Synthesis of 5,6-Dihydro-4*H*-1,3,5-dithiazines, 2,3-Dihydro-6-thioxo-6*H*-1,3-thiazine, and 6-Amino-1,3-dithiins

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Dithiolates (1) or (2), derived from compounds containing an active methylene or a sulphonamido-group, carbon disulphide and sodium or potassium hydroxide, underwent a Mannich reaction with formaldehyde and a primary amine to form 5,6-dihydro-1,3,5-dithiazines (3) or (4). The dithiolate (12), derived from ethyl acetoacetate, cyclised under the above conditions to ethyl 2,3-dihydro-3,4-dimethyl-6-thioxo-6*H*-1,3-thiazine-5-carboxylate (18). The dithiolates (20), derived from cyanoacetic ester, or (10), derived from acetophenone, interacted with formaldehyde and cyanoacetic esters or with 2-cyanoacrylates to form 6-amino-1,3-dithiins (26) or imino-dithians (28). Methyl 6-amino-2-[(1-cyano-1-ethoxycarbonyl)methylene]-1,3-dithiin-5-carboxylate (26; R^1 = Et, R^2 = Me) formed *N*-acyl derivatives with aliphatic acid chlorides. On oxidation the dithiin (26; R^1 = Et, R^2 = Me) contracted to ethyl 2-cyano-2-(4-cyano-1,3-dithiolan-5-ylidene)acetate (31).

DITHIOLATES (1; R^1 = CN, CO_2-alkyl, or aralkyl; M = Na or K) derived from malononitrile or an alkyl or aralkyl cyanoacetate, carbon disulphide, and sodium or potassium hydroxide, or dithiolates (2; R^1 = H or Me) derived from benzene- or toluene-*p*-sulphonamide in a similar manner (Table 1), formaldehyde, and a primary amine underwent a Mannich reaction to form the novel 5,6-dihydro-4*H*-1,3,5-dithiazines (3; R^1 = CN), (3; R^1 = CO_2-alkyl), (3; R^1 = CO_2CH_2Ph), or (4; R^1 = H or Me) which separated from the reaction mixture on acidification.

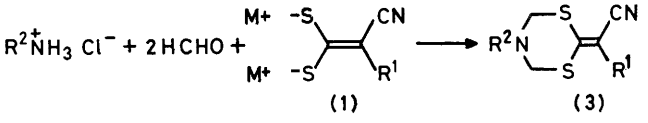
The primary amines which formed the dithiazines (3) or (4) could be unsubstituted or substituted with various groups (OH, OEt, CN, CO_2H, CO_2-alkyl); they could be araliphatic or benzenoid, unsubstituted or substituted with electron-donating or electron-withdrawing groups; hydrazines or substituted hydrazines, hydrazides, or *N*-aminomorpholine. However, secondary amines (dimethylamine or 2,6-dimethylmorpholine), formaldehyde, and dithiolate (1) did not yield a Mannich product, indicating that the formation of the cyclic dithiazines (3) or (4) is favoured. Primary diamines

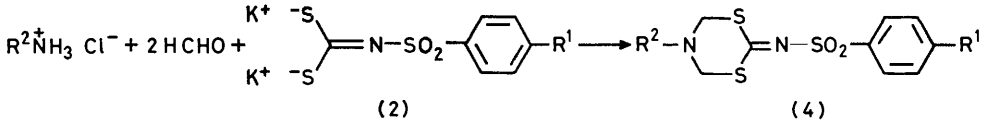
TABLE 1

Preparation of dithiolates from esters containing an active methylene group, cyanamide, or sulphonamides, CS_2, and KOH or NaOH

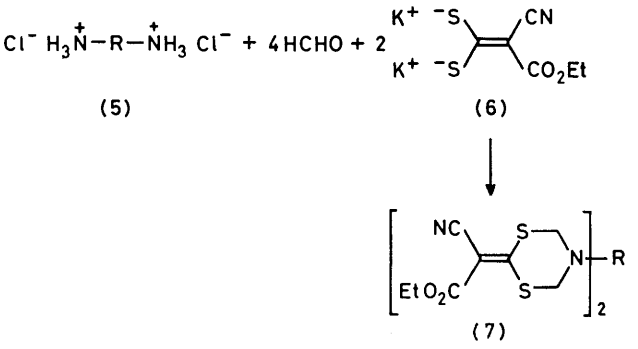
Dithiolate	From compound with active CH_2 or NH_2	Reaction solvent	M.p. (°C)	Yield (%)
(1; R^1 = CO_2Me, M = K)	Methyl cyanoacetate	dioxan	>360 [a]	83
(6)	Ethyl cyanoacetate	dioxan	>360 (ref. 13)	95
(1; R^1 = CO_2Pr^n, M = K)	n-Propyl cyanoacetate	dioxan	not determined [b]	
(1; R^1 = CO_2Pr^n, M = Na)	n-Propyl cyanoacetate	water	>330	9
(1; R^1 = $CO_2C_8H_{17}$, M = K)	Octyl cyanoacetate	dioxan	>300	86
(1; R^1 = $CO_2C_{12}H_{25}$, M = K)	Dodecyl cyanoacetate	dioxan	>250	84
(1; R^1 = CO_2CH_2Ph, M = K)	Benzyl cyanoacetate	dioxan	200 (decomp.)	73
(1; R^1 = CN, M = Na)	Malononitrile	ethanol	>350 [c]	54
(2; R^1 = H, M = K)	Benzenesulphonamide	DMF	>300 [d]	72
(2; R^1 = Me, M = K)	*p*-Tolylsulphonamide	DMF	>300 [d]	72
(9)	Cyanamide	water	>330 [b] (ref. 13)	90
(11)	Diethyl malonate	dioxan	>300 [b] (ref. 13)	60
(12)	Ethyl acetoacetate	dioxan	>300 [a]	100

[a] Jensen and Henriksen, ref. 13, prepared the disodium salt. [b] Very hygroscopic. [c] W. R. Hatchard, *J. Org. Chem.*, 1964, **29**, 660. [d] K. Hartke, *Arch. Pharm.*, 1966, **299**, 179.





(5), formaldehyde, and dithiolate (6) yielded bisdithiazines (7). After storage for 3 years at room temperature the dithiazines (3; $R^1 = CO_2Et$, R^2 = alkyl) were found to have decomposed, but the dithiazines (3; $R^1 = CN$, R^2 = alkyl) had not. Dithiazines (3; $R^1 = CO_2Et$, R^2 = aralkyl, aryl, substituted NH, or morpholino) were generally more stable. The dithiazines (4; R^1 = Me) were more stable than the dithiazines (4; R^1 = H).

