# The Reactions of *C*-Methylheterocycles with Thionyl Chloride.
## Part 3.
## The Transformation of Some Five-and Six-membered Heterocycles

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Reactions of various five-and six-membered *C*-methylheterocycles with hot thionyl chloride gave chlorothio intermediates which were not characterized but which gave 1,2,4-thiadiazole derivatives when reacted with amidines and gave thioamides when reacted with amines. When 2,3-dimethyl-6-ethoxycarbonylimidazo[4,5-*b*]pyridine (**26**) was treated with thionyl chloride a trisulphane **27** was isolated.

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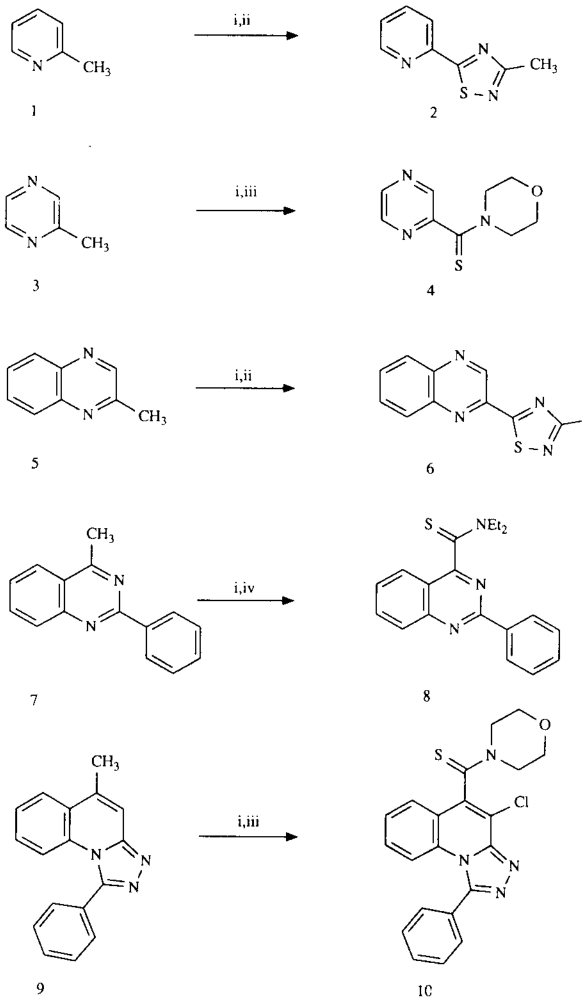
We have described the oxidation of the *C*-methyl groups in 2- and 4-methylquinolines to chlorothio functions using thionyl chloride [1,2]. In particular, 2-methylquinolines give dichloro(2-quinolyl)methanesulphenyl chlorides ($ArCCl_2SCl$) and 4-methylquinolines give *bis*[dichloro(4-quinolyl)methyl]trisulphanes [$(ArCCl_2S)_2S$]. The chlorothio function in each of these systems can be transformed into thioamides by reaction with amines and into 1,2,4-thiadiazoles by reaction with amidines. These modifications of *C*-methyl substituents provide a simple but largely unexplored method of generating novel heterocyclic derivatives [3]. We now describe the application of this approach to some other *C*-methylheterocycles. In most of these studies we have not attempted to characterize the chlorothio derivatives but have simply reacted the crude product, after removal of excess reagent, with amines or amidines.

### Six-membered Heterocycles.

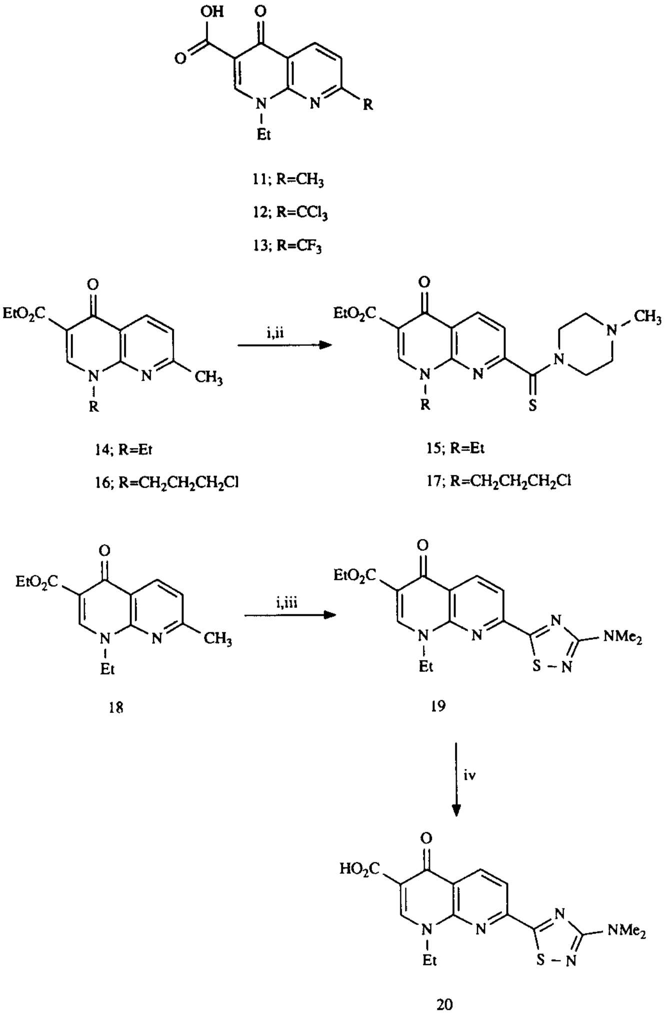
We have investigated a number of six-membered heterocyclic derivatives in which a *C*-methyl substituent is activated by an electron-withdrawing ring nitrogen. Although the anticipated products were obtained in most cases, the yields were low.

