The Preparation and Rearrangements of 5-Acyl-2-phenyl-4-substituted 6*H*-1,3-Thiazines. *X*-Ray Molecular Structure of 3-Acetyl-2-ethoxycarbonyl-4-(3-oxobutylthio)-5-phenylpyrrole

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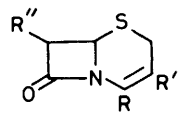
5-Acyl-2-phenyl-4-substituted 6*H*-1,3-thiazines are prepared by the reaction of *N'*,*N'*-substituted *N*²-thiobenzoylformamidines with methyl vinyl ketone or acrylaldehyde. Rearrangement catalysed by base and subsequent condensation with the acrylic reagent gives substituted pyrrolyl sulphides or substituted 2,6-dihydrothiopyrano[2,3-*c*]pyrrole.

6-*H*-1,3-Thiazines, 3,6-dihydro-2*H*-1,3-thiazines, and their derivatives are important intermediates in the total synthesis of cephems (**1a**)[1-3] and cephalosporins (**1b**).[4] The principle of the

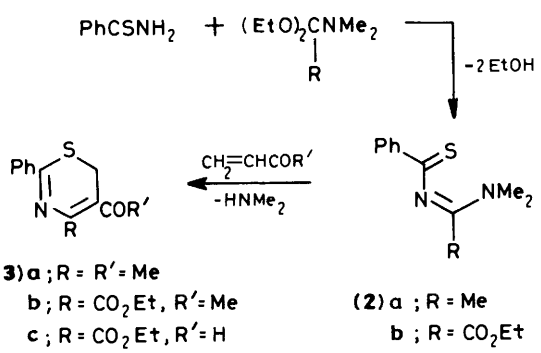


(**1**) a ; R = H
b; R = CO_2H

preparation of the 6*H*-1,3-thiazines by a [4 + 2] cycloaddition between thioacylformamidines and acrylic compounds is illustrated in our previous publications.[5,6] We now report our work on a thiazine model substituted at position 2 by a phenyl group, since we were interested in the possibility of introducing an ester group or a potentially oxidizible methyl group in order to obtain the required substitution pattern corresponding to the carboxyl group at position 4 of the cephalosporins.

Results and Discussion

Orthoamides react with thiobenzamide to give the *N*²-thioacylformamidines (**2a** and **b**) (Scheme 1).



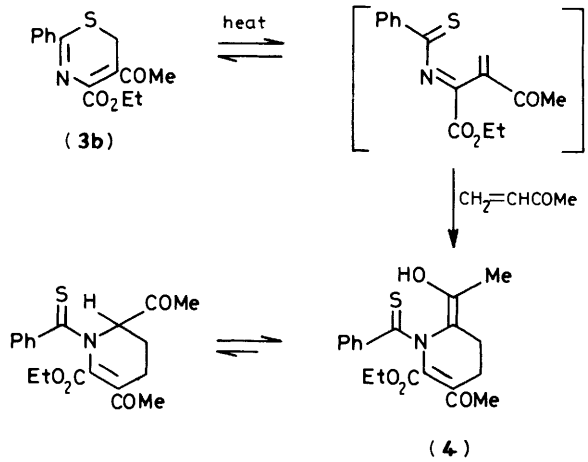
(**3**) a ; R = R' = Me
b ; R = CO_2Et, R' = Me
c ; R = CO_2Et, R' = H

(**2**) a ; R = Me
b ; R = CO_2Et

Scheme 1.

Monocondensation of the Acrylic Reagents.—The monocondensation of methyl vinyl ketone (MVK) with the acetamidine (**2a**) is carried out at 140 °C in an autoclave: the 6*H*-1,3-thiazine (**3a**) is obtained in quantitative yield (Scheme 1). In the case of the thioacylformamidine (**2b**) substituted by an ester group, condensation of the acrylic reagent only occurs under acid catalysis ($AlCl_3$; Amberlyst 15). Under these conditions, the monocondensation of the acrylic takes place at room temperature and affords, as in the previous case, the expected thiazines (**3b** and **c**).