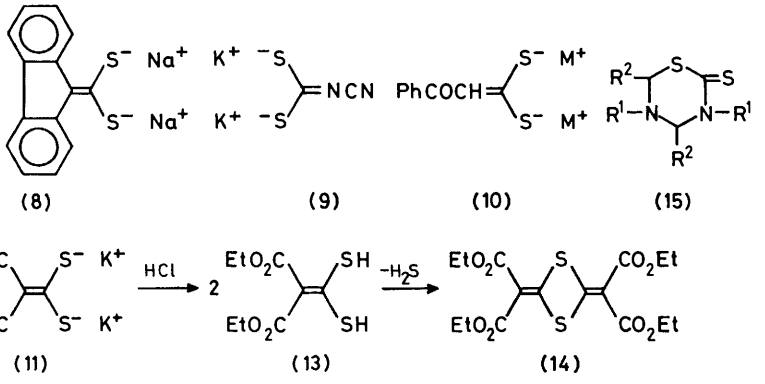


(5) (6) (7)

Certain primary amines did not form dithiazines with dithiolate (6) and formaldehyde: sterically hindered aliphatic amines (t-butylamine or t-octylamine), ' puckered ' amines (*e.g.* cyclohexylamine), bulky amines (*e.g.* 1-adamantaneamine), aliphatic amines substituted with a sulphonic group or basic group, aromatic bicyclic amines with a nuclear hydroxy-substituent, or heterocyclic amines. Dithiolates derived from fluorene (8), acetophenone (10; M = Na), cyanamide (9), diethyl malonate (11), or ethyl acetoacetate (12) did not form dithiazines with formaldehyde and methylamine. From the reaction involving the dithiolate (11) the dithietan (14) was isolated which probably resulted from self-condensation of (13), with loss of H_2S during acidification [dithietan (14) has been previously prepared from diethyl sodiomalonate and thiophosgene].[1,2] The formation of dithiazines succeeded only with formaldehyde. With acetaldehyde, benzaldehyde, or glyoxylic acid the reaction to dithiazines failed. Yet 2,3,4,5-tetrahydro-1,3,5-thiadiazine-2-thiones (15) were produced from a primary amine, carbon disulphide and one of a variety of aldehydes [formaldehyde yielded (15; R^2 = H),[3] benzaldehyde yielding (15; R^2 = Ph),[4] and phenylacetaldehyde yielding (15; $R^2 = CH_2Ph$)].[5]

The dithiolate (12) interacted with formaldehyde and methylamine to form the thione (18). Formation of (18) may involve enolisation of the dithiolate (12) to (16), reaction with formaldehyde on the more nucleophilic thiolate centre to the anion (17), followed by cyclisation with methylamine to the mechanistically favoured six-membered ring (18).

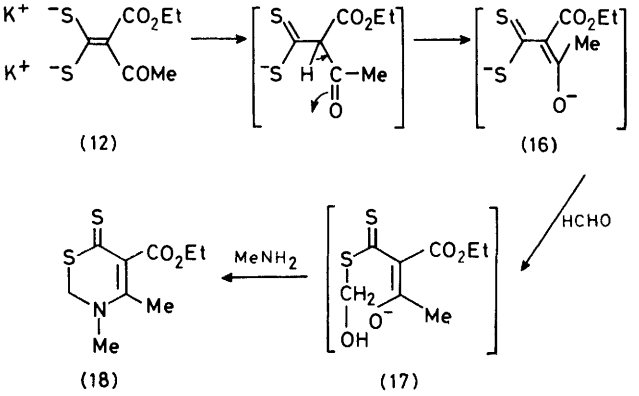
As an extension of this investigation we hoped to produce, by a Knoevenagel-type reaction, 1,3-dithians (21) from the dithiolate (20), formaldehyde, and a compound containing an active methylene group [*e.g.* (19)] instead of a primary amine. However, when the dithiolate (20; R^1 = Et), formaldehyde, and ethyl cyanoacetate were condensed under the conditions used for the preparation of dithiazines (3), the 6-amino-2,6-dihydro-1,3-dithiin (26; $R^1 = R^2$ = Et) was obtained in low yield together with a small amount of the 1,2,4-trithiolan (23; R^1 = Et) [which may have resulted from the dimerisation of (22) with extrusion of sulphur]. A possible mechanism for the formation of the dithiin (26)



(8) (9) (10) (15)

(11) (13) (14)

involves condensation of the dithiol with 1 mol of formaldehyde and of ethyl cyanoacetate to (24) and cyclisation to (25) through a nucleophilic attack of the thiolate on the nitrile. Reproducible and better yields of the dithiins (26) were obtained by the interaction of 2-cyanoacrylates (27) with dithiols (22). The dithiins (Table 2) derived from dithiols (22) exist in the amino-