The simplest system which we have studied is 2-methylpyridine (**1**) for which the reaction conditions were typical of the general procedure followed. After heating overnight with a ten molar excess of thionyl chloride, evaporation gave a residue which was extracted (dichloromethane) and treated with acetamidine (< 10°) to give 2-(3-methyl-1,2,4-thiadiazol-5-yl)pyridine (**2**) (3% yield). When 2,4-lutidine was used only intractable tars were formed and no product was isolated. Davis and Scanlon reported no reaction of 2-methylpyridine (**1**) (or 3-methylpyridine) with hot thionyl chloride (6 hours) [4]. These workers also reported that treatment of 2-methylpyrazine (**3**) with hot thionyl chloride gave only decomposition and formation of intractable tars. We have found that treatment of 2-methylpyrazine (**3**) with a ten molar excess of hot thionyl chloride (3.5 hours) followed by evaporation and addition of morpholine to the ether soluble extract gave 2-morpholinothiocarbamoylpyrazine (**4**) (yield 10%).



SCHEME 1 : Reagents; i, $SOCl_2$ ; ii, acetamidine ; iii, morpholine ; iv, diethylamine.

We have not optimised the conditions for reaction of either 2-methylpyridine (**1**) or 2-methylpyrazine (**3**). Al-



SCHEME 2 : Reagents; i, SOCl$_2$; ii, N-methylpiperazine ; iii, Me$_2$NC(=NH)NH$_2$ ; iv, OH$^-$ ; H$^+$

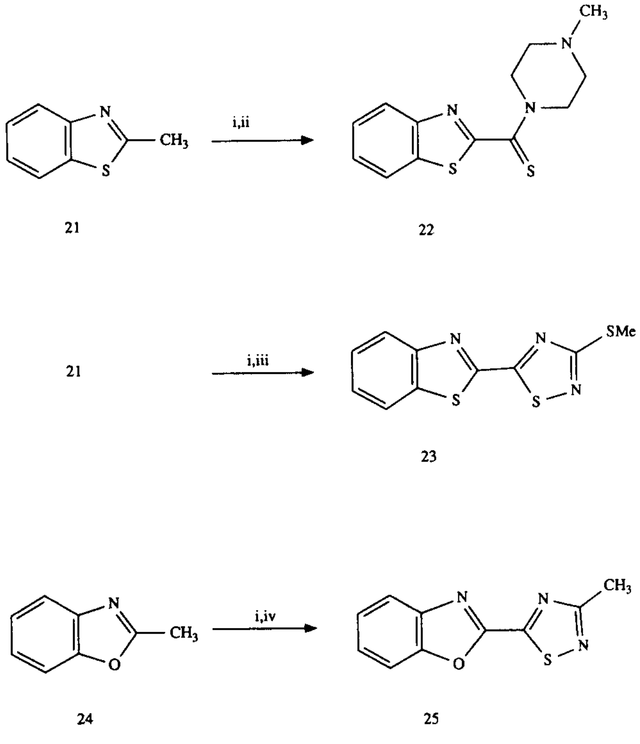
though yields are low, these systems are reacting in a manner analogous to methylquinolines but we have not established whether the intermediates are dichloromethanesulphenyl chlorides [RCCl$_2$SCl] or *bis*[dichloromethyl]trisulphanes [(RCCl$_2$S)$_2$S]. Using similar conditions, 2-methylquinoxaline (**5**) and acetamidine gave the 1,2,4-thiadiazole derivative **6** (7%) and 4-methyl-2-phenylquinazoline (**7**) and diethylamine gave the thioamide **8** (10%). No reaction was observed between 3-methylisoquinoline and thionyl chloride.

When 5-methyl-1-phenyl-1,2,4-triazolo[3,4-*a*]quinoline (**9**) was used as substrate, chlorination of the 4-position occurred giving, after treatment with morpholine, the thioamide **10** (16%). When 5-methyltetrazolo[1,5-*a*]quinoline was investigated no reaction was observed.

Nishigaki and co-workers have described the formation of the trichloromethyl derivative of nalidixic acid (**12**) by treatment of the parent acid **11** with hot thionyl chloride [5]. Singh and Lesher subsequently employed this approach in a synthesis of the trifluoromethyl derivative **13** [6]. We now report an investigation of the reactions of the ethyl ester of nalidixic acid (**14**) with thionyl chloride. Use of a ten molar excess of the reagent followed by treatment with *N*-methylpiperazine gave the thioamide **15** (yield 30%). When the 1(3'-chloropropyl) derivative **16** was used, a 36% yield of the corresponding thioamide **17** was isolated. We propose that these products **15** and **17** are formed by reactions of an intermediate dichloromethanesulphenyl chloride [ArCCl$_2$SCl] or *bis*[dichloromethyl]trisulphane [(ArCCl$_2$S)$_2$S] with *N*-methylpiperazine. Upon prolonged treatment with thionyl chloride the intermediate presumably reacts further giving the trichloromethyl function described by previous workers [5,6]. When dimethylaminoguanidine was used as a trapping agent, the 3-dimethylamino-1,2,4-thiadiazole **19** was obtained and, after saponification, was fully characterized as the acid **20**.

## Five-membered Heterocycles.

The simplest five-membered *C*-methylheterocycles which have previously been investigated are 2-methylbenzothiazole (**21**) and 2-methylbenzoxazole (**24**). Davis and Scanlon reported that both these systems react rapidly with hot thionyl chloride (1 hour) resulting in complete replacement of the *C*-methyl protons with chlorine and sulphur functions [4]. Using similar conditions Oka and Hara concluded that the products were thioacyl chlorides and



SCHEME 3 : Reagents : i, SOCl$_2$ ; ii, N-methylpiperazine ; iii, MeSC(=NH)NH$_2$ , iv, MeC(=NH)NH$_2$.

these proposals were supported by the structures of the products formed upon reaction with amines [7,8]. However, the proposed thioacyl chloride intermediates have not been isolated and the available spectroscopic and chemical evidence does not exclude the possibility that the true intermediates are trisulphanes [$(ArCCl_2S)_2S$] or sulphenyl chlorides ($ArCCl_2SCl$).

