Amino Acids in the Synthesis of Heterocyclic Compounds. Transformations of Thiazolones into Imidazole Derivatives

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5(4*H*)-Thiazolone derivative **4**, obtained from *N*-dithiocarbobenzoxyglycine (**1**) and *N,N*-dimethyl-*N'*-heteroarylformamidines **3** in acetic anhydride, was rearranged with sodium methoxide in methanol followed by acidification with acetic acid into imidazole-4-carboxylic acid derivatives **5**, **6** and **7**. These were further converted with methyl iodide into methylthio derivatives **8**, with hydrogen peroxide into the corresponding disulphide **9**, with hydrazine and amines into hydrazide **10** and amides **11**. In the reactions of **4a** and **6a** with amines in the presence of dichloromethane symetrically disubstituted methanes **14-18** were formed.

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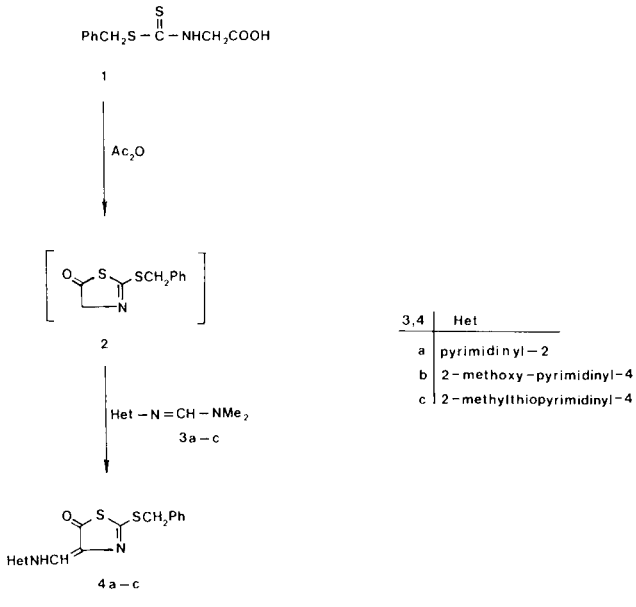
Recently, β-heteroarylamino-α,β-dehydro- and β-heteroarylamino-α-amino acid derivatives have been prepared by ring-opening of the corresponding 4-heteroarylaminomethylene-5(4*H*)-oxazolones [1-4].

In continuation of our investigations in the field of heteroaryl substituted amino acids and derivatives our intention was to prepare the corresponding 4-heteroarylaminomethylene-5(4*H*)-thiazolones **4** from 2-benzylthio-5(4*H*)-thiazolone (**2**). This compound has been previously

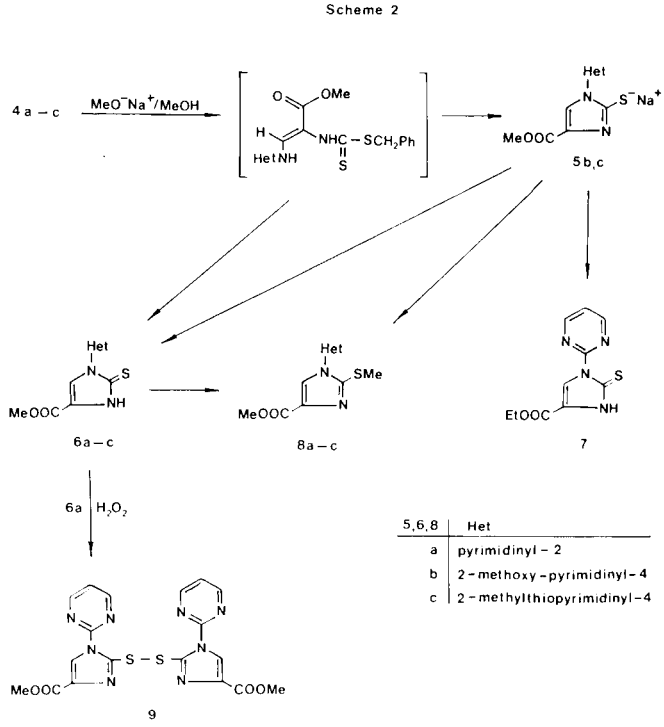
Scheme 1



3,4	Het
a	pyrimidinyl-2
b	2-methoxy-pyrimidinyl-4
c	2-methylthiopyrimidinyl-4

prepared from *N*-dithiocarbobenzoxyglycine (**1**) by dehydration with phosphorus tribromide [5] or trifluoroacetic anhydride [6]. Since it is unstable in the presence of air [5], we prepared this compound *in situ* from *N*-dithiocarbobenzoxyglycine **1** and acetic anhydride and transformed in the presence of *N,N*-dimethyl-*N'*-heteroarylformamides **3a-c** into 4-heteroarylaminomethylene-2-benzylthio-5(4H)-thiazolones **4a-c**. However, attempts to prepare heteroaryl substituted α-amino acid derivatives from these intermediates were unsuccessful, instead, a rearrangement of the thiazolone ring into imidazole system was observed.