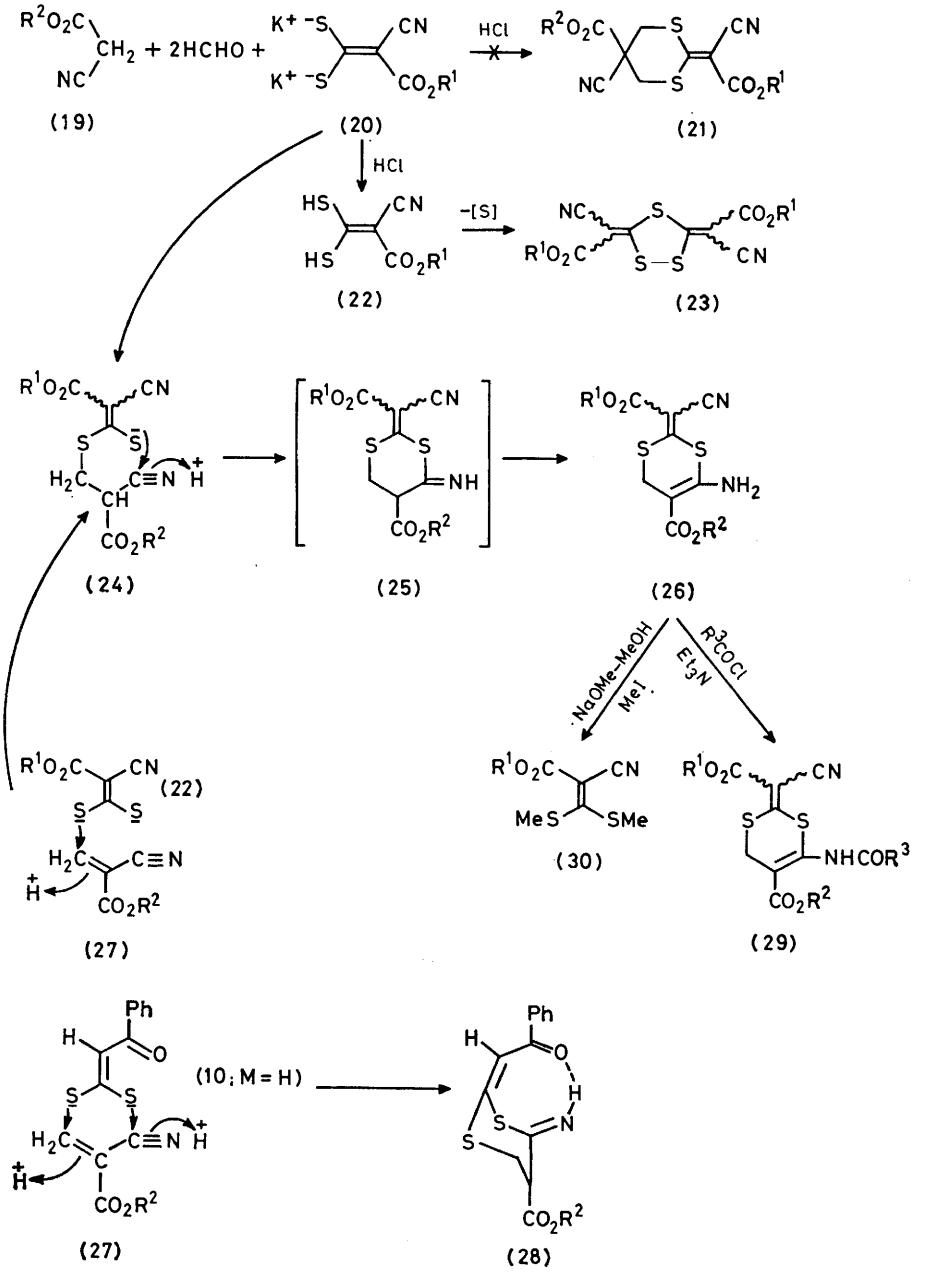
(12) (16) (18) (17)

TABLE 2

Dithiins (26) obtained as yellow crystals by treating dithiols (22) with alkyl 2-cyanoacrylates (27)

Compound (26)	Dithiol (22)	Acrylate (27)	M.p. (°C) (M)	Yield (%)	Formula	Analysis (%) Required C	H	N	S	Found C	H	N	S
(26; R^1 = Me R^2 = Et)	(22; R^1 = Me)	(27; R^2 = Et)	158.6	24	$C_{11}H_{12}N_2O_4S_2$	44.0	4.0	9.3	21.3	44.0	4.1	9.1	21.1
(26; R^1 = Pr^i R^2 = Et)	(22; R^1 = Pr^i)	(27; R^2 = Et)	149.6	34	$C_{13}H_{16}N_2O_4S_2$	47.5	4.9	8.5	19.5	47.5	5.1	8.3	18.9
(26; R^1 = Me R^2 = Me)	(22; R^1 = Me)	(27; R^2 = Me) (ref. 14)	170.6	25	$C_{10}H_{10}N_2O_4S_2$	41.9	3.5	9.8	22.4	41.9	3.5	9.6	22.0
(26; R^1 = Et R^2 = Me)	(22; R^1 = Et)	(27; R^2 = Me)	150.5	28	$C_{11}H_{12}N_2O_4S_2$	44.0	4.0	9.3	21.3	43.9	4.0	9.2	21.1
(26; R^1 = Pr^i R^2 = Me)	(22; R^1 = Pr^i)	(27; R^2 = Me)	152.8	23	$C_{12}H_{14}N_2O_4S_2$	45.8	4.5	8.9	20.4	45.7	4.4	9.2	19.8

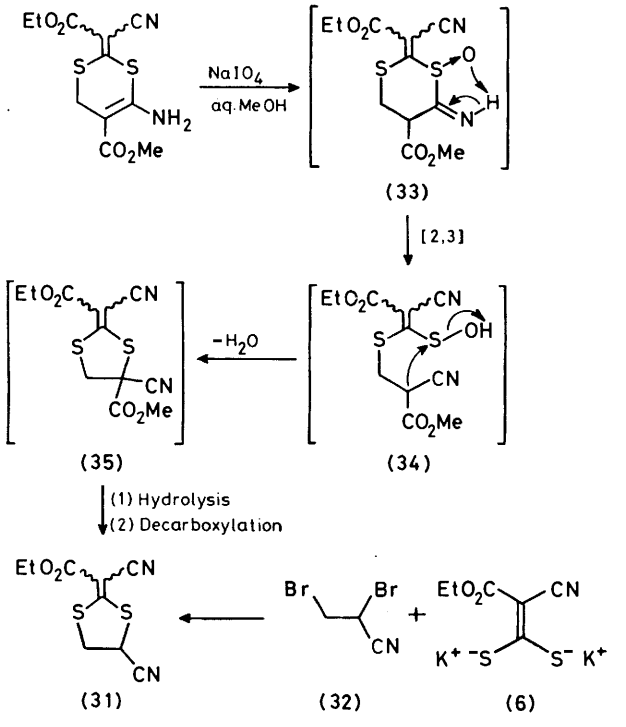
form (26). The ^{1}H n.m.r. spectra of these compounds exhibit 2-proton singlets corresponding to the protons in the 6-position and a broad 2-proton resonance for the NH protons. The compound obtained from dithiol (10; M = H) and cyanoacrylate (27) was isolated in the imino-form (28). The imino-proton was very strongly



hydrogen-bonded to the benzoyl group, exhibiting a sharp singlet at τ −5 in the ^{1}H n.m.r. spectrum and a carbonyl stretching frequency at 1 560 cm^{-1} in the i.r. spectrum.

The imino-dithians (28) are presumed to be single isomers since no evidence for the presence of geometric isomers was found in the ^{13}C n.m.r. spectrum of (28; R^2 = Me).