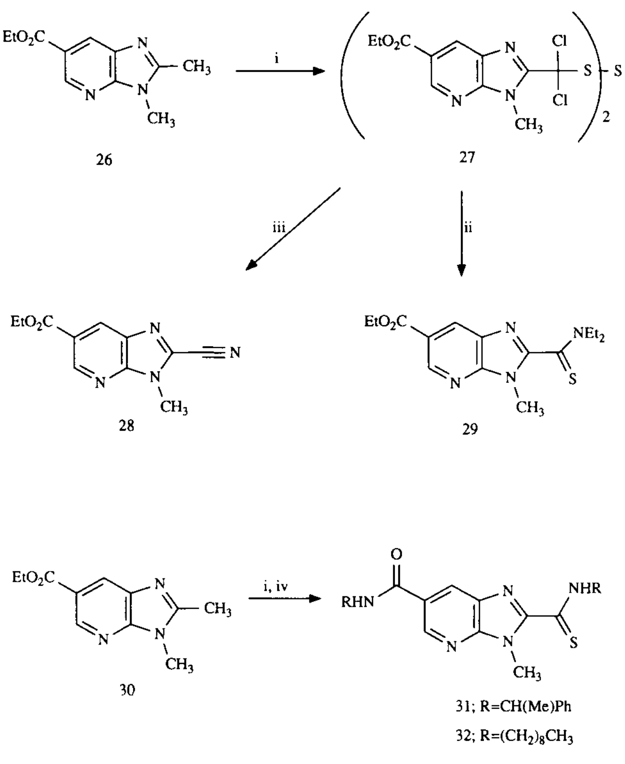
We have independently investigated the reactions of 2-methylbenzothiazole (**21**) and 2-methylbenzoxazole (**24**). In neither case did we isolate the products initially formed but have transformed them into stable derivatives using amines and amidines. 2-Methylbenzothiazole (**21**) was reacted with an excess of thionyl chloride at reflux temperature (2 hours). Evaporation gave a residue which was treated with *N*-methylpiperazine giving the thioamide **22** (yield 25%). Similarly, when the crude intermediate was reacted with *S*-methylisothiourea the 1,2,4-thiadiazole (**23**) was isolated (yield 12%) and the same procedure using 2-methylbenzoxazole (**24**) and acetamidine gave the 1,2,4-thiadiazole **25** (yield 17%).

2-Methylbenzimidazole has been reported to react slowly (72 hours) with thionyl chloride [4]. We have investigated the behaviour of 1,2-dimethylbenzimidazole and observed no reaction. However, when we reacted 2,3-dimethyl-6-ethoxycarbonylimidazo[4,5-*b*]pyridine (**26**) with hot thionyl chloride (5.5 hours), the trisulphane **27** was isolated (yield 23%).

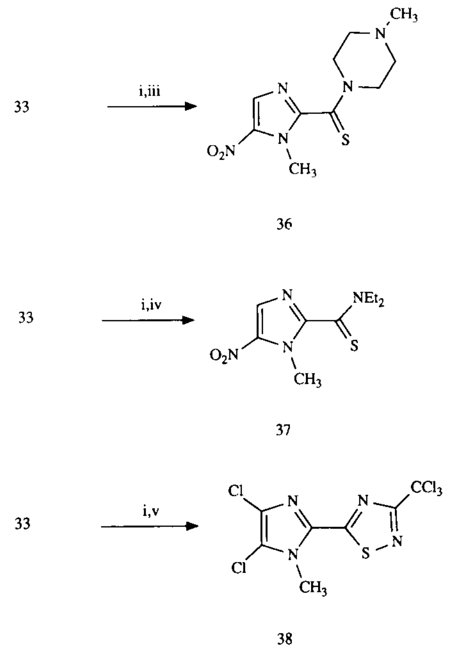
Reaction of a dichloromethane solution of the trisulphane **27** with diethylamine gave the thioamide **29** (56%). Reaction with 33% w/w ammonia solution under similar conditions gave the nitrile **28** (48%), presumably formed *via* a thioamide intermediate.

When the parent acid **30** was used the intermediate formed upon reaction with hot thionyl chloride was not isolated but reaction of the crude product with primary amines gave products consistent with the initial formation of a *bis*-carbonylchloride trisulphane. Reaction of the crude product with $\alpha$-methylbenzylamine gave the anticipated amide **31** (31%) and a similar procedure using *n*-nonylamine gave the amide **32** (39%).

The formation of the trisulphane **27** is consistent with the formation of similar products when pinacolone (*t*-BuCOMe) [9], acetophenone (PhCOMe) [9] and 2-chloro-4-methylquinoline [2] react with thionyl chloride. The isolation of the product **27**, and its mode of reaction with amines, lends support to the proposal that trisulphanes and not thioacyl chlorides are the major products when 2-methylbenzothiazole (**21**) and 2-methylbenzoxazole (**24**) react with thionyl chloride.



SCHEME 4 : Reagents; i, $SOCl_2$; ii, $Et_2NH$; iii, $NH_3$; iv, $RNH_2$



SCHEME 5 : Reagents ; i, $SOCl_2$; ii, morpholine; iii, N-methylpiperazine; iv, $Et_2NH$; v, $Cl_3CC(=NH)NH_2$.