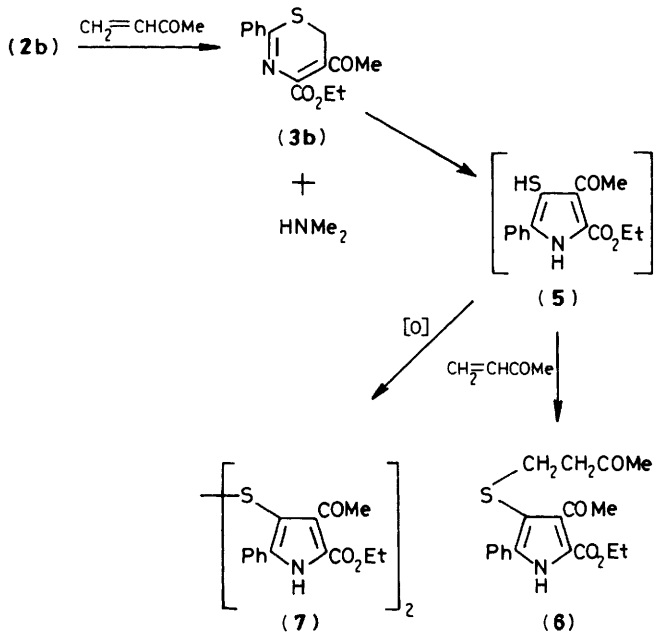
Bicondensation of the Acrylic Reagents.—If the condensation of the formamidine (**2b**) with MVK is carried out in refluxing toluene or in benzene (140 °C, autoclave), instead of the thiazine (**3b**) a product with a molecular weight corresponding to the addition of a second molecule of methyl vinyl ketone is obtained (Scheme 2). We observed no reaction between MVK dimer[7]



Scheme 2.

and the *N*-thioacylformamidine (**2b**). We thought that we could obtain the thiobenzoyltetrahydropyridine (**4**) from the condensation of the MVK with the thiobenzoylazadiene intermediate.[8] This was itself the product of the cycloreversion of the thiazine formed in the first step.[9]

The n.m.r. spectra, however, were not in complete agreement with the proposed structures. The structure was established by *X*-ray crystallography as the pyrrol-3-yl sulphide (Figure), (**6**) formed in three steps (Scheme 3): (a) condensation of the thioacylformamidine (**2b**) with one molecule of MVK to give the 6*H*-1,3-thiazine (**3b**); (b) contraction of the thiazine ring of compound (**3b**) to give the mercaptopyrrole (**5**); (c) Michael



Scheme 3.

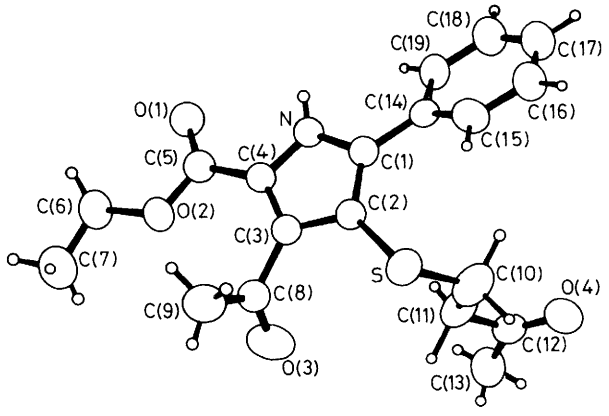


Figure. General view of pyrrol-3-yl sulphide (6)

addition of the thiol group to a second molecule of MVK to give the isolated product (6).

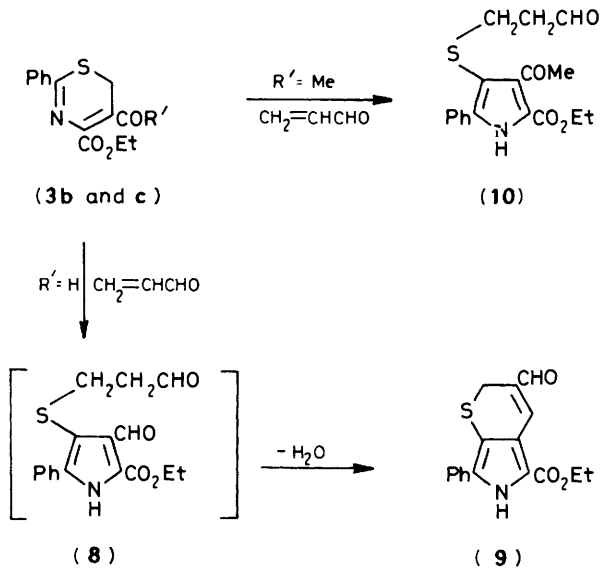
We confirmed that the thiazine (3b) did indeed react with MVK (140 °C, autoclave), with or without dimethylamine, to give the pyrrolyl sulphide (6).