N-Acylation of the 6-amino-2,6-dihydro-1,3-dithiins (26) with strongly electrophilic aliphatic acid chlorides proceeded smoothly to (29; R^1 = Et, R^2 = R^3 = Me, 4-$ClC_6H_4CH_2$, or Cl_2CH). However, no *N*-acyl compounds were obtained with aromatic acid chlorides (which are *ca.* 100 times less reactive than acetyl chloride),[6] or *N*-ethoxycarbonyl derivative with ethyl



chloroformate, or carbamate with methyl isocyanate. Failure of the dithiins (26) to react in a manner characteristic of amines prompts us to regard them formally rather as vinylogous carbamates in which the amino-group is conjugated with the alkoxycarbonyl group. However, the dithiin (26; R^1 = Pr^i, R^2 = Et) failed to give the expected pyrimidinone with formamide, under the conditions described by Lehmann and Wamhoff[7] [in a way that is characteristic of vinylogous carbamates]. Nor did it react cleanly with ethyl benzimidate to give the expected cyclic derivative; a complex mixture was obtained. There was little interaction between the dithiin (26; R^1 = Et, R^2 = Me) and ethyl acetoacetate. The dithiins (26) are stable at room temperature to acetic acid, but unstable to strong acids or strong alkalis. With sodium methoxide the dithiin ring broke down to dithiolate which was isolated as the methylated derivative (30). It is the instability of the dithiin ring system that may be responsible for its failure to react as a vinylogous carbamate under the conditions required for cyclisation.

Oxidation of the 6-amino-1,3-dithiin (26; R^1 = Et, R^2 = Me) with sodium metaperiodate in aqueous methanol resulted in ring contraction to the 1,3-dithiolan (31), which was identical with an authentic sample prepared by an unambiguous route from 2,3-dibromopropionitrile (32) and the dithiolate (6). A possible mechanism involves a [2,3]-sigmatropic rearrangement of the sulphoxide (33) and ring-opening (34), then cyclisation with loss of water to (35), hydrolysis of the ester group, and decarboxylation to (31). The proposed mechanism resembles the oxidative conversion of penicillins to cephalosporins,[8] the ring-expansion of 1,3-dithiolans to dihydro-1,4-dithiins[9] and of 1,3-oxathiolans to dihydro-1,4-oxathiins,[10] and the ring-contraction of 1,2,4-triazin-3(2*H*)-ones to 1,2,3-triazoles[11] and of 5-aryl-3,6-dihydro-1,3,4-thiadiazin-2-ones to 4-aryl-1,2,3-thiadiazoles.[12] Electronic and steric considerations might be expected to favour oxidation of the sulphur at position 3 which is less hindered and more nucleophilic than the sulphur at position 1, but the influence of the 6-amino-group must be sufficient to outweigh these factors.

EXPERIMENTAL

Melting points were determined in open capillaries with an Electrothermal apparatus or with a Mettler apparatus (M). I.r. spectra were recorded with a Perkin-Elmer 521 or Perkin-Elmer 21 spectrophotometer for solutions in bromoform or for Nujol mulls. ^{1}H N.m.r. spectra were recorded with a Varian A60D, JEOL MH 100, or a Perkin-Elmer R10 spectrophotometer for solutions in $CDCl_3$, [$^2H_6$]DMSO, D_2O, [$^2H_6$]acetone, or a mixture of $CDCl_3$ and [$^2H_6$]DMSO. Mass spectra were recorded with a Varian MAT 311A. T.l.c. was carried out on pre-coated plates of silica gel 60 F_{254}. Spots were observed under u.v. or developed with iodine vapour. Column chromatography was performed on Merck Kieselgel 60.

Dipotassium [Isopropoxycarbonyl(cyano)methylene]-methanedithiolate (1; R^1 = CO_2Pr^i, M = K).—Isopropyl cyanoacetate (12.7 g, 100 mmol) and carbon disulphide (6.2 ml, 7.6 g, 100 mmol), in dioxan (250 ml), were added dropwise to an ice-cooled suspension of finely powdered potassium hydroxide (11.2 g, 200 mmol) in dioxan (100 ml). The suspension was stirred at 10—20 °C for 2 h, diluted with ether (200 ml), and left for 16 h at room temperature. The solid was filtered off, washed well with ether, and dried at 60 °C and 0.1 mmHg; yield 23.9 g (86%), m.p. >300 °C. Other dithiolates were prepared similarly and are listed in Table 1. They were not analysed, but their structures were confirmed by i.r. and ^{1}H n.m.r. spectra. Typically the data for the dithiolate (1; R^1 = CO_2Me, M = K) were $\nu_{max.}$ (Nujol) 2 180 cm^{-1} (CN) and 1 660 cm^{-1} (CO); τ([$^2H_6$]-DMSO) 6.58 (s, 3 H); for dithiolate (12) $\nu_{max.}$ (Nujol) 1 690 and 1 650 cm^{-1} (CO); τ(D_2O) 5.80 (q, 2 H), 8.10 (s, 3 H), and 8.72 (t, 3 H); for dithiolate (2; R^1 = H) $\nu_{max.}$ (Nujol) 2 160 cm^{-1} (CN) and 1 130 cm^{-1} (SO_2); τ([$^2H_6$]-DMSO) 1.90—3.80 (m, 5 H).

Disodium Fluoren-9-ylidenemethanedithiolate (8).—Fluorene (33.2 g, 200 mmol), in dry toluene (250 ml), was added

dropwise, with stirring, to a suspension of sodium hydride (400 mmol) in dry toluene (150 ml). Carbon disulphide (15.2 g, 200 mmol) was added to the stirred ice-cooled mixture. Dry dimethylformamide was added, the mixture was stirred for 1 h, and warmed to 40—45 °C when a red solution resulted. Ethyl acetate (1.5 l) was then added and the solution stirred at room temperature. The dithiolate precipitated as a yellow solid. It was filtered off, washed with ether (500 ml), and dried *in vacuo* (P_2O_5) (15.1 g, 28%). It was hygroscopic (Jensen and Henriksen [13] prepared this salt, but did not isolate it).

Preparation of the Dithiazines (3), (4), *and* (7).—To a stirred solution of the amine hydrochloride (50 mmol) [used as such or prepared by the addition of concentrated HCl (6.0 ml, 50 mmol + 10%) to the amine (50 mmol)] in water (150 ml) was added at 10—15 °C (ice–water cooling) a solution of the dithiolate (1) or (2) (50 mmol) in water (200 ml), then formalin (38%, 10.8 ml, 110 mmol formaldehyde). The reaction mixture was left stirring until pH 7—8 was reached (*ca.* 30 min). Concentrated HCl was then added to bring the reaction mixture to pH 1. A solid precipitated. The reaction mixture was then stirred for a further hour at room temperature and filtered. The solid was washed well with water and dried in a vacuum desiccator (P_2O_5). It was then recrystallised from a suitable solvent. Dithiazines prepared by the above method are listed in Tables 2—4 and 6—12 of SUP 22692 (29 pp.).* Bis-dithiazines (7) (Table 5 of SUP 22692 *) were prepared similarly from the diamine (5) (50 mmol), the dithiolate (6) (100 mmol), and formalin (38%, 220 mmol of formaldehyde). The i.r. and ^{1}H n.m.r. spectra of the dithiazines confirmed their structures.