Finally, we have studied the reactions of 2-methyl-5-nitroimidazoles with thionyl chloride. When 1,2-dimethyl-5-nitroimidazole (**33**) was heated with thionyl chloride (24 hours) and the crude product reacted with morpholine, a mixture was obtained from which two major components were isolated using medium pressure liquid chromatography. These were identified as the 5-nitroimidazole derivative **34** (9%) and the 4,5-dichloroimidazole derivative **35** (7%). By analogy with other heterocyclic systems which we have studied, we assume that the anticipated product **34** is formed *via* a trisulphane intermediate. Further reaction of this intermediate with thionyl chloride probably results in *O*-sulphinylation of the nitro-group. Subsequent displacement of the sulphinylated function by chloride then leads to a 5-chloroimidazole, sulphur dioxide and nitric oxide. Under the conditions of the reaction the 5-chloroimidazole is then presumably rapidly chlorinated at the 4-position leading to the observed product **35**.

When the procedure described above was repeated using *N*-methylpiperazine, the thioamide **36** (9%) was obtained and by using diethylamine, the thioamide **37** (7%) was isolated. In neither of these cases was the corresponding 4,5-dichloroimidazole derivative obtained, but the reaction mixtures were complex and it is probable that these products were present. When the crude reaction mixture was treated with trichloromethylacetamidine, the only isolated product was 4,5-dichloro-1-methyl-2-(3-trichloromethyl-1,2,4-thiadiazol-5-yl)imidazole (**38**) (6%).

No reaction was observed when either 1,2-dimethyl-4-nitroimidazole or 5-methyl-4-nitroimidazole was treated with thionyl chloride.

## EXPERIMENTAL

The $^1$H nmr spectra were recorded on Varian CFT-20 (80 MHz) and XL-200 (200 MHz) spectrometers; ir spectra on a Pye-Unicam SP3-200 spectrometer, ms on a VG Micromass 6F or VG 7070E spectrometer, and analyses on a Carlo-Erba 1106. Unless otherwise stated, ir spectra were measured using potassium bromide discs and 80 and 200 MHz nmr spectra in deuteriochloroform (tetramethylsilane as internal reference). Only significant bands from ir spectra are quoted.

Thin layer chromatography (tlc) was carried out on Merck silica gel (layer thickness 0.2 mm) pre-coated plastic plates and visualized under ultra violet light (254 and 366 nm).

Separations by column chromatography were carried out using Merck Kieselgel 60 (230-400 mesh). Evaporation refers to the removal of volatile materials under reduced pressure. Substances stated to be identical were so with respect to melting points, mixed melting points, and ir spectra. Melting points are uncorrected. For all preparations, May & Baker colourless laboratory chemical grade (>99%) thionyl chloride was used without further purification.

### WARNING.

Reaction of thionyl chloride with certain *C*-methylheterocycles can be vigorous. We recommend preliminary experiments on a small scale and addition of substrate to thionyl chloride (**NOT** *vice versa*).

### The Preparation of 1,2,4-Thiadiazoles.

### 2-(3-Methyl-1,2,4-thiadiazol-5-yl)pyridine (**2**).

2-Methylpyridine (**1**) (9.3 g, 0.1 mole) and thionyl chloride (11.9 g, 1.0 mole) were heated under reflux (18 hours). After evaporation, the residue was extracted with dichloromethane (2 × 50 ml) and the combined solutions chilled to 0° and stirred. Acetamidine hydrochloride (2.35 g, 0.025 mole) was added followed by sodium hydroxide solution (50% w/v, 13 ml) at a rate which maintained the temperature of the reaction mixture below 10°. After addition was complete, the solution was stirred at room temperature (0.5 hours) and the organic layer was separated, washed (2 × 50 ml) and dried (magnesium sulfate). Evaporation gave an oil which was subjected to mplc (chloroform as eluent). The major component (Rf 0.15) was collected and crystallized from light petroleum (bp 60-80°) giving compound (**2**), 0.5 g, (2.8%), pale orange crystals, mp 81-83°; ir: 1585, 1510, 1465, 1430, 1310, 1295, 1255, 1025 cm$^{-1}$; $^1$H nmr: $\delta$ 2.75 (s, C$H_3$), 7.25-7.5 (m, 1 aromatic *H*), 7.75-8.25 (m, 2 aromatic *H*), 8.6-8.75 (m, 1 aromatic *H*); ms: m/e 178 (MH$^+$).

*Anal.* Calcd. for $C_8H_7N_3S$: C, 54.2; H, 3.98; N, 23.7; S, 18.1. Found: C, 54.1; H, 3.73; N, 23.7; S, 18.3.

### 2-(3-Methyl-1,2,4-thiadiazol-5-yl)quinoxaline (**6**).

Following the method described for **2**, the title compound was obtained from **5** (14.4 g, 0.1 mole), yield 1.5 g, (6.6%), buff solid, mp 115-119°; ir: 1495, 1440, 1425, 1360, 1280, 1125, 1025, 930 cm$^{-1}$; $^1$H nmr: $\delta$ 2.8 (s, C$H_3$), 7.75-7.95 (m, 2 aromatic *H*), 8.05-8.30 (m, 2 aromatic *H*), 9.7 (s, 1 aromatic *H*); ms: m/e 229 (MH$^+$).

*Anal.* Calcd. for $C_{11}H_8N_4S$: C, 57.9; H, 3.53; N, 24.5; S, 14.0. Found: C, 57.7; H, 3.45; N, 24.6; S, 14.0.

### 2-(3-Methyl-1,2,4-thiadiazol-5-yl)benzoxazole (**25**).

Following the method described for **2**, the title compound was obtained from **24** (6.65 g, 0.05 mole), yield 1.8 g, (17%), pale yellow solid, mp 133-134°; ir: 1470, 1440, 1310, 1270, 1045 cm$^{-1}$; $^1$H nmr: $\delta$ 2.85 (s, C$H_3$), 7.4-8.0 (m, 4 aromatic *H*); ms: m/e 217 (M$^+$).

*Anal.* Calcd. for $C_{10}H_7N_3OS$: C, 55.3; H, 3.25; N, 19.3; S, 14.8. Found: C, 55.1; H, 3.09; N, 19.4; S, 14.8.