The second step was also verified. The previous procedure was repeated without addition of MVK. At 140 °C (autoclave) with dimethylamine (or triethylamine), the thiazine (3b) afforded the disulphide (7), which resulted from the oxidation, in basic medium, of the mercaptopyrrole (5). The role of base in the rearrangement was also confirmed. Thus, compound (3b), when treated with sodium hydride [tetrahydrofuran (THF); 0 °C] gave the disulphide (7) in excellent yield.

If the above procedures are carried out using acrylaldehyde instead of MVK, the corresponding pyrrolyl sulphide (8) is not isolated: it undergoes dehydrative cyclization to give the 2,6-dihydrothiopyrano[2,3-*c*]pyrrole (9) (Scheme 4).

This dehydration seems related to the nature of the functional group in position 4 of the pyrrolyl sulphide (8). Thus the action of acrylaldehyde on compound (3b) affords the pyrrolyl sulphide (10) (Scheme 4).

With *N*-thioacylformamidines (2) as starting materials, it is



Scheme 4.

therefore possible to obtain 6*H*-1,3-thiazines (3) in an acid medium, and functionalized pyrrolyl sulphides (6) and (9) in a basic medium.

Experimental

^{1}H N.m.r. spectra were recorded at 60 (Perkin-Elmer R24) and 250 MHz (Bruker instruments). ^{13}C N.m.r. spectra were determined on a 90 MHz (Bruker WH 90) spectrometer. $SiMe_4$ was used as internal reference. Column chromatography was carried out using silica gel (Merck Art. 1385 Kieselgel 60). M.p.s were determined using an RCH (C. Reichert) microscope with a Kofler heating stage. Light petroleum refers to that fraction boiling in the range 40—65 °C.

N^1,N^1-*Dimethyl*-N^2-*thiobenzoylacetamidine* (2a).—The orthoamide of dimethylacetamide[10] (1.18 g, 7.3 mmol) was added to thiobenzamide (1 g, 7.3 mmol). Orange crystals of the title formamidine were formed rapidly and were recrystallized from ethanol to give *compound* (2a) (1.47 g, 98%), m.p. 113—114 °C; $\delta_H(CDCl_3)$ (*inter alia*) 3.06 (6 H, s, NMe_2) and 2.40 (3 H, s, CH_3); $\delta_C(CDCl_3)$ (*inter alia*) 201.3 (C=S) and 168.2 p.p.m. (C=N) (Found: C, 64.3; H, 6.7; S, 15.7. $C_{11}H_{14}N_2S$ requires C, 64.04; H, 6.84; S, 15.54%).

Preparation of the Orthoamide of Ethyl N,N-*Dimethyloxamate* [*Ethyl Tris(dimethylamino)acetate*].—Diethyl oxalate (146 g, 1 mol) was treated with dimethylamine (45 g, 1 mol) in an autoclave at room temperature for 5 h. The ethyloxamate was distilled under reduced pressure, b.p. 84 °C at 0.8 mmHg (124.70 g, 86%). Triethyloxonium tetrafluoroborate[10] (190 g, 1 mol) was added to the ethyl oxamate (145 g, 1 mol). The mixture was stirred for 1 h under reflux of the liberated ether. The viscous layer which formed was added dropwise to a stirred solution of sodium ethoxide (68 g, 1 mol) in ethanol (640 ml). The ethanol solution was filtered to remove the sodium tetrafluoroborate which had formed. After evaporation of the ethanol, the orthoamide was distilled under reduced pressure, b.p. 58—64 °C at 0.8 mmHg (131.4 g, 60%).

Preparation of 1-*Ethoxycarbonyl*-N^1,N^1-*dimethyl*-N^2-*thiobenzoylformamidine* (2b).—The orthoamide of ethyl *N,N*-dimethyloxamate (1.59 g, 7.3 mmol) was added to a solution of

Table 1. Calculated fractional co-ordinates ($\times 10^4$; for S, $\times 10^5$) for the non-hydrogen atoms with estimated standard deviations in parentheses