Attempted Condensations to Dithiazines.—The following amines failed to yield dithiazines (3) with dithiolate (6) and formaldehyde under the conditions described above: t-butylamine, t-octylamine, cyclohexylamine, 1-adamantaneamine, 2-aminoethanesulphonic acid, L-cysteic acid, 3-diethylaminopropylamine, *N*-(2-aminoethyl or 3-aminopropyl)morpholine, L-histidine, 4-amino-*N*-2-pyrimidinylbenzenesulphonamide, 4-aminopyridine, 2-amino-4,6-dichloropyrimidine, 4-amino-3,5,6-trichloropicolinic acid, 4-amino-1-naphthol, 8-hydroxy-5-aminoquinoline, 2-aminobenzyl alcohol, anthranilaldehyde oxime, and 2-aminobenzothiazole.

The dithiolates (8), (9), or (10) (M = Na) failed to yield dithiazines with formaldehyde and methylamine. On acidification with hydrochloric acid intractable oils separated from the reaction mixtures involving dithiolates (8) or (9). From the reaction mixture involving dithiolate (11), the dithietan (14), m.p. 180—182 °C (from aqueous ethanol), was isolated (lit.,[1] m.p. 177—178; lit.,[2] m.p. 180—181 °C); $\nu_{max.}$ ($CHBr_3$) 1 715 and 1 670 cm^{-1} (CO); τ($CDCl_3$) 5.68 (q, 8 H, 4 × CH_2), 8.67 (t, 12 H, 4 × Me) (Found: C, 47.3; H, 5.0; S, 15.7. Calc. for $C_{16}H_{20}O_8S_2$: C, 47.5; H, 4.9; S, 15.8%).

Methylamine or ethylamine, the dithiolate (6), and acetaldehyde, benzaldehyde, or glyoxylic acid gave intractable oils.

Reaction of the Dithiolate (1; R^1 = CN, M = Na) *or* (6) *with Formaldehyde and Dimethylamine Hydrochloride.*—To a stirred solution of the dithiolate (50 mmol) in water (20 ml), were added formalin (38—40%, 11 ml, 100 mmol) and dimethylamine hydrochloride (8.15 g, 100 mmol). The solution was stirred for 5 h at room temperature. The reaction mixture involving dithiolate (1; R^1 = CN, M = Na) was concentrated leaving an oil which was repeatedly triturated with water, then with propan-2-ol to yield a solid (3.7 g), m.p. 175—205 °C (decomp.). Its ^{1}H n.m.r. spectrum did not show the presence of NMe; the i.r. spectrum showed the presence of CN at $\nu_{max.}$ 2 170 and 2 195 cm^{-1}. The oil that separated from the reaction mixture involving dithiolate (6) was extracted with chloroform, washed with water, and dried (Na_2SO_4). On removing the volatiles an oil remained which was eluted on a column with ethyl acetate. A viscous green oil (5 g) was obtained which was kept at 50 °C and 0.1 mmHg for 2 h. Its i.r. spectrum showed no CN; its ^{1}H n.m.r. spectrum was incompatible with that of the expected Mannich product. Nor was the expected Mannich product obtained when, instead of dimethylamine hydrochloride, 2,6-dimethylmorpholine hydrochloride was used.

Ethyl 2,3-*Dihydro*-3,4-*dimethyl*-6-*thioxo*-6H-1,3-*thiazine*-5-*carboxylate* (18).—To a stirred solution of methylamine hydrochloride (2.025 g, 30 mmol) in water (30 ml) was added a solution of the salt (12) (8.5 g, 30 mmol) in water (100 ml). To this stirred solution (pH 9—10) formalin (38%, 6.5 ml, 60 mmol) was added with cooling. A yellow solid appeared. Concentrated hydrochloric acid (3.3 ml, 30 mmol) was then added (pH 1) and the suspension was stirred for 3 h at room temperature. The sticky precipitate was extracted with chloroform (2 × 100 ml), the extracts were washed with water (200 ml), and dried ($MgSO_4$). The solvent was removed leaving a red viscous oil. Recrystallisation from carbon tetrachloride (with the aid of charcoal) gave an orange-yellow solid (0.75 g, 10.8%), m.p. 105.1 °C (M); $\nu_{max.}$ ($CHBr_3$) 1 702 cm^{-1} (ester carbonyl); τ($CDCl_3$) 5.39 (s, 2 H, NCH_2S); 5.69 (q, 2 H, $CO_2CH_2CH_3$), 6.68 (s, 3 H, NMe), 7.82 (s, 3 H, MeC=C), 8.62 (t, 3 H, $CO_2CH_2CH_3$) (Found: C, 46.4; H, 5.7; N, 5.5; S, 27.4; M^+ 231.038 8. $C_9H_{13}NO_2S_2$ requires C, 46.7; H, 5.7; N, 6.0; S, 27.7%; *M*, 231.038 8).

Ethyl 6-*Amino*-2-(1-*cyano*-1-*ethoxycarbonylmethylene*)-2,4-*dihydro*-1,3-*dithiin*-5-*carboxylate* (26; R^1 = R^2 = Et).—*Method* (*a*). Concentrated HCl (1.75 ml, 20 mmol) was added to ethyl cyanoacetate (2.26 g, 20 mmol) suspended in water. To the mixture, cooled to below 10 °C, were added, with stirring, a solution of the dithiolate (6 = 20; R^1 = Et) (5.3 g, 20 mmol) in water (200 ml), formalin (38%, 4 ml), and then aqueous sodium carbonate to pH 5. The mixture was stirred for 3 h while its temperature rose to 25 °C. It was then acidified to pH 1 with concentrated HCl and extracted with toluene (2 × 250 ml). The toluene extracts were washed with brine (100 ml), dried ($MgSO_4$), the solvent removed under reduced pressure, and the residue was eluted with dichloromethane on the chromatographic column. A small amount (0.11 g) of 3,5-bis-(1-cyano-1-ethoxycarbonylmethylene)-3,5-dihydro-1,2,4-trithiolan (23), m.p. 214.3 °C (decomp.) (M), was obtained.† Further elution yielded compound (26; R^1 = R^2 = Et) (1.02 g, 16%) as yellow crystals, m.p. 131.3 °C (M); $\nu_{max.}$ ($CHBr_3$) 3 310, 3 490 cm^{-1} (NH), 2 215 cm^{-1} (CN), and 1 705, 1 680 cm^{-1} (ester carbonyls); τ($CDCl_3$) 3.45 (br, 2-H, NH_2), 5.4—6.0 (2 q, 4 H, 2 × $CO_2CH_2CH_3$), 6.15 (s, 2 H, CH_2S), 8.68 (t, 6 H, 2 × Me) (Found: C, 44.9; H, 4.4; N, 9.0; S, 19.8%; M^+ 314.038 8. $C_{12}H_{14}N_2O_4S_2$ requires

* For details of the Supplementary Publications scheme see *J.C.S. Perkin I*, 1979, Index issue.