### 2-(3-Methylthio-1,2,4-thiadiazol-5-yl)benzothiazole (**23**).

Following the method described for **2**, the title compound was obtained from **21** (5.96 g, 0.04 mole), yield 1.3 g, (12%), buff solid, mp 186-188°; ir: 1525, 1450, 1420, 1215, 955, 895, 760 cm$^{-1}$; $^1$H nmr: $\delta$ 2.75 (s, SC$H_3$), 7.45-7.65 (m, 2 aromatic *H*), 7.9-8.25 (m, 2 aromatic *H*); ms: m/e 266 (MH$^+$).

*Anal.* Calcd. for $C_{10}H_7N_3S_3$: C, 45.3; H, 2.66; N, 15.8; S, 36.2. Found: C, 45.0; H, 2.63; N, 15.8; S, 36.4.

### 1-Ethyl-1,4-dihydro-7-(3-dimethylamino-1,2,4-thiadiazol-5-yl)-4-oxo-1,8-naphthyridine-3-carboxylic Acid (**20**).

Compound **18** (10.4 g, 0.04 mole) and thionyl chloride (47.6 g, 0.4 mole) in dichloromethane (150 ml) were heated under reflux (1.5 hours). Evaporation gave a residue which was dissolved in dichloromethane (100 ml) and the solution was chilled to 0°. Dimethylaminoguanidine hydrochloride (4.92 g, 0.04 mole) was added to the stirred solution followed by aqueous sodium hydroxide (50% w/v, 25 ml) at a rate which maintained the temperature below 10°. After stirring at room temperature (0.5 hours), the organic layer was collected, washed (2 × 100 ml) and dried (magnesium sulfate). Evaporation gave a mixture which was subjected to mplc (19:1 chloroform-methanol as eluent). Collection of the major component (Rf 0.5) gave **19** 0.9 g, (6%), yellow solid, mp 243-246° which, without further purification, was added to a mixture of 2*N* sodium hydroxide solution (5 ml) and ethanol (5 ml) and heated under reflux (20 minutes). The hot solution was filtered and acidified with glacial acetic acid (3 ml). The product was collected and crystallised from dimethylformamide to give compound **20** 0.7 g, (5%), orange solid, mp 323-324°; ir: 3060, 1720, 1615, 1600, 1560, 1480, 1435, 1230 cm$^{-1}$; $^1$H nmr (DMSO-d$_6$): $\delta$ 1.5 (t, J = 7 Hz, $CH_2CH_3$), 3.2 (s, $N(CH_3)_2$), 4.65 (q, J = 7 Hz, $CH_2CH_3$), 8.3 (d, J = 8 Hz, 1 aromatic *H*), 8.95 (d, J = 8 Hz, 1 aromatic *H*), 9.2 (s, 1 aromatic *H*), 14.0 (s, v broad, $CO_2H$); ms: m/e 346 (MH$^+$).

*Anal.* Calcd. for $C_{15}H_{15}N_5O_3S$: C, 52.2; H, 4.38; N, 20.3; S, 9.3. Found: C, 51.8; H, 4.16; N, 20.3; S, 9.4.

### The Preparation of Thioamides.

### 2-Morpholinothiocarbamoylpyrazine (**4**).

Compound **3** (9.4 g, 0.1 mole) and thionyl chloride (119 g, 1 mole) were heated under reflux (3.5 hours). After evaporation, the residue was extracted with ether (3 × 50 ml). Morpholine was then added to the combined ethereal extracts with cooling until no further reaction was observed. The residue obtained upon evaporation was subjected to mplc (dichloromethane as eluent). The major component (Rf 0.05) was collected and concentrated. Addition of ether and storage at 0° (24 hours) gave compound **4** 2.1 g, (10%), yellow crystals, mp 93-95°; ir: 2975, 2865, 1490, 1470, 1440, 1390, 1300, 1270, 1230, 1110, 1060, 1035, 1015 cm$^{-1}$; $^1$H nmr: $\delta$ 3.5-4.0 (m, 6 aliphatic *H*), 4.3-4.5 (m, 2 aliphatic *H*), 8.35-8.6 (m, 2 aromatic *H*), 8.9 (d, J = 1 Hz, 1 aromatic *H*); ms: m/e 210 (MH$^+$).

*Anal.* Calcd. for $C_9H_{11}N_3OS$: C, 51.7; H, 5.30; N, 20.1; S, 15.3. Found: C, 51.4; H, 5.19; N, 20.1; S, 15.5.

### 4-Diethylthiocarbamoyl-2-phenylquinazoline (**8**).

Following the method described for **4**, the title compound was obtained from **7** (1.65 g, 7.5 mmoles), yield 0.25 g, (10%), yellow solid, mp 136-138°; ir: 2980, 1510, 1499, 1435, 1340, 1280, 1220, 1140 cm$^{-1}$; $^1$H nmr: $\delta$ 1.20 (t, J = 7 Hz, $CH_2CH_3$), 1.55 (t, J = 7 Hz, $CH_2CH_3$), 3.3 (m, 1 aliphatic *H*), 3.45 (m, 1 aliphatic *H*), 4.00 (m, 1 aliphatic *H*), 4.52 (m, 1 aliphatic *H*), 7.46-7.60 (m, 4 aromatic *H*), 7.82-8.10 (m, 3 aromatic *H*), 8.56-8.65 (m, 2 aromatic *H*); ms: m/e 321 (M)$^+$.

*Anal.* Calcd. for $C_{19}H_{19}N_3S$: C, 71.0; H, 5.96; N, 13.1. Found: C, 71.3; H, 5.94; N, 12.8.