Atom	*x*	*y*	*z*
S	76 160(1)	−413(9)	3 834(5)
O(1)	5 746(3)	5 224(2)	1 468(2)
O(2)	6 843(3)	5 131(2)	360(1)
O(3)	9 172(3)	2 847(3)	−74(2)
O(4)	10 819(3)	−1 382(4)	2 294(2)
N	5 994(3)	2 608(3)	1 589(2)
C(1)	6 270(3)	1 388(3)	1 493(2)
C(2)	7 018(3)	1 299(3)	832(2)
C(3)	7 180(3)	2 499(3)	538(2)
C(4)	6 522(3)	3 299(3)	1 007(2)
C(5)	6 319(4)	4 641(3)	996(2)
C(6)	6 718(4)	6 466(4)	259(2)
C(7)	7 324(5)	6 775(4)	−491(3)
C(8)	7 991(3)	2 816(3)	−157(2)
C(9)	7 274(4)	2 982(5)	−929(2)
C(10)	8 783(5)	−683(4)	1 111(3)
C(11)	9 849(5)	136(4)	1 378(4)
C(12)	10 888(4)	−403(4)	1 975(2)
C(13)	12 074(5)	359(4)	2 069(3)
C(14)	5 862(3)	447(3)	2 062(2)
C(15)	5 658(4)	−782(4)	1 838(2)
C(16)	5 352(4)	−1 667(4)	2 385(2)
C(17)	5 203(4)	−1 327(4)	3 153(2)
C(18)	5 352(4)	−11(4)	3 377(2)
C(19)	5 693(4)	763(3)	2 844(2)

Table 2. Interatomic distances (Å) and angles (°), with estimated standard deviations in parentheses

(a) Bond lengths

S–C(2)	1.760(2)	C(3)–C(8)	1.517(3)
S–C(10)	1.792(4)	C(4)–C(5)	1.464(3)
O(1)–C(5)	1.197(3)	C(6)–C(7)	1.485(4)
O(2)–C(5)	1.340(3)	C(8)–C(9)	1.469(4)
O(2)–C(6)	1.456(3)	C(10)–C(11)	1.442(5)
O(3)–C(8)	1.189(3)	C(11)–C(12)	1.527(5)
O(4)–C(12)	1.193(3)	C(12)–C(13)	1.452(5)
N–C(1)	1.359(3)	C(14)–C(15)	1.392(4)
N–C(4)	1.373(3)	C(14)–C(19)	1.394(3)
C(1)–C(2)	1.395(3)	C(15)–C(16)	1.382(4)
C(1)–C(14)	1.478(3)	C(16)–C(17)	1.373(4)
C(2)–C(3)	1.403(3)	C(17)–C(18)	1.373(4)
C(3)–C(4)	1.373(3)	C(18)–C(19)	1.368(4)

(b) Bond angles

C(2)–S–C(10)	104.3(1)	O(2)–C(6)–C(7)	106.7(3)
C(5)–O(2)–C(6)	116.8(2)	O(3)–C(8)–C(3)	119.8(2)
C(1)–N–C(4)	110.5(2)	O(3)–C(8)–C(9)	128.4(3)
N–C(1)–C(2)	106.7(2)	C(3)–C(8)–C(9)	117.7(2)
N–C(1)–C(14)	121.4(2)	S–C(10)–C(11)	115.0(3)
C(2)–C(1)–C(14)	131.7(2)	C(10)–C(11)–C(12)	116.1(4)
S–C(2)–C(1)	128.5(2)	O(4)–C(12)–C(11)	125.8(3)
S–C(2)–C(3)	123.7(2)	O(4)–C(12)–C(13)	121.5(3)
C(1)–C(2)–C(3)	107.7(2)	C(11)–C(12)–C(13)	112.5(3)
C(2)–C(3)–C(4)	107.7(2)	C(1)–C(14)–C(15)	121.3(2)
C(2)–C(3)–C(8)	124.5(2)	C(1)–C(14)–C(19)	120.7(2)
C(4)–C(3)–C(8)	127.8(2)	C(15)–C(14)–C(19)	118.0(2)
N–C(4)–C(3)	107.4(2)	C(14)–C(15)–C(16)	120.8(3)
N–C(4)–C(5)	119.2(2)	C(15)–C(16)–C(17)	119.8(3)
C(3)–C(4)–C(5)	133.4(2)	C(16)–C(17)–C)18)	120.2(3)
O(1)–C(5)–O(2)	124.3(2)	C(17)–C(18)–C(19)	120.3(3)
O(1)–C(5)–C(4)	125.8(2)	C(14)–C(19)–C(18)	120.9(3)
O(2)–C(5)–C(4)	109.9(2)		