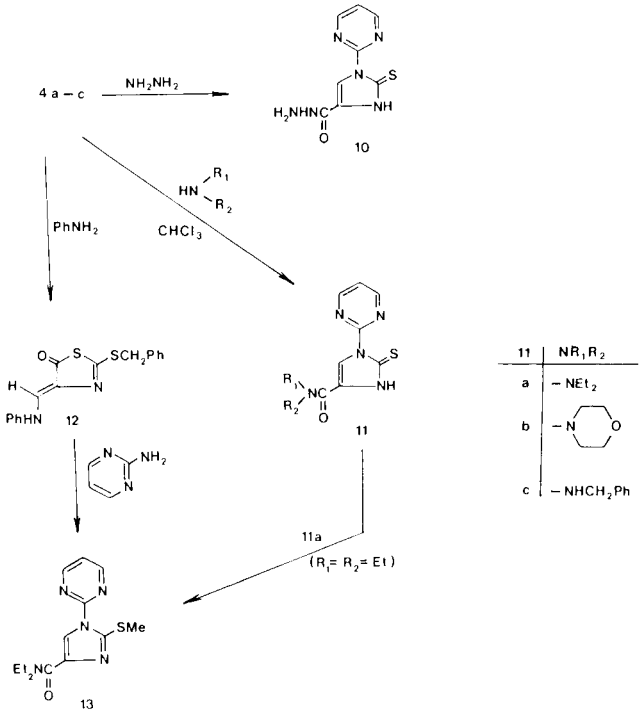
Scheme 2



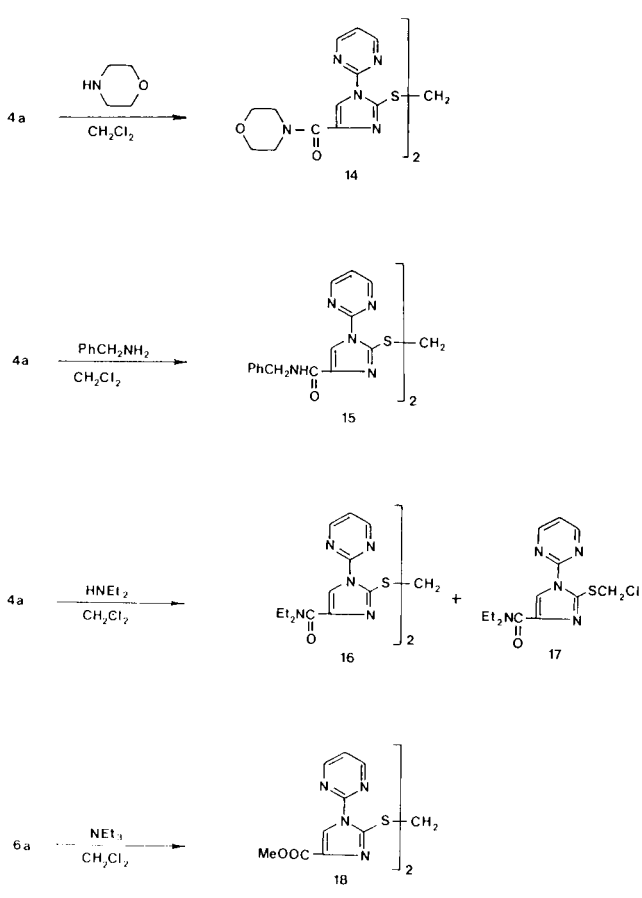
5,6,8	Het
a	pyrimidinyl-2
b	2-methoxy-pyrimidinyl-4
c	2-methylthiopyrimidinyl-4

1-Substituted derivatives of imidazole-4-carboxylic acid have been prepared from *N*-substituted α,β-diamino acids and triethylortho formate followed by dehydrogenation of the intermediate with manganese dioxide [7], by decarboxylation of the corresponding imidazole-4,5-dicarboxylic acids [8], by oxidation of polyhydroxy substituents, attached at position 4, with sodium periodate [9], and from 3-dimethylaminopropenoates, with a nitrogen containing substituent at position 2, and primary amines [10-12].