### 4-Chloro-5-morpholinothiocarbamoyl-1-phenyl-1,2,4-triazolo[3,4-*a*]quinoline (**10**).

Following the method described for **4**, the title compound was obtained from **9** (3.89 g, 15 mmoles), yield 0.98 g, (16%), pale pink plates, mp 292-294°; ir: 2960, 2850, 1500, 1440, 1270, 1240, 1110, 1030 cm$^{-1}$; $^1$H nmr (DMSO-d$_6$): $\delta$ 3.5-3.75 (m, 4 aliphatic *H*), 3.8-4.05 (m, 2 aliphatic *H*), 4.4-4.55 (m, 2 aliphatic *H*), 7.4-7.65 (m, 4 aromatic *H*), 7.7-7.8 (m, 5 aromatic *H*); ms: m/e 409 [MH$^+$($^{35}$Cl)].

*Anal.* Calcd. for $C_{21}H_{17}ClN_4OS$: C, 61.7; H, 4.19; Cl, 8.7; N, 13.7; S, 7.8. Found: C, 61.6; H, 4.20; Cl, 8.4; N, 13.4; S, 7.6.

### Ethyl 1-Ethyl-1,4-dihydro-7-(*N*-methylpiperazino)thiocarbamoyl-4-oxo-1,8-naphthyridine-3-carboxylate (**15**).

Compound **14** (7.8 g, 0.03 mole), thionyl chloride (35.7 g, 0.3 mole) and dichloromethane (85 ml) were heated under reflux (1.25 hours). After evaporation, the residue was dissolved in dichloromethane (100 ml) and the solution added to a stirred solution of *N*-methylpiperazine (15 g, 0.15 mole) in dichloromethane (50 ml) at 0°. The mixture was stirred at room temperature (1 hour), evaporated, and the residue was extracted with dichloromethane (2 × 50 ml). The extract was subjected to mplc (19:1 chloroform:methanol as eluent). The major component (Rf 0.2) was collected and concentrated. Ether was added and the solution chilled to give compound **15**, 3.6 g, (31%), yellow solid, mp 165-166°; ir: 2990, 2805, 1730, 1630, 1590, 1490, 1435, 1290, 1235 cm$^{-1}$; $^1$H nmr: $\delta$ 1.4 (t, J = 7 Hz, $CH_2CH_3$), 1.5 (t, J = 7 Hz, $CH_2CH_3$), 2.35 (s, $NCH_3$), 2.4-2.55 (m, 2 aliphatic *H*), 2.6-2.8 (m, 2 aliphatic *H*), 3.45-3.7 (m, 2 aliphatic *H*), 4.25-4.6 (m, 6 aliphatic *H*), 7.55 (d, J = 8 Hz, 1 aromatic *H*), 8.65 (s, 1 aromatic *H*), 8.8 (d, J = 8 Hz, 1 aromatic *H*); ms: m/e 289 (MH$^+$).

*Anal.* Calcd. for $C_{19}H_{24}N_4O_3S$: C, 58.7; H, 6.23; N, 14.4; S, 8.3. Found: C, 58.5; H, 6.39; N, 14.2; S, 8.2.

### Ethyl 1-(3′-Chloropropyl)-1,4-dihydro-7-(*N*-methylpiperazino)thiocarbamoyl-4-oxo-1,8-naphthyridine-3-carboxylate (**17**).

Following the method described for **15**, the title compound was obtained from **16** (9.24 g, 30 mmoles), yield 4.7 g, (36%), yellow solid from chloroform/ether (1:1), mp 115-117°; ir: 2985, 2960, 2805, 1730, 1700, 1640, 1610, 1585, 1500, 1440, 1290, 1235 cm$^{-1}$; $^1$H nmr: $\delta$ 1.4 (t, J = 7 Hz, $CH_2CH_3$), 2.25-2.75 (m, 9 aliphatic *H*), 3.45-3.7 (m, 4 aliphatic *H*), 4.25-4.65 (m, 6 aliphatic *H*), 7.55 (d, J = 8 Hz, 1 aromatic *H*), 8.7 (s, 1 aromatic *H*), 8.8 (d, J = 8 Hz, 1 aromatic *H*); ms: m/e 436 [M$^{+\cdot}$($^{35}$Cl)].

*Anal.* Calcd. for $C_{20}H_{25}ClN_4O_3S$: C, 55.0; H, 5.77; Cl, 8.1; N, 12.8; S, 7.3. Found: C, 55.2; H, 6.11; Cl, 8.5; N, 12.6; S, 7.2.

### 2-*N*-Methylpiperazinothiocarbamoyl-benzothiazole (**22**).

Following the method described for **15**, the title compound was obtained from **21** (3.73 g, 25 mmoles), yield 1.7 g, (25%), yellow crystals from light petroleum (bp 60-80°), mp 77-78°; ir: 2930, 2800, 1500, 1440, 1290, 1255, 1175, 1135 cm$^{-1}$; $^1$H nmr: $\delta$ 2.35 (s, $NCH_3$), 2.4-2.7 (m, 4 aliphatic *H*), 4.1-4.5 (m, 4 aliphatic *H*), 7.35-7.55 (m, 2 aromatic *H*), 7.8-8.1 (m, 2 aromatic *H*); ms: m/e 278 (MH$^+$).

*Anal.* Calcd. for $C_{13}H_{15}N_3S_2$: C, 56.3; H, 5.45; N, 15.1; S, 23.1. Found: C, 56.2; H, 5.41; N, 15.1; S, 23.1.

### 3-Methyl-6-(1′-methylbenzyl)-carbamoyl-2-(1′-methylbenzyl)thiocarbamoylimidazo[4,5-*b*]pyridine (**31**).

Following the method described for **15**, the title compound was obtained from **30** (3.82 g, 20 mmoles), yield 2.7 g, (31%), yellow solid from cyclohexane, mp 80-95° indistinct; ir: 3320, 2980, 1640, 1520, 1500, 1455, 1370 cm$^{-1}$; $^1$H nmr: $\delta$ 1.6 (d, J = 7 Hz, $NHCHCH_3$), 1.7 (d, J = 7 Hz, $CHCH_3$), 4.3 (s, $NCH_3$), 5.3 (quint, J = 7 Hz, $NHCHCH_3$), 5.8 (quint, J = 7 Hz, $NHCHCH_3$), 6.5 (d, J = 7 Hz, 1 exchangeable N*H*), 7.15-7.4 (m, 10 aromatic *H*), 8.3 (d, J = 2 Hz, 1 aromatic *H*), 8.85 (d, J = 2 Hz, 1 aromatic *H*), 9.8 (d, J = 7 Hz, 1 exchangeable *N*H); ms: m/e 443 (M$^{+\cdot}$).