thiobenzamide (1 g, 7.3 mmol) in THF (30 ml). The reaction mixture was stirred at 60°C for 12 h. The formamidine was purified over silica gel. Elution with light petroleum–ethyl acetate (80:20) gave compound (**2b**) (1.73 g, 90%), m.p. 124 °C; $\delta_H(CDCl_3)$ (*inter alia*) 4.16 (2 H, q, $^3J_{HH}$ 7 Hz, CH_2), 3.10 (6 H, s, NMe_2), and 1.23 (3 H, t, $^3J_{HH}$ 7 Hz, CH_3); $\delta_C(CDCl_3)$ (*inter alia*) 212.7 (C=S) and 160.6 p.p.m. (C=N) (Found: C, 59.2; H, 5.9; N, 10.4. $C_{13}H_{16}N_2O_2S$ requires C, 59.06; H, 6.10; N, 10.60%).

5-Acetyl-4-methyl-2-phenyl-6H-1,3-*thiazine* (**3a**).—A solution of compound (**2a**) (1 g, 4.85 mmol) in benzene (30 ml) containing freshly distilled MVK (3 ml) was stirred at 140 °C (autoclave) for 5 h. The thiazine thus obtained was purified over silica gel. Elution with light petroleum–ethyl acetate (80:20) gave the *title thiazine* (**3a**) (1.09 g, 98%), m.p. 75—77 °C; $\delta_H(CDCl_3)$ (*inter alia*) 3.61 (2 H, s, CH_2) and 2.40 (6 H, s, CH_3 and $COCH_3$); $\delta_C(CDCl_3)$ (*inter alia*) 164.9 (s, C=N) and 25.1 p.p.m. (t, $J_{^{13}C-H}$ 145 Hz, heterocyclic CH_2); (Found: C, 67.9; H, 5.6; S, 13.9. $C_{13}H_{13}NOS$ requires C, 67.49; H, 5.66; S, 13.86%).

General Procedure for the Preparation of 4-*Ethoxycarbonyl*-6H-1,3-*thiazines* (**3b** and **c**).—To a solution of compound (**2b**) (1.14 g, 4.3 mmol) in CH_2Cl_2 (30 ml) at 0 °C were added MVK or acrylaldehyde (2 ml) and $AlCl_3$ (0.4 g, 3 mmol). The mixture was stirred for 3 h at this temperature and then for 12 h at room temperature. After hydrolysis [water (40 ml)] and decantation, the thiazine was purified over silica gel. Elution with light petroleum–ethyl acetate (80:20) gave the thiazine (**3b** or **c**).

5-Acetyl-4-ethoxycarbonyl-2-phenyl-6H-1,3-*thiazine* (**3b**). Yield 1.11 g (90%), m.p. 66—67 °C; $\delta_H(CDCl_3)$ (*inter alia*) 3.69 (2 H, s, CH_2) and 2.42 (3 H, s, $COCH_3$); $\delta_C(CDCl_3)$ (*inter alia*) 167 (s, C=N) and 24.5 p.p.m. (t, $J_{^{13}C-H}$ 145 Hz, heterocyclic CH_2); (Found: C, 62.0; H, 5.2; S, 11.0. $C_{15}H_{15}NO_3S$ requires C, 62.26; H, 5.22; S, 11.08%).

4-Ethoxycarbonyl-5-formyl-2-phenyl-6H-1,3-*thiazine* (**3c**). Yield 1.06 g (90%), m.p. 88—90 °C; $\delta_H(CDCl_3)$ (*inter alia*) 10.54 (1 H, s, CHO) and 3.72 (2 H, s, CH_2); $\delta_C(CDCl_3)$ (*inter alia*) 171 (s, C=N) and 21 p.p.m. (t, $J_{^{13}C-H}$ 147 Hz, heterocyclic CH_2); (Found: C, 60.9; H, 4.6; S, 11.6. $C_{14}H_{13}NO_3S$ requires C, 61.07; H, 4.76; S, 11.65%).

General Procedure for the Preparation of Pyrroles (**6**) and (**9**) *from the Amidine* (**2b**).—Compound (**2b**) (1.14 g, 4.3 mmol) and freshly distilled MVK or acrylaldehyde (3 ml) were stirred in benzene (30 ml) at 140 °C (autoclave) for 5 h. The reaction product was purified over silica gel. Elution with light petroleum–ethyl acetate (50:50) gave the pyrrole (**6**) or (**9**).

