_{17}NO_2S_3$ requires (C, 51.38; H, 6.00; N, 4.28; S, 29.36%).
Compound 9 was an orange solid (m.p. 120°C ± 2°C):

^{1}H N.M.R., 270 MHz, $CDCl_3$, δ: 1.40 {t, 3H, CH_2 (7), ethyl}, 2.35 {s, 3H, SCH_3 (8)}, 4.30 {q, 2H, CH_2 (7), ethyl}, 6.65 {m, 2H, H (2) and H (3)}, 7.00 {t, 1H, H (1)}, 8.40 {t, 1H, H (4)}.
mass spectrum (E.I.): m/z = 532 ($M^{+\cdot}$); m/z = 266 (100%) (M/2, monomer radical).
Elemental analysis: found (C, 54.00; H, 4.49; N, 5.15; S, 24.00%) $C_{24}H_{24}N_2S_4O_4$ requires (C, 54.14; H, 4.51; N, 5.26; S, 24.06%).

6,8-Dimethylthio-7-methyl-pyrrolo[1,2-a]pyrazine 10, 7-methyl-8-methylthio-pyrrolo[1,2-a]pyrazine unsymmetrical disulphide 11 and 7-methyl-8-methylthio-pyrrolo[1,2-a]pyrazine disulphide 12.

Using OLTIPRAZ as the starting material, the above method (EtS^- = 0.2 mmol and ICH_3 = 10 mmol) gave a mixture of products. Preparative T.L.C. (toluene-acetone 90:10 v/v) provided compounds 10 (8 mg, 35% yield), 11 (9.5 mg, 20% yield) and 12 (2 mg, 5% yield).

^{1}H N.M.R., U.V.-visible and mass spectroscopic data concerning 10 and 12 were in agreement with previous data[4,5].
Compound 11 was a pale yellow oil:

^{1}H N.M.R., 270 MHz, $CDCl_3$, δ: 1.40 {t, 3H, CH_2, ethyl}, 2.25 {s, 3H, SCH_3 (8) or CH_3 (7)}, 2.55 {s, 3H, SCH_3 (8) or CH_3 (7)}, 2.80 {q, 2H, CH_2, ethyl}, 7.80 {d, 1H, H (3), J (H_3-H_4) = 5 Hz}, 8.25 {dd, 1H, H (4), J (H_4-H_3) = 5 Hz, J (H_4-H_1) = 2 Hz}, 9.05 {s, 1H, H (1), J (H_1-H_4) = 2 Hz}.
mass spectrum (E.I.): m/z = 270 ($M^{+\cdot}$); m/z = 209 (100%) (M - SC_2H_5).
U.V.-visible (100% ethanol), λ_{nm} (ε_M cm^{-1}): 245 (18000), 304 (3500), 314 (3500), 350 (3500).
Elemental analysis: found (C, 48.75; H, 5.15; N, 10.29; S, 35.49%) $C_{11}H_{14}N_2S_3$ requires (C, 48.89; H, 5.19; N, 10.37; S, 35.55%).

3-Methylthio-3-(5-pyrimidinyl)-2-propene-methyl-dithioate 13.

Sodium ethanethiolate (2 mmol) was added to a solution of 3 (0.1 mmol) in ethanol (100 ml), under nitrogen at 20°C. The resulting mixture was allowed to react for 10 min and then methylated with an excess of methyl iodide (10 mmol). The solution was neutralised with dry-ice and evaporated to dryness in vacuo at 35°C. The residue was poured into water (20 ml) and then extracted with ethyl acetate (20 ml). The organic phase was dried over anhydrous sodium sulphate and evaporated to dryness in vacuo.
Chromatography (hexane-acetone 5:1 v/v) enabled the separation of a major product 13 as the E isomer (16 mg, 60% yield, m.p. 49°C ± 2°C).
^{1}H, ^{13}C N.M.R. spectra, U.V.-visible absorption and mass spectroscopic data have been reported previously[4].

6,8-Dimethylthio-7-methyl-3H-thiopyrano[3,2-d]pyrimidine 14.