† T. Takeshima, M. Yokoyama, N. Fukada, and M. Akano, *J. Org. Chem.*, 1970, **35**, 2438, reported m.p. 223—224 °C for this compound.

C, 45.8; H, 4.5; N, 8.9; S, 20.4%; *M*, 314.039 5). Similar experiments gave negligible yields of dithiin (26; $R^1 = R^2 = Et$).

Method (*b*). Concentrated HCl (6.6 ml, 75 mmol), was added to a stirred mixture of the dithiolate (6 = 20; R^1 = Et) (9.9 g, 37.5 mmol), water (300 ml), and dichloromethane (750 ml). The mixture was immediately filtered through phase-separating paper. Ethyl 2-cyanoacrylate (27; R^2 = Et) [14] (4.65 g, 37.5 mmol) was added to the filtrate, then after 1 h glacial acetic acid (5 drops). After 16 h the solvent was removed and the residue was eluted on a short column with chloroform. The compound (2.5 g, 22%), m.p. 132.5 °C, was identical with that obtained in method (a). Details of other esters prepared by method (b) are summarised in Table 2. The i.r. and ^1H n.m.r. spectra of the dithiins (26) were: (26; R^1 = Me, R^2 = Et) $\nu_{max.}$ ($CHBr_3$) 3 450, 3 360 cm^{-1} (weak) (NH_2), 2 203 cm^{-1} (CN), and 1760, 1670 cm^{-1} (ester carbonyls); τ($CDCl_3$) 3.5 (br, 2 H, NH_2), 5.74 (q, 2 H, $CO_2CH_2CH_3$), 6.19 (5 H, CO_2Me and CH_2S), and 8.65 (t, 3 H, $CO_2CH_2CH_3$); for (26; R^1 = Pr^i, R^2 = Et) $\nu_{max.}$ ($CHBr_3$) 3 460, 3 380 cm^{-1} (NH_2), 2 220 cm^{-1} (CN), 1 690, 1 670 cm^{-1} (ester carbonyls); τ($CDCl_3$) 3.5 (br, 2 H, NH_2), 4.90 (m, 1 H, CO_2CHMe_2), 5.76 (q, 2 H, $CO_2CH_2CH_3$), 6.19 (s, 2 H, CH_2S), 8.5—8.8 (d, 6 H, CO_2CHMe_2), 8.70 (t, 3 H, $CO_2CH_2CH_3$); for (26; $R^1 = R^2$ = Me) $\nu_{max.}$ ($CHBr_3$) 3 450, 3 360, 3 300, 3 180 cm^{-1} (free and bonded NH_2), 2 202 cm^{-1} (CN), and 1700, 1 672 cm^{-1} (ester carbonyls); τ($CDCl_3$ + [$^2H_6$]DMSO) 2.20 (br, 2 H, NH_2), 6.18 (s, 2 H, CH_2S), 6.20 (s, 3 H, CO_2Me), and 6.28 (s, 3 H, CO_2Me); for (26; R^1 = Et, R^2 = Me) $\nu_{max.}$ ($CHBr_3$) 3 450, 3 360, 3 300, 3 180 cm^{-1} (free and bonded NH_2), 2 203 cm^{-1} (CN), and 1 691, 1 671 cm^{-1} (ester carbonyls); τ($CDCl_3$) 3.45 (br, 2 H, NH_2), 5.71 (q, 2 H, $CO_2CH_2CH_3$), 6.20 (s, 2 H, CH_2S), 6.23 (s, 3 H, CO_2Me), and 8.68 (t, 3 H, $CO_2CH_2CH_3$); for (26; R^1 = Pr^i, R^2 = Me) $\nu_{max.}$ ($CHBr_3$) 3 460, 3 360, 3 300, 3 180 cm^{-1} (free and bonded NH_2), 2 203 cm^{-1} (CN), and 1 688, 1 675 cm^{-1} (ester carbonyls); τ($CDCl_3$) 3.50 (br, 2 H, NH_2), 4.90 (m, 1 H, CO_2CHMe_2), 6.20 (s, 2 H, CH_2S), 6.23 (s, 3 H, CO_2Me), and 8.69 (d, 6 H, CO_2CHMe_2).

2-*Benzoyl*-1,1-*dimercaptoethylene* (10; M = H).—t-Pentyl alcohol (88 g, 1 mol), in toluene (500 ml), was heated under reflux with sodium (30 g, 1.3 mol) for 3 h. The solution was decanted from an excess of sodium and cooled in an ice bath. A mixture of acetophenone (60 g, 0.5 mol) and carbon disulphide (38 g, 30 ml, 0.5 mol) was added dropwise with stirring. The mixture was stirred at room temperature overnight yielding a solid (10; M = Na).[13] The mixture was extracted with water (1 l), the aqueous extract washed with ether (2 × 500 ml), cooled to below 5 °C, acidified with 2N-H_2SO_4, and extracted with ether (2 × 500 ml). The ether extracts were then dried ($MgSO_4$). Portions of this solution were used as required for subsequent reactions.