Scheme 3



Scheme 4



When the compounds **4b,c** were treated with sodium methoxide in methanol, benzylthiol was eliminated and the products **5b,c** were formed as precipitates. The product formed from **4a** can be isolated by dilution of acidified solution with water, the structure of which was shown to be **6a**. When aqueous suspensions of **5b,c** were acidified with acetic acid the compounds **6b,c** were obtained. The compounds **6a-c** were also formed, when **4a-c** were heated under reflux in a mixture of methanol and triethylamine. The acidification of **4a** with acetic acid in ethanol solution gave the corresponding ethyl ester **7a**. The compounds **5a-c** and **6a-c** were methylated with methyl iodide to give the corresponding methylthio derivatives **8a-c**, while with hydrogen peroxide the transformation or **6a** into **9a** took place. The compound **4a** reacted quickly with hydrazine hydrate to give the hydrazide **10**, while the reactions with amines such as morpholine, benzylamine and diethylamine, in chloroform are much slower producing the corresponding amides **11a-c**. An exception is the reaction of **4a** with aniline. In this case only the substitution of the heterocyclic amine with aniline took place to give **12**, which according to the ^{1}H nmr spectrum is a mixture of (*Z*)- and (*E*)-isomers. The compound **11a** was transformed with methyl iodide into the corresponding *S*-methyl derivative **13**. When the reactions of **4a** with morpholine or benzylamine were carried out in dichloromethane, new products **14** and **15** were isolated, while in the reaction with diethylamine two products **16** and **17** were formed. Similarly, the ester **6a** was transformed with dichloromethane in the presence of triaethylamine into **18**.

The structures of new compounds were confirmed by elemental analyses for C, H, and N and ^{1}H nmr spectra. The spectra for the compounds **4** show a singlet at δ = 4.68-4.78 ppm for the CH_2 part of the benzyl group, a multiplet at δ = 7.2-7.8 ppm for the phenyl part of the benzyl group, a doublet at δ = 8.25-8.29 ppm for the methyne proton coupled to the adjacent NH group, which appears as a doublet at δ 11.2-11.4 ppm, with a coupling constant J_{CHNH} = 12.0 Hz, indicating the anti arrangement around the C-N bond, and the corresponding signals for the heterocyclic substituents. The compounds **6** exhibit a heteroaromatic singlet at δ = 8.18-8.35 ppm and a singlet at δ = 3.82-3.86 ppm, the compounds **8** an additional singlet at δ = 2.64-2.69 ppm, characteristic for the *S*-methyl group and the compounds **14**, **15**, **16**, **17** and **18** a singlet at δ = 4.93-5.33 ppm, characteristic for a methylene group, confirming thus that dichloromethane took an active part in the formation of the latter derivatives. On the basis of these spectral data and some chemical evidence, such as the elimination of benzylthiol, and S-methylation with methyl iodide, one can conclude

that the thiazolone ring of the compounds **4** rearranges during these transformations into the imidazole ring in compounds **6-11** and **13-18**.

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^1H nmr spectra were obtained on a JEOL 90 Q FT spectrometer with TMS as internal standard and elemental analyses for C, H, and N on Perkin-Elmer Analyser 240 C.

The following compounds were prepared according to the procedures described in the literature: *N*-dithiocarbobentoxyglycine [5] and *N*,*N*-dimethyl-*N'*-heteroarylformamidines **3a-c** [13,14].

2-Benzylthio-4-heteroarylaminomethylene-5(4*H*)-oxazolones (**4**). General Procedure.

A mixture of formamidine derivative **3** (0.006 mole) and *N*-dithiocarbobenzoxyglycine (**1**, 2.2 g, 0.009 mole) in acetic anhydride (10 ml) was stirred from 5 minutes to 24 hours at temperature between 25 and 80°. The mixture was left in the refrigerator for 12 hours, and the precipitate, which was formed during this time, was collected by filtration, washed with diethyl ether and recrystallized from an appropriate solvent. In this manner the following compounds were prepared.

2-Benzylthio-4-(2-pyrimidinylamino)methylene-5(4*H*)-thiazolone (**4a**).

This compound was prepared from **3a** and **1** by heating at 80° for five minutes in 40% yield, mp 150-153° (from acetonitrile); ^1H nmr (DMSO-d_6): δ 4.78 (s, 2H, C*H*$_2$Ph), 7.2-7.8 (m, 6H, 5'-H, CH$_2$*Ph*), 8.29 (d, 1H, C*H*NH), 8.79 (d, 2H, 4'-H, 6'-H), 11.40 (d, 1H, CHN*H*), $J_{4'\text{-}H,5'H} = J_{5'\text{-}H,6'\text{-}H} = 5.0$ Hz, $J_{CHNH} = 12.0$ Hz.

Anal. Calcd. for $C_{15}H_{12}N_4OS_2$: C, 54.84; H, 3.68; N, 17.06. Found: C, 54.83; H, 3.70; N, 17.18.

2-Benzylthio-4-(2-methoxy-4-pyrimidinylamino)methylene-5(4*H*)-thiazolone (**4b**).

This compound was prepared from **3b** and **1** by heating at 60° for two hours in 61% yield, mp 163-164° (from acetonitrile); ^1H nmr (DMSO-d_6): δ 3.97 (s, 3H, Me), 4.69 (s, 2H, C*H*$_2$Ph), 7.07 (d, 1H, 5'-H), 7.2-7.6 (m, 5H, CH$_2$*Ph*), 8.25 (d, 1H, C*H*NH), 8.50 (d, 1H, 6'-H), 11.24 (d, 1H, CHN*H*), $J_{5'\text{-}H,6'\text{-}H} = 5.5$ Hz, $J_{CHNH} = 12.0$ Hz.