*Anal.* Calcd. for $C_{25}H_{25}N_5OS$: C, 67.7; H, 5.68; N, 15.8; S, 7.2. Found: C, 67.6; H, 5.63; N, 15.6; S, 7.0.

### 3-Methyl-6-*n*-nonylcarbamoyl-2-*n*-nonylthiocarbamoyl-imidazo[4,5-*b*]pyridine (**32**).

Following the method described for (**15**), the title compound was obtained from (**30**) (3.82 g, 20 mmoles), yield 3.8 g, (39%), yellow solid from acetonitrile, mp 119-121°; ir: 3300, 2970, 2930, 2860, 1635, 1540, 1520, 1460 cm$^{-1}$; $^1$H nmr: $\delta$ 0.8-1.9 (m, 34 aliphatic *H*), 3.45 (q, J = 7 Hz, C*H*$_2$NH), 3.8 (q, J = 7 Hz, C*H*$_2$NH), 4.35 (s, NC*H*$_3$), 6.4 (t, J = 7 Hz, 1 exchangeable N*H*), 8.35 (d, J = 2 Hz, 1 aromatic *H*), 8.8 (d, J = 2 Hz, 1 aromatic *H*), 9.6 (br, 1 exchangeable N*H*); ms: m/e 487 ($M^{+\cdot}$).

*Anal.* Calcd. for $C_{27}H_{45}N_5OS$: C, 66.5; H, 9.3; N, 14.4; S, 6.6. Found: C, 66.2; H, 9.4; N, 14.4; S, 6.7.

### Reactions of 1,2-Dimethyl-5-nitroimidazole (**33**).

### 1-Methyl-2-(*N*-methylpiperazino)thiocarbamoyl-5-nitroimidazole (**36**).

1,2-Dimethyl-5-nitroimidazole (**33**) (7.06 g, 0.05 moles) and thionyl chloride (59.5 g, 0.5 moles) were heated under reflux (24 hours). The dark solution was cooled and unreacted starting material (**33**) (1.5 g) was removed by filtration. Evaporation of the filtrate gave a residue which was dissolved in dichloromethane (70 ml). *N*-Methylpiperazine was added to the cooled solution until reaction was complete. Filtration and evaporation of the filtrate gave a residue which was subjected to mplc (chloroform:methanol 19:1 as eluent). Addition of light petroleum to the concentrated major fraction (Rf 0.2) affected crystallisation of compound (**36**) 1.2 g, (8.9%), yellow solid, mp 119-120°; ir: 2945, 2800, 1495, 1465, 1435, 1370, 1290, 1240, 1195, 1140, 1035 cm$^{-1}$; $^1$H nmr: $\delta$ 2.35 (s, NC*H*$_3$), 2.4-2.7 (m, 4 aliphatic *H*), 3.5-3.7 (m, 2 aliphatic *H*), 4.0 (s, NC*H*$_3$), 4.3-4.45 (m, 2 aliphatic *H*), 8.0 (s, 4-*H*); ms: m/e 269 ($M^{+\cdot}$).

*Anal.* Calcd. for $C_{10}H_{15}N_5O_2S$: C, 44.6; H, 5.61; N, 26.0; S, 11.9. Found: C, 44.8; H, 5.79; N, 25.8; S, 11.8.

### 2-Diethylthiocarbamoyl-1-methyl-5-nitroimidazole (**37**).

Following the method described for **36**, the title compound was obtained from **33** (7.06 g, 0.05 mole) yield 0.8 g, (6.6%) (Rf 0.6), yellow solid, mp 91-93°; ir: 1520, 1465, 1365, 1260, 1220, 1185 cm$^{-1}$; $^1$H nmr: $\delta$ 1.25 (t, J = 7 Hz, CH$_2$C*H*$_3$), 1.40 (t, J = 7 Hz, CH$_2$C*H*$_3$), 3.45 (q, J = 7 Hz, C*H*$_2$CH$_3$), 3.95 (s, NC*H*$_3$), 4.1 (q, J = 7 Hz, C*H*$_2$CH$_3$), 8.0 (s, 4-*H*); ms: m/e 243 ($MH^+$).

*Anal.* Calcd. for $C_9H_{14}N_4O_2S$: C, 44.6; H, 5.82; N, 23.1; S, 13.2. Found: C, 44.6; H, 5.87; N, 23.4; S, 13.6.

### 1-Methyl-2-morpholinothiocarbamoyl-5-nitroimidazole (**34**).

Following the method described for **36**, the title compound was obtained from **33** (7.06 g, 0.05 mmole), yield 1.1 g, (8.6%) (Rf 0.5), yellow solid, mp 169-171°; ir: 2980, 2860, 1460, 1370, 1260, 1230, 1180, 1110, 1040 cm$^{-1}$; $^1$H nmr: $\delta$ 3.5-3.95 (m, 6 aliphatic *H*), 4.0 (s, NC*H*$_3$), 4.3-4.45 (m, 2 aliphatic *H*), 8.0 (s, 4-*H*); ms: m/e 257 ($MH^+$).

*Anal.* Calcd. for $C_9H_{12}N_4O_3S$: C, 42.2; H, 4.72; N, 21.9; S, 12.5. Found: C, 42.1; H, 4.60; N, 21.9; S, 12.5.