3-Acetyl-2-ethoxycarbonyl-4-(3-oxobutylthio)-5-phenyl-pyrrole (**6**). Yield 1.08 g (70%), m.p. 119—120 °C; $\nu_{max.}$(KBr) 3 280 cm^{-1} (NH); $\delta_H(CDCl_3)$ (*inter alia*) 2.72 (2 H, t, $^3J_{HH}$ 7 Hz, CH_2); and 2.49 (2 H, t, $^3J_{HH}$ 7 Hz, CH_2); $\delta_C(CDCl_3)$ (*inter alia*) 206.6 (s, C=O), 200.8 (s, C=O), 160.2 (s, C=O ester), 139.7, 137.4, 118.5, and 109.6 p.p.m. (C=C pyrrole); M^+, 359 (Found: C, 63.5; H, 5.8; N, 3.9; S, 8.7. $C_{19}H_{21}NO_4S$ requires C, 63.48; H, 5.89; N, 3.90; S, 8.92%).

5-Ethoxycarbonyl-3-formyl-7-phenyl-2,6-dihydrothiopyrano-[2,3-c]pyrrole (**9**). Yield 0.94 g (70%), m.p. 208—209 °C; $\nu_{max.}$(KBr) 3 260 cm^{-1} (NH); $\delta_H(CDCl_3)$ (*inter alia*) 9.62 (1 H, s, CHO), 7.84 (1 H, s, CH), and 3.70 (2 H, s, heterocyclic CH_2); $\delta_C(CDCl_3)$ (*inter alia*) 191.3 (d, $J_{^{13}C-H}$ 182.5 Hz, CH), 160.3 (s, C=O ester), and 22.9 p.p.m. (t, $J_{^{13}C-H}$ 147.50 Hz, heterocyclic CH_2); M^+, 313 (Found: C, 65.2; H, 4.8; N, 4.3; S, 9.8. $C_{17}H_{15}NO_3S$ requires C, 65.15; H, 4.82; N, 4.47; S, 10.23%).

Bis-(4-acetyl-5-ethoxycarbonyl-2-phenylpyrrol-3-yl) Disulphide (**7**).—The same procedure as for the preparation of compound (**6**) by starting with the thiazine (**3b**) in the presence

of dimethylamine or triethylamine and without the acrylic reagent gave the *title compound* (1.48 g, 60%), m.p. 235 °C; $\nu_{max.}$(KBr) 3 290 cm^{-1} (NH); δ_C[$(CD_3)_2SO$] (*inter alia*) 199 (s, C=O), 159 (s, C=O ester), 141.3, 135.7, 119.6, and 108.5 p.p.m. (C=C pyrrole); M^+, 576 (Found: C, 62.75; H, 5.2; N, 4.8; S, 11.0. $C_{30}H_{28}N_2O_6S_2$ requires C, 62.48; H, 4.89; N, 4.86; S, 11.12%).

Crystal Data for Compound (**6**).—$C_{19}H_{21}NO_4S$, M = 359.43, monoclinic, space group $P2_1/n$, a = 10.071(2), b = 10.801(2), c = 17.001(3) Å, β = 93.56(2)°, Z = 4. The intensities of 5 360 unique reflexions [2 525 with $I > \sigma(I)$] with R_{int} = 0.022 were measured (Mo-K_α, scan $\omega/2\ \theta$ = 1, $\theta_{max.}$ = 30°) with an automatic Enraf-Nonius CAD-4 diffractometer at the 'Centre de Diffractométrie,' University of Rennes. The structure was solved by direct methods[11] with the SDP Enraf-Nonius package.[12] All the non-hydrogen atoms were found in one Fourier synthesis and all the hydrogen atoms in one Difference Fourier (between 0.49 and 0.30 e $Å^{-3}$) synthesis. The best least-square calculation gave a final R-value of 0.030. The atomic co-ordinates are listed in Table 1. The bond lengths and bond angles with estimated standard deviations are in Table 2. Thermal parameters are available as Supplementary Publication (SUP 56273, 3 pp.).*

* For details of the Supplementary Publications Scheme, see Instructions for Authors (1985), *J. Chem. Soc., Perkin Trans. 1*, 1985, Issue 1. Structure factors are available from the editorial office on request.

Note added in proof.—A review related to thiopyrano-pyrroles has recently been published; R. L. N. Harris and H. G. McFadden, *Aust. J. Chem.*, 1984, **37**, 1473.

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