Anal. Calcd. for $C_{16}H_{14}N_4O_2S_2$: C, 53.61; H, 3.94; N, 15.63. Found: C, 53.71; H, 3.80; N, 15.75.

2-Benzylthio-4-(2-methylthio-4-pyrimidinylamino)methylene-5(4*H*)-thiazolone (**4c**).

This compound was prepared from **3c** and **1**, by stirring at room temperature for 24 hours in 52% yield, mp 194-195° (from acetonitrile); ^1H nmr (DMSO-d_6): δ 2.58 (s, 3H, Me), 4.68 (s, 2H, C*H*$_2$Ph), 7.12 (d, 1H, 5'-H), 7.2-7.7 (m, 5H, CH$_2$*Ph*), 8.25 (d, 1H, C*H*NH), 8.54 (d, 1H, 6'-H), 11.2 (d, 1H, CHN*H*), $J_{5'\text{-}H,6'\text{-}H} = 5.5$ Hz, $J_{CHNH} = 12.0$ Hz.

Anal. Calcd. for $C_{16}H_{14}N_4OS_3$: C, 51.31; H, 3.77; N, 14.96. Found: C, 51.29; H, 3.84; N, 15.06.

Sodium 1-Heteroaryl-4-methoxycarbonyl-2-imidazolylthiolates General Procedure.

A mixture of **4** and sodium methoxide, prepared from sodium (100 mg) in methanol (6 ml) was stirred at room temperature for two hours. The precipitate was then collected by filtration and recrystallized from acetonitrile. In this manner the following compounds were prepared.

Sodium 1-(2-Methoxy-4-pyrimidinyl)-4-methoxycarbonyl-2-imidazolylthiolate (**5b**).

This compound was prepared from **4b** in 52% yield, mp 199-202° (from acetonitrile); ^1H nmr (DMSO-d_6): δ 3.75 (s, 3H, COOMe), 3.96 (s, 3H, OMe), 8.22 (s, 1H, 5-H), 8.60 (d, 1H, 5'-H), 9.54 (d, 1H, 6'-H), $J_{5'\text{-}H,6'\text{-}H} = 5.5$ Hz.

Anal. Calcd. for $C_{10}H_9NaN_4O_3S \cdot H_2O$: C, 39.08; H, 3.60; N, 18.23; Found: C, 39.15; H, 3.57; N, 18.28.

Sodium 1-(2-Methylthio-4-pyrimidinyl)-4-methoxycarbonyl-2-imidazolylthiolate (**5c**).

This compound was prepared from **4c** in 83% yield, mp 284-288° (from acetonitrile); ^1H nmr (DMSO-d_6): δ 2.57 (s, 3H, SMe), 3.75 (s, 3H, COOMe), 8.20 (s, 1H, 5-H), 8.62 (d, 1H, 5'-H), 9.53 (d, 1H, 6'-H), $J_{5'\text{-}H,6'\text{-}H} = 5.5$ Hz.

Anal. Calcd. for $C_{10}H_9N_4NaO_2S_2 \cdot H_2O$: C, 37.15; H, 3.43; N, 17.32. Found: C, 37.33; H, 3.37; N, 17.37.

Methyl 2,3-dihydro-1-heteroaryl-2-thiooxoimidazole-4-carboxylates **6**. General Procedure.

Method A.

A mixture of **4** (0.004 mole) and sodium methoxide, prepared from sodium (180 mg) in methanol (25 ml) was stirred at room temperature for six hours. Methanol was evaporated *in vacuo*, water (20 ml) was added and acidified with acetic acid. The precipitate was collected by filtration and recrystallized.

Method B.

A mixture of **5** (0.001 mole), acetic acid (0.5 ml) and methanol (4 ml) was stirred at room temperature for 30 minutes. Methanol was evaporated *in vacuo*, water (5 ml) was added to the residue and the solution was extracted with chloroform (3 times, 5 ml each time). The combined extracts were dried with anhydrous magnesium sulphate, and chloroform evaporated *in vacuo*. The residue was recrystallized from an appropriate solvent.

Method C.

A mixture of **5** (0.001 mole), triethylamine (0.6 ml) and methanol (5 ml) was heated under reflux three hours. The solvent was evaporated *in vacuo*, water (5 ml) was added to the residue and the solution was extracted with chloroform (3 times, 5 ml each time). The combined extracts were dried over anhydrous magnesium sulphate. Chloroform was evaporated *in vacuo* and the residue was purified by column chromatography (silica gel 0.063-0.200 mm, E. Merck, and a mixture of chloroform and methanol, 50:1).

The following compounds were prepared according to these procedures.

Methyl 2,3-Dihydro-1-(2-pyrimidinyl)-2-thiooxoimidazole-4-carboxylate (**6a**).