Using the previous method (EtS^- = 2 mmol and ICH_3 = 10 mmol), and allowing the reaction with 3 (0.1 mmol) to go to completion at 35°C, gave a yellow oil.
Chromatography (hexane-acetone 3:1 v/v) enabled the separation of compound 14 as a pale yellow solid (20 mg, 80% yield, m.p. 138°C ± 2°C).

^{1}H N.M.R., 270 MHz, DMSO d^6, δ: 2.2 {s, 3H, CH_3 (7) or SCH_3 (6) or SCH_3 (8)}, 2.3 {s, 3H, CH_3 (7) or SCH_3 (6) or SCH_3 (8)}, 2.4 {s, 3H, CH_3 (7) or SCH_3 (6) or SCH_3 (8)}, 7.7 {bd, 1H, H (4)}, 7.9 {bd, 1H, H (2)}, 12.3 {bs, 1H, NH}.
^{13}C N.M.R., 50.3 MHz, $CDCl_3$, δ: 14.5 {q, $\underline{C}H_3$ (7) or $S\underline{C}H_3$ (6) or $S\underline{C}H_3$ (8)}, 18.8 {q, $\underline{C}H_3$ (7) or $S\underline{C}H_3$ (6) or $S\underline{C}H_3$ (8)}, 21.5 {q, $\underline{C}H_3$ (7) or $S\underline{C}H_3$ (6) or $S\underline{C}H_3$ (8)}, 117.7 {d, $\underline{C}H$ (4)}, 135.3 {d, $\underline{C}H$ (2)}, 127.0 {s, quaternary $\underline{C}$}, 141.0 {s, quaternary $\underline{C}$}, 144.0 {s, quaternary $\underline{C}$}.
mass spectrum (E.I.): m/z = 256 ($M^{+\cdot}$); m/z = 223 (M - $S\underline{H}$).
U.V.-visible (100% ethanol), λ_{nm} (ε_M cm^{-1}): 230 (8000, sh), 265 (4500, sh), 310 (10000).
Elementeal analysis: found (C, 46.63; H, 4.72; N, 10.69; S, 37.60%) $C_{10}H_{12}N_2S_3$ requires (C, 46.87; H, 4.69; N, 10.94; S, 37.50%).

7-Methyl-3H-thiopyrano[3,2-d]pyrimidine 15.

120 mg of Raney Nickel (50% in neutral aqueous suspension) was added to a solution of 14 (0.8 mmol) in dioxane (5 ml), under nitrogen at 70°C. After allowing the mixture to react for 4 hrs, a black precipitate was filtered off and the filtrate extracted with dichloromethane. The organic phase was dried over anhydrous sodium sulphate and evaporated to dryness in vacuo at 35°C.
Chromatography (hexane-acetone 2:1 v/v) enabled the separation of compound 15 as a yellow oil (40 mg, 20% yield).

^{1}H N.M.R., 270 MHz, DMSO d^{6}, δ: 2.25 {dd, 3H, CH_3 (7)}, 6.80 {quintuplet, 1H, H (6)}, 7.05 {d, 1H, H (8)}, 7.25 {bd, 1H, H (4)}, 7.65 {bd, 1H, H (2)}, 10.70 {bs, 1H, NH}.
^{13}C N.M.R., 50.3 MHz, DMSO d^{6}, δ: 16.1 {q, $\underline{C}H_3$ (7)}, 114.3 {d, $\underline{C}$ (8)}, 119.2 {d, $\underline{C}$ (6)}, 125.1 {d, $\underline{C}$ (4)}, 135.8 {d, $\underline{C}$ (2)}, 135.1 {s, quaternary $\underline{C}$}, 136.8 {s, quaternary $\underline{C}$}, 138.6 {s, quaternary $\underline{C}$}
mass spectrum (E.I.): m/z = 164 ($M^{+\cdot}$); m/z = 137 (M - HCN); m/z = 131 (M - SH); m/z = 124; m/z = 110; m/z = 69.
U.V.-visible (100% ethanol), λ_{nm} (ε_M-1$_{cm}$-1): 282 (9350, maximum).

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