### 4,5-Dichloro-1-methyl-2-morpholinothiocarbamoylimidazole (**35**).

Following the method described for **36**, the title compound was obtained from **33** (7.06 g, 0.05 mole), yield 0.9 g, (6.5%) (Rf 0.6), yellow solid, mp 146-148°; ir: 2860, 1500, 1430, 1275, 1240, 1110, 1040 cm$^{-1}$; $^1$H nmr: $\delta$ 3.65-3.9 (m, 6 aliphatic *H* + NC*H*$_3$), 4.25-4.45 (m, 2 aliphatic *H*); ms: m/e 279 [$M^{+\cdot}$($^{35}$Cl)].

*Anal.* Calcd. for $C_9H_{11}Cl_2N_3OS$: C, 38.6; H, 3.96; C, 25.3; N, 15.0; S, 11.4. Found: C, 38.6; H, 3.78; Cl, 25.3; N, 15.1; S, 11.5.

### 4,5-Dichloro-1-methyl-2-(3-trichloromethyl-1,2,4-thiadiazol-5-yl)-imidazole (**38**).

Following the method described for **36**, the title compound was obtained from **33** (7.06 g, 0.05 mole), yield 1.1 g, (6.3%) (Rf 0.7), pale orange solid, mp 139-141°; ir: 1555, 1485, 960, 830, 795, 690 cm$^{-1}$; $^1$H nmr: $\delta$ 4.2 (s, C*H*$_3$); ms: m/e 350 [$M^{+\cdot}$($^{35}$Cl).].

*Anal.* Calcd. for $C_7H_3Cl_5N_4S$: C, 23.9; H, 0.86; Cl, 50.3; N, 15.9; S, 9.1. Found: C, 23.8; H, 0.75; Cl, 50.6; N, 15.8; S, 8.8.

### Preparation of Bis[dichloro-2-(6-ethoxycarbonyl-3-methylimidazo-[4,5-*b*]pyridine)methyl]trisulphane (**27**).

Compound **26** (5.5 g, 0.025 mole) and thionyl chloride (29.75 g, 0.25 mole) were heated under reflux (5.5 hours). Evaporation gave an orange residue which was extracted with ether (3 × 100 ml). Concentration of the extracts and chilling (0°) afforded a solid which was collected and dried to give compound (**27**) 1.9 g, (23%), pale pink/orange solid, mp 142-144°; ir: 2980, 1720, 1605, 1365, 1300, 1205, 1085, 930, 765 cm$^{-1}$; $^1$H nmr: $\delta$ 1.45 (t, J = 7 Hz, 2 × CH$_2$C*H*$_3$), 4.25 (s, 2 × C*H*$_3$), 4.45 (s, J = 7 Hz, 2 × C*H*$_2$CH$_3$), 8.75 (d, J = 2 Hz, 2 aromatic *H*), 9.15 (d, J = 2 Hz, 2 aromatic *H*).

*Anal.* Calcd. for $C_{22}H_{20}Cl_4N_6O_4S_3$: C, 39.4; H, 3.00; Cl, 21.2; N, 12.5; S, 14.3. Found: C, 39.2; H, 3.03; Cl, 21.1; N, 12.7; S, 14.3.

### 2-Diethylthiocarbamoyl-6-ethoxycarbonyl-3-methyl-3*H*-imidazo[4,5-*b*]pyridine (**29**).

Compound **27** (3.35 g, 0.005 mole) in dichloromethane (30 ml) was added slowly to a stirred solution of diethylamine (3.65 g, 0.05 mole) in dichloromethane (30 ml) at 0°, and the brown solution was then stirred at room temperature (1 hour). Evaporation gave a residue which was extracted with ethyl acetate and the extract was subjected to mplc (4:1 ether:ethyl acetate as eluent). The major component (Rf 0.4) was collected. Concentration of the fractions and addition of light petroleum (bp 40-60°) with chilling afforded yellow crystals which were collected and identified as compound (**29**) 1.8 g, (56%), yellow crystals, mp 95-97°; ir: 2780, 2740, 1610, 1510, 1410, 1360, 1325, 1290, 1260, 1200, 1140, 1110 cm$^{-1}$; $^1$H nmr: $\delta$ 1.25 (t, J = 7 Hz, OCH$_2$C*H*$_3$), 1.4 (t, J = 7 Hz, N(CH$_2$C*H*$_3$)$_2$), 3.55 (q, J = 7 Hz, OC*H*$_2$CH$_3$), 3.9 (s, NC*H*$_3$), 4.15 (q, J = 7 Hz, NC*H*$_2$CH$_3$), 4.45 (q, J = 7 Hz, NC*H*$_2$CH$_3$), 8.6 (d, J = 2 Hz, 1 aromatic *H*), 9.1 (d, J = 2 Hz, 1 aromatic *H*).

*Anal.* Calcd. for $C_{15}H_{20}N_4O_2S$: C, 56.2; H, 6.29; N, 17.5; S, 10.0. Found: C, 56.5; H, 6.43; N, 17.5; S, 9.9.

### 2-Cyano-6-ethoxycarbonyl-3-methylimidazo[4,5-*b*]pyridine (**28**).

Following the method described for **29**, the title compound was obtained from **27** (3.35 g, 0.005 moles), yield 1.1 g, (48%) (Rf 0.6), colourless crystals, mp 133-134°; ir: 3055, 2990, 2240, 1720, 1605, 1470, 1355, 1310, 1250, 1220 cm$^{-1}$; $^1$H nmr: $\delta$ 1.45 (t, J = 7 Hz, CH$_2$C*H*$_3$), 4.1 (s, C*H*$_3$), 4.5 (q, J = 7 Hz, C*H*$_2$CH$_3$), 8.8 (d, J = 2 Hz, 1 aromatic *H*), 9.25 (d, J = 2 Hz, 1 aromatic *H*); ms: m/e 231 ($MH^+$).

*Anal.* Calcd. for $C_{11}H_{10}N_4O_2$: C, 57.4; H, 4.38; N, 24.3. Found: C, 57.2; H, 4.22; N, 24.7.

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