This compound was prepared from **4a** according to Method A in 35% yield, mp 215-217° (from methanol); ^1H nmr (DMSO-d_6): δ 3.82 (s, 3H, COOMe), 7.69 (t, 1H, 5'-H), 8.18 (s, 1H, 5-H), 9.04 (s, 2H, 4'-H, 6'-H), 13.32 (br s, 1H, 3-H), $J_{4'\text{-}H,5'\text{-}H} = 5.0$ Hz.

Anal. Calcd. for $C_9H_8N_4O_2S$: C, 45.76; H, 3.41; N, 23.71. Found: C, 45.99; H, 3.38; N, 23.42.

Methyl 2,3-Dihydro-1-(2-methoxy-4-pyrimidinyl)-2-thiooxoimidazole-4-carboxylate (**6b**).

This compound was prepared either from **5b** according to Method B or **4c** according to Method C in 98% and 50%, respectively, mp 198-203° (from acetonitrile); ^{1}H nmr (DMSO-d_6): δ 3.86 (s, 3H, COOMe), 4.01 (s, 3H, OMe), 8.35 (s, 1H, 5-H), 8.84 (s, 2H, 5'H,6'-H), 13.7 (br s, 1H, 3-H).

Anal. Calcd. for $C_{10}H_{10}N_4O_3S$: C, 45.11; H, 3.79; N, 21.13. Found: C, 45.33; H, 3.81; N, 21.16.

Methyl 2,3-Dihydro-1-(2-methylthio-4-pyrimidinyl)-2-thiooxoimidazole-4-carboxylate (**6c**).

This compound was prepared from **5c** according to Method B in 96% yield or according to Method C in 80% yield, mp 196-201° (from acetonitrile); ^{1}H nmr (DMSO-d_6): δ 2.57 (s, 3H, SMe), 3.83 (s, 3H, COOMe), 8.24 (s, 1H, 5-H), 8.69 (s, 2H, 5'-H, 6'-H), 13.5 (s, 1H, 3-H).

Anal. Calcd. for $C_{10}H_{10}N_4O_2S_2$: C, 42.45; H, 3.57; N, 19.84. Found: C, 42.52; H, 3.71; N, 19.88.

Ethyl 2,3-Dihydro-1-(2-pyrimidinyl)-2-thiooxoimidazole-4-carboxylate (**7**).

A mixture of **4a** (0.0015 mole) and sodium ethoxide, prepared from sodium (70 mg) in ethanol (8 ml), was stirred for seven days at room temperature. Acetic acid (0.3 ml) was added and the precipitate was collected by filtration to give **7** in 63% yield, mp 211-214° (from water); ^{1}H nmr (DMSO-d_6): δ 1.32 (t, 3H, CH_2*Me*), 4.30 (q, 2H, C*H*$_2$Me), 7.70 (t, 1H, 5'-H), 8.21 (s, 1H, 5-H), 9.08 (d, 1H, 6'-H), 13.3 (br s, 1H, 3-H), J_{CH_2Me} = 7.5 Hz, $J_{5'-H,6'-H}$ = 5.0 Hz.

Anal. Calcd. for $C_{10}H_{10}N_4O_2S$: C, 47.99; H, 4.03; N, 22.39. Found: C, 47.72; H, 4.35; N, 21.98.

Methyl 1-Heteroaryl-2-methylthioimidazole-4-carboxylates (**8**). General Procedures.

Method A.

A mixture of **4** (0.001 mole), sodium methoxide, prepared from sodium (45 mg) in methanol (8 ml), and methyl iodide (210 mg, 0.0015 mole) was stirred for 10 minutes at room temperature. The precipitate was, after cooling to 0°, collected by filtration and recrystallized from methanol.

Method B.

A mixture of **5** (0.001 mole) and methyl iodide (0.0015 mole) in methanol (5 ml) was stirred for 15 minutes at room temperature. The precipitate was, after cooling to 0°, collected by filtration and recrystallized from methanol.

The following compounds were prepared according to these methods.

Methyl 1-(2-Pyrimidinyl)-2-methylthioimidazole-4-carboxylate (**8a**).

This compound was prepared from **4a** by Method A in 94% yield, mp 178°; ^{1}H nmr (DMSO-d_6): δ 2.64 (s, 3H, SMe), 3.88 (s, 3H, COOMe), 7.62 (t, 1H, 5'-H), 8.57 (s, 1H, 5-H), 9.03 (d, 2H, 4'-H, 6'-H) $J_{4'-H,5'-H}$ = $J_{5'-H,6'-H}$ = 5.0 Hz.

Anal. Calcd. for $C_{10}H_{10}N_4O_2S$: C, 47.99; H, 4.03; N, 22.39. Found: C, 47.82; H, 4.19; N, 22.40.