Ethyl 2-(*Benzoylmethylene*)-4-*imino*-1,3-*dithian*-5-*carboxylate* (28; R^2 = Et).—2-Benzoyl-1,1-dimercaptoethylene (10; M = H) * (5.88 g, 30 mmol), in ether (100 ml), was treated with ethyl 2-cyanoacrylate (3.75 g, 30 mmol), in ether (10 ml), and the mixture was set aside at room temperature overnight. The solid was filtered off, washed with a little light petroleum (b.p. 40—60 °C), and dried *in vacuo* to give the compound (3.98 g, 41%) as yellow needles, m.p. 95.6 °C (M). A second crop (0.80 g, 8%) was obtained from the mother-liquors; $\nu_{max.}$ ($CHBr_3$) 2 800—2 300 cm^{-1} (bonded NH), 1 744 cm^{-1} (ester carbonyl), and 1 560 cm^{-1} (benzoyl carbonyl); τ($CDCl_3$) —4.8 (s, 1 H, NH), 2.0—2.7 (m, 5 H, aromatic), 3.03 (s, 1 H, C=CH), 5.70 (q, 2 H, $CO_2CH_2CH_3$), 5.8—6.7 (complex, 3 H, SCH_2CH), and 8.63 (t, 3 H, $CO_2CH_2CH_3$) (Found: C, 56.2; H, 4.7; N, 4.4; S, 19.6. $C_{15}H_{15}NO_3S_2$ requires C, 56.05; H, 4.7; N, 4.4; S, 19.95%).

Methyl 2-(*benzoylmethylene*)-4-*imino*-1,3-*dithian*-5-*carboxylate* (28; R^2 = Me) was prepared similarly in 51% yield as yellow needles, m.p. 90.8 °C (M); $\nu_{max.}$ ($CHBr_3$) 2 900—2 200 cm^{-1} (bonded NH), 1 750 cm^{-1} (ester carbonyl), and 1 560 cm^{-1} (benzoyl carbonyl); τ($CDCl_3$) —4.8 (s, 1 H, NH), 2.0—2.7 (m, 5 H, aromatic), 3.09 (s, 1 H, C=CH), 5.7—6.6 (complex, 3 H, SCH_2CH), and 6.18 (s, 3 H, CO_2Me); ^{13}C n.m.r. δ 31.5 (6-C in dithian ring), 36.6 (5-C in dithian ring), 53.9 (CO_2CH_3), 108.3 (exocyclic methylene), 115.0 (2-C in dithian ring), 127.0, 128.9 (2-C and 3-C in benzene ring), 132.6 (4-C in benzene ring), 133.6 (1-C in benzene ring), 164.9 (4-C in dithian ring), 171.6 (CO_2Me), and 212.4 (benzoyl carbonyl) (Found: C, 54.5; H, 4.3; N, 4.6; S, 20.6. $C_{14}H_{13}NO_3S_2$ requires C, 54.7; H, 4.3; N, 4.6; S, 20.9%).

Methyl 6-(*Acetylamino*)-2-[(1-*cyano*-1-*ethoxycarbonyl*)-*methylene*)]-2,6-*dihydro*-1,3-*dithiin*-5-*carboxylate* (29; R^1 = Et, $R^2 = R^3$ = Me).—The 1,3-dithiin-5-carboxylate (26; R^1 = Et, R^2 = Me) (300 mg, 10 mmol), in hot toluene (50 ml), was treated with a large excess of acetyl chloride (5 ml) and triethylamine (1 ml). The mixture was heated at 100 °C for 2 h, cooled, and evaporated to dryness. The residue was extracted with ether (100 ml), the ether was removed, and the solid residue was washed with water (100 ml). A solution of this solid in ethyl acetate (200 ml) showed a single spot when examined by t.l.c. The ethyl acetate solution was dried ($MgSO_4$) and solvent was removed *in vacuo* to give the acetylated product (29; R^1 = Et, $R^2 = R^3$ = Me) (170 mg) as white crystals, m.p. 180.2 °C (M). Elution of the original ether extract on a column with ether gave a further quantity of this compound (110 mg) (total yield 82%); $\nu_{max.}$ ($CHBr_3$) 3 230 cm^{-1} (NH), 2 205 cm^{-1} (CN), and 1 692 cm^{-1} (CO); τ($CDCl_3$) 5.69 (q, 2 H, $CO_2CH_2CH_3$), 6.10 (br, 1 H, NH), 6.15 (s, 3 H, CO_2Me), 6.30 (s, 2 H, CH_2S), 7.83 (s, 3 H, COMe), and 8.66 (t, 3 H, $CO_2CH_2CH_3$) (Found: C, 45.75; H, 4.5; N, 8.3. $C_{13}H_{14}N_2O_5S_2$ requires C, 45.6; H, 4.1; N, 8.2%).

Similarly were prepared: (29; R^1 = Et, R^2 = Me, R^3 = 4-$ClC_6H_4CH_2$), *white crystals* (42%), m.p. 140.3 °C (M); $\nu_{max.}$ ($CHBr_3$) 3 200 cm^{-1} (NH), 2 200 cm^{-1} (CN), and 1 690, 1 685, 1 588 cm^{-1} (ester + amide carbonyls); τ($CDCl_3$) 2.4—2.7 (m, 4 H, aromatic), 5.65 (q, 2 H, $CO_2CH_2CH_3$), 6.0—6.20 (7 H, complex, CH_2S + CO_2Me + $COCH_2C_6H_4Cl$), and 8.63 (t, 3 H, $CO_2CH_2CH_3$) (Found: C, 50.35; H, 4.1; Cl, 7.7; N, 5.9; S, 14.0. $C_{19}H_{17}ClN_2O_5S_2$ requires C, 50.4; H, 3.8; Cl, 7.8; N, 6.2; S, 14.2%); (29; R^1 = Et, R^2 = Me, R^3 = Cl_2CH), *off-white solid* (38%), m.p. 181.3 °C (M); $\nu_{max.}$ ($CHBr_3$) 3 280, 3 170 cm^{-1} (NH), 2 200 cm^{-1} (CN), 1 700, 1 690 cm^{-1} (CO); τ($CDCl_3$) — 1.90 (s, 1 H, NH), 4.09 (s, 1 H, Cl_2CH), 5.78 (q, 2 H, $CO_2CH_2CH_3$), 6.04 (s, 3 H, CO_2Me), 6.29 (s, 2 H, CH_2S), and 8.69 (t, 3 H, $CO_2CH_2CH_3$) (Found: C, 36.9; H, 2.9; Cl, 17.3; N, 6.7; S, 15.3. $C_{13}H_{12}Cl_2N_2O_5S_2$ requires C, 38.0; H, 2.9; Cl, 17.2; N, 6.8; S, 15.6%). Under the above conditions ethyl chloroformate, and benzoyl, 4-methoxybenzoyl, 4-chlorobenzoyl, 4-nitrobenzoyl, or *O*-acetyl salicyloyl chlorides failed to form the acylated dithiin (29).