Methyl 1-(2-Methoxy-4-pyrimidinyl)-2-methylthioimidazole-4-carboxylate (**8b**).

This compound was prepared from **5b** by Method B in 84% yield, mp 211°; ^{1}H nmr (DMSO-d_6): δ 2.69 (s, 3H, SMe), 3.97 (s, 3H, COOMe), 4.19 (s, 3H, OMe), 7.80 (d, 1H, 5'-H), 8.90 (s, 1H, 5-H), 8.95 (d, 1H, 6'-H), $J_{5'-H,6'-H}$ = 5.5 Hz.

Anal. Calcd. for $C_{11}H_{12}N_4O_3S$: C, 47.13; H, 4.32; N, 19.99. Found: C, 46.87; H, 4.47; N, 20.17.

Methyl 1-(2-Methylthio-4-pyrimidinyl)-2-methilthioimidazole-4-carboxylate (**8c**).

This compound was prepared from **5c** by Method B in 92% yield, mp 190-191°; ^{1}H nmr (DMSO-d_6): δ 2.66 (s, 3H, SMe), 2.73 (s, 3H, SMe), 3.89 (s, 3H, COOMe), 7.78 (d, 1H, 5'-H), 8.83 (s, 1H, 5-H), 8.87 (d, 1H, 6'-H), $J_{5'-H,6'-H}$ = 5.5 Hz.

Anal. Calcd. for $C_{11}H_{12}N_4O_2S_2$: C, 44.58; H, 4.08; N, 18.90. Found: C, 44.35; H, 4.13; N, 18.92.

Bis[4-methoxycarbonyl-1-(2-pyrimidinyl)-2-imidazolyl] Disulphide (**9**).

To a solution of **6a** (360 mg, 0.0015 mole) in methanol (10 ml) aqueous solution of hydrogen peroxide (30%, 3 ml) was added and the mixture was stirred for 30 minutes at room temperature. The solvent was evaporated *in vacuo*, water (6 ml) was added to the residue and the precipitate was collected by filtration to give **9** in 33% yield, mp 248-251° (from DMF); ^{1}H nmr (DMSO-d_6): δ 3.61 (s, 3H, OMe), 7.20 (t, 1H, 5'-H), 8.05 (s, 1H, 5-H), 8.48 (d, 2H, 4'-H, 6'-H), $J_{4'-H,5'-H}$ = $J_{5'-H,6'-H}$ = 5.0 Hz.

Anal. Calcd. for $C_{18}H_{14}N_8O_4S_2$: C, 45.95; H, 3.00, N, 23.82. Found: C, 45.86; H, 3.20; N, 23.64.

2,3-Dihydro-1-(2-pyrimidinyl)-2-thiooxoimidazole-4-carbohydrazide (**10**).

A mixture of **4a** (320 mg, 0.001 mole) and hydrazine hydrate (80%, 0.2 ml) in ethanol (4 ml) was stirred for one hour at room temperature. The precipitate was collected by filtration and washed with ethanol to give **10** in quantitative yield, mp >310° (from DMF); ^{1}H nmr (DMSO-d_6): δ 6.98 (t, 1H, 5'-H), 7.5 (br s, 1H, 5-H), 8.48 (d, 2H, 4'-H, 6'-H), 9.8 (br s, 3H, $NHNH_2$), 11.2 (br s, 1H, 3-H), $J_{4'-H,5'-H}$ = $J_{5'-H,6'-H}$ = 5.0 Hz.

Anal. Calcd. for $C_8H_8N_6OS$: C, 40.67; H, 3.41; N, 35.57. Found: C, 40.77; H, 3.60; N, 35.45.

2,3-Dihydro-1-(2-pyrimidinyl)-2-thiooxoimidazol-4-carboxamides **11**. General Procedure.

A mixture of **4a** (0.003 mole) and alkylamine (2 ml) in chloroform (20 ml) was stirred from three to six hours at room temperature. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (silicagel 0.063-0.200 mm, E. Merck and a mixture of chloroform and methanol, 20:1, as eluent). The solvent was evaporated and the residue recrystallized from appropriate solvent. The following compounds were prepared in this manner.

N,N-Diethyl-2,3-dihydro-1-(2-pyrimidinyl)-2-thiooxoimidazole-4-carboxamide (**11a**).

This compound was prepared from **4a** in 52% yield, mp 227-230° (from acetonitrile); ^{1}H nmr (deuteriochloroform): δ 1.30 (t, 3H, CH_2*Me*), 3.62 (q, 2*H*, C*H*$_2$Me), 7.37 (t, 1H, 5'-H), 7.76 (s, 1H, 5-H), 8.92 (d, 2H, 4'-H, 6'-H), 10.7 (br s, 1H, 3-H), $J_{4'-H,5'-H}$ =

$J_{5'\text{-}H,6'\text{-}H}$ = 5.0 Hz.

Anal. Calcd. for $C_{12}H_{15}N_5OS$: C, 51.97; H, 5.45; N, 25.25. Found: C, 51.71; H, 5.55; N, 25.01.

[2,3-Dihydro-1-(2-pyrimidinyl)-2-thiooxoimidazole-4-carbonyl]-morpholide (**11b**).

This compound was prepared **4a** in 72% yield, mp (decomp above 230°) (from methanol); ^{1}H nmr (DMSO-d_6): δ 3.64 (s, 4H, NCH_2CH_2O), 7.74 (t, 1H, 5'-H), 7.97 (s, 1H, 5-H), 9.09 (d, 2H, 4'-H, 6'-H), 13.0 (s, 1H, 3-H), $J_{4'\text{-}H,5'\text{-}H}$ = 5.0 Hz.

Anal. Calcd. for $C_{12}H_{13}N_5O_2S$: C, 49.47; H, 4.50; N, 24.04. Found: C, 49.48; H, 4.64; N, 23.72.

N-Benzyl-2,3-dihydro-1-(2-pyrimidinyl)-2-thiooxoimidazole-4-carboxamide (**11c**).

This compound was prepared from **4a** in 66% yield, mp 228-230° (from acetonitrile); ^{1}H nmr (DMSO-d_6): δ 4.54 (d, 2H, $NHCH_2$), 7.45 (s, 5H, Ph), 7.79 (t, 1H, 5'-H), 8.27 (s, 1H, 5-H), 9.02 (t, 1H, $NHCH_2$), 9.19 (d, 2H, 4'-H, 6'-H), 13.0 (br s, 3-H), J_{NHCH_2} = 6.5 Hz, $J_{4'\text{-}H,5'\text{-}H}$ = $J_{5'\text{-}H,6'\text{-}H}$ = 5.0 Hz.

Anal. Calcd. for $C_{15}H_{13}N_5OS$: C, 57.86; H, 4.21; N, 22.49. Found: C, 57.88; H, 4.26; N, 22.47.

2-Benzylthio-4-phenylaminomethylene-5(4*H*)-oxazolone (**12**).

A mixture of **4a** (480 mg, 0.0015 mole) and aniline (0.5 ml) in toluene (6 ml) was heated under reflux for five hours. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (silica gel 0.063-0.200 mm, E. Merck, and chloroform as eluent). The solvent was evaporated *in vacuo* to give **12** in 81% yield, mp 108-110° (from acetonitrile); ^{1}H nmr (deuteriochloroform): δ 4.48 (s, 2H, CH_2), 7.07-7.70 (m, 11H, CH_2Ph,N*H*Ph) 8.10 (d, 1*H*, NHC*H*), J_{NHCH} = 13.5 Hz.

Anal. Calcd. for $C_{17}H_{14}N_2OS_2$: C, 62.54; H, 4.32; N, 8.58. Found: C, 63.08; H, 4.39; N, 8.44.

N,N-Diethyl-2-methylthio-1-(2-pyrimidinyl)imidazole-4-carboxamide (**13**).

To a solution of sodium methoxide, prepared from sodium (80 mg) in methanol (8 ml), **11a** (690 mg, 0.0025 mole) and methyl iodide (500 mg, 0.0035 mole) were added. The mixture was stirred for 15 minutes at room temperature. The solvent was evaporated *in vacuo*, water (6 ml) was added to the residue and the mixture was extracted with chloroform (3 times, 4 ml each time). The combined extracts were dried over anhydrous magnesium sulphate. The residue obtained after evaporation of chloroform was purified by column chromatography (silica gel 0.063-0.200 mm, E. Merck, and chloroform as eluent) to give **13** in 21% yield, mp 88-89° (from diisopropyl ether); ^{1}H nmr (deuteriochloroform, 300 MHz): δ 1.29 (t, 3H, CH_2Me), 3.59 (s, 3H, SMe), 3.80 (q, 2H, CH_2Me), 7.34 (t, 1H, 5'-H), 8.64 (s, 1H, 5-H), 8.87 (d, 2H, 4'-H, 6'-H), J_{CH_2Me} = 7.5 Hz, $J_{4'\text{-}H,5'\text{-}H}$ = $J_{5'\text{-}H,6'\text{-}H}$ = 5.0 Hz.

Anal. Calcd. for $C_{13}H_{17}N_5OS$: C, 53.59; H, 5.88; N, 24.03. Found: C, 53.59; H, 6.02; N, 24.03.

Reactions of **4a** with Amines in Dichloromethane. General Procedure.

A mixture of **4a** (0.004 mole) and alkylamine (2 ml) in dichloromethane (25 ml) was stirred for five days at room temperature. The products were isolated and purified as described below.

The following compounds were prepared in this manner.

Methylene-S,S'-bis[*N*-(2-mercapto-1-(2-pyrimidinyl)imidazole-4-carbonylmorpholide] (**14**).