* A. Thullier and J. Vialle, *Bull. Soc. chim. France*, 1959, 1398, reported m.p. 63 °C for this thiol.

Reaction of Dithiin (26; R^1 = Et, R^2 = Me) *with Methyl Isocyanate*.—Methyl isocyanate (0.114 g, 2 mmol), in acetone (10 ml), and triethylamine (2 drops) were added to the dithiin (0.3 g, 1 mmol), in acetone (40 ml). The reaction mixture was heated under reflux and the progress of the reaction was monitored by t.l.c., which showed the gradual formation of a complex array of products.

Reaction of dithiin (26; R^1 = Pr^i, R^2 = Et) *with Formamide*.—Sodium methoxide (from 25 mg sodium, 1.1 mmol) in formamide (5 ml) was added to the dithiin (0.328 g, 1 mmol) and the mixture was heated under reflux for 3 h. After cooling to room temperature, the black residue was diluted with water and extracted with ether (3 × 150 ml). The ether extracts were washed with brine (100 ml) and dried ($MgSO_4$). Ether was removed *in vacuo* to leave an intractable residue (<50 mg).

Reaction of Dithiin (26; R^1 = Prl, R^2 = Et) *with Ethyl Benzimidate*.—(*a*) A mixture of the dithiin (0.328 g, 1 mmol), ethyl benzimidate [15] (0.152 g, 1.1 mmol), and polyphosphoric acid (1 drop) was heated on a steam-bath for 14 h. The mixture was diluted with ethanol (5 ml) and ether (5 ml) and stored at −15 °C for 3 d. T.l.c. of the solution (dichloromethane) indicated the presence of some 14 different compounds.

(*b*) The dithiin, ethyl benzimidate, boron trifluoride etherate (1 drop), and dioxan (25 ml) were heated on a steam-bath for 30 h. The solvent was removed, the residue was shaken with ether (20 ml), and filtered to give a solid (<10 mg) and a filtrate which was shown by t.l.c. (chloroform) to contain the starting dithiin as the major component and many minor components.

Reaction of the Dithiin (26; R = Et, R^1 = Me) *with Ethyl Acetoacetate*.—The dithiin (0.30 g, 1 mmol), in dioxan (50 ml), ethyl acetoacetate (0.13 g, 1 mmol) in dioxan (10 ml), and triethylamine (2 drops) were heated on a steam-bath for 4 d. T.l.c. of the reaction mixture indicated no appreciable change.

Effect of pH *on the Dithiin* (26; R^1 = Et, R^2 = Me).—Four solutions were prepared each containing the dithiin (13.3 mg), water (0.67 ml), and methanol (3.33 ml). To solution (a) no addition was made, to solution (b) glacial acetic acid (10 drops) was added, to solution (c) concentrated HCl (2 drops), and to solution (d) aqueous 2N-NaOH (1 drop). The solutions were kept at room temperature for 24 h and examined by t.l.c. ($CHCl_3$). Solutions (a) and (b) contained only the dithiin, solution (c) the dithiin and a product which stayed at the base-line, and solution (d) contained only the base-line product.

Reaction of Dithiin (26; R^1 = Et, R^2 = Me) *with Sodium Methoxide and Iodomethane*.—A solution of sodium methoxide (1 mmol) in methanol (1 ml) was added to a solution of the dithiin (0.30 g, 1 mmol) in dioxan (50 ml). Iodomethane (1.40 g, 10 mmol) was added and the mixture was kept at room temperature for 2 h. The volatiles were removed *in vacuo* and the residue was partitioned between water (100 ml) and ethyl acetate (100 ml). The organic layer was washed with brine (50 ml) and dried ($MgSO_4$). The solvent was removed and the residue was eluted on a column using dichloromethane. Ethyl 2-cyano-3,3-bis-(methylthio)acrylate (30; R^1 = Et) (0.11 g, 51%), m.p. 58.5 °C (M), was obtained as pale yellow crystals (lit.,[13] m.p. 58.5—59 and 52.5—53 °C); $\nu_{max.}$ ($CHBr_3$) 2 200 cm^{-1} (CN), and 1 700 cm^{-1} (ester carbonyl); τ($CDCl_3$), 5.72 (q, 2 H, $CO_2CH_2CH_3$), 7.29 (s, 3 H, MeS), 7.32 (s, 3 H, MeS), and 8.68 (t, 3 H, $CO_2CH_2CH_3$).

Conversion of the Dithiin (26; R^1 = Et, R^2 = Me) *into Ethyl 2-Cyano-2-(4-cyano-1,3-dithiolan-5-ylidene)acetate* (31).—The dithiin (0.30 g, 1 mmol) in methanol (40 ml), was treated with sodium metaperiodate (0.43 g, 2 mmol), in methanol (20 ml) and water (10 ml), and the mixture was stored at room temperature overnight. Sodium iodate was filtered off. The filtrate was evaporated to dryness, and then partitioned between water and ethyl acetate. The organic layer was separated and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a yellow gum which was eluted on a column with dichloromethane–ether (1 : 1) to give the dithiolan (31) (0.10 g, 42%) as white crystals, m.p. 118.7 °C (M); $\nu_{max.}$ ($CHBr_3$) 2 203 cm^{-1} (CN), 1 695 cm^{-1} (ester carbonyl) (absorption due to SO or SO_2 absent); τ($CDCl_3$) 5.25 (t, 1 H, CHCN), 5.70 (q, 2 H, $CO_2CH_2CH_3$), 6.18 (d, 2 H, CH_2S), and 8.64 (t, 3 H, $CO_2CH_2CH_3$) (Found: C, 44.4; H, 3.3; N, 11.6; S, 27.05; M^+ 240.002 3. $C_9H_8N_2O_2S_2$ requires C, 44.9; H, 3.35; N, 11.7; S, 26.8%; *M*, 240.002 7).

Compound (31) was also prepared as follows. 2,3-Dibromopropionitrile [16] (32) (3.2 g, 15 mmol), in ethane-1,2-diol (10 ml), was added all at once to the dithiolate (6) (3.9 g, 15 mmol), in ethane-1,2-diol (100 ml). The mixture was stirred at room temperature for 18 h, poured into water (1 l), and extracted with ether (2 × 500 ml). The extracts were washed with water (1 l) and brine (500 ml), and dried ($MgSO_4$). The volatiles were removed *in vacuo* and the residue was eluted on the column with dichloromethane–ether (1 : 1). The dithiolan (31) was obtained as an off-white solid (0.65 g, 21%), m.p. 122—125 °C (not depressed by admixture with the product of conversion reported above).

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