This compound was obtained from **4a** and morpholine in 98% yield, mp 278-280° (from acetonitrile); ^{1}H nmr (DMSO-d_6): δ 3.84 (m, 16H, NCH_2CH_2O), 4.93 (s, 2H, SCH_2), 7.19 (t, 2H, 5'-H), 8.49 (s, 2H, 5-H), 8.63 (d, 4H, 4'-H, 6'-H), $J_{4'\text{-}H,5'\text{-}H}$ = $J_{5'\text{-}H,6'\text{-}H}$ = 5.0 Hz.

Anal. Calcd. for $C_{25}H_{26}N_{10}O_4S_2$: C, 50.49; H, 4.40; N, 23.55. Found: C, 50.32; H, 4.52; N, 23.82.

Methylene-*S,S'*-bis[*N*-benzyl-2-mercapto-1-(2-pyrimidinyl)imidazole-4-carboxamide] (**15**).

This compound was obtained from **4a** and benzylamine in 83% yield, mp 262-264° (from DMF); ^{1}H nmr (DMSO-d_6): δ 4.56 (d, 4H, $NHCH_2$), 5.33 (s, 2H, SCH_2), 7.37 (m, 10H, Ph), 7.57 (t, 2H, 5'-H), 8.47 (s, 2H, 5-H), 8.96 (d, 4H, 4'-H, 6'-H), J_{NHCH_2} = 6.5 Hz, $J_{4'\text{-}H,5'\text{-}H}$ = $J_{5'\text{-}H,6'\text{-}H}$5.0 Hz.

Anal. Calcd. for $C_{31}H_{26}N_{10}O_2S_2$: C, 58.66; H, 4.12; N, 22.07. Found: C, 58.72; H, 4.18; N, 21.85.

Reaction with Diethylamine.

The reaction mixture obtained from **4a** and diethylamine was evaporated *in vacuo* and the dry residue separated by column chromatography (silica gel 0.063-0.200, E. Merck) gave three products in the following order:

1. *N,N*-Diethyl-2-chloromethylthio-1-(2-pyrimidinyl)imidazole-4-carboxamide (**17**).

This compound was obtained by elution with chloroform, followed by evaporation of the solvent *in vacuo*, in 34% yield, mp 94-98° (from a mixture of diethyl ether and petroleum ether, 1:1); ^{1}H nmr (deuteriochloroform, 300 MHz): δ 1.26 (t) and 1.36 (t) (6H, CH_2Me), 3.54 (q) and 3.95 (q) (4H, CH_2Me), 5.29 (s, 2H, SCH_2), 7.25 (t, 2H, 5'-H), 8.58 (s, 2H, 5-H), 8.75 (d, 4H, 4'-H, 6'-H), J_{CH_2Me}=6.5 Hz, $J_{4'\text{-}H,5'\text{-}H}$ = $J_{5'\text{-}H,6'\text{-}H}$ = 5.5 Hz.

Anal. Calcd. for $C_{13}H_{16}ClN_5OS$: C, 47.92; H, 4.95; N, 21.49. Found: C, 48.35; H, 5.06; N, 21.24.

2. Methylene-*S,S'*-bis[*N,N*-diethyl-2-mercapto-2-(2-pyrimidinyl)-imidazole-4-carboxamide] (**16**).

This compound was obtained by elution with a mixture of chloroform and methanol, 40:1, in 47% yield, mp 208-211° (from acetonitrile); ^{1}H nmr (deuteriochloroform, 300 MHz): δ 1.28 (t) and 1.42 (t) (12H, CH_2Me), 3.56 (q) and 4.00 (q) (8H, CH_2Me), 5.04 (s, 2H, SCH_2), 7.21 (t, 2H, 5'-H), 8.55 (s, 2H, 5-H), 8.69 (d, 4H, 4'-H, 6'-H), J_{CH_2Me} = 6.0 Hz, $J_{4'\text{-}H,5'\text{-}H}$ = $J_{5'\text{-}H,6'\text{-}H}$ = 5.0 Hz.

Anal. Calcd. for $C_{25}H_{30}N_{10}O_2S_2$: C, 52.98; H, 5.34; N, 24.71. Found: C, 53.19; H, 5.44; N, 24.78.

3. The compound **11a** was obtained by elution with a mixture of chloroform and methanol, 9:1, in 11% yield.

Methylene-*S,S'*-bis[4-methoxycarbonyl-2-mercapto-1-(2-pyrimidinyl)imidazole] (**18**).

A mixture of **6a** (0.0015 mole) and triethylamine (1 ml) in dichloromethane (8 ml) was stirred for 7 hours at room temperature. The precipitate was collected by filtration and washed with water to give **18** in 34% yield, mp > 300° (from DMF). The compound is not soluble enough in order to obtain the nmr spectrum).

Anal. Calcd. for $C_{19}H_{16}N_8O_4S_2$: C, 47.10; H, 3.33, N, 23.13. Found: C, 46.92; H, 3.44; N, 22.